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

EN3835-401

MOBI: A PHASE 4, OPEN-LABEL STUDY TO ASSESS EFFECTS OF MITIGATION TREATMENTS ON BRUISING OF CCH-AAES TREATMENT OF BUTTOCK CELLULITE IN ADULT FEMALES

Sponsor Name: Endo Pharmaceuticals Inc.

Sponsor Legal Registered Address: 1400 Atwater Drive, Malvern, PA 19355

Regulatory Agency Identifier Number: Investigational New Drug Application (IND) 110077

Original Protocol: 20 May 2022

[redacted]

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1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Marketed Product: QWO™(CCH-aaes)

Name of Active Ingredient: Collagenase clostridium histolyticum (CCH)

Title of Study: MOBI: A Phase 4, Open-Label Study to Assess Effects of Mitigation Treatments on Bruising of CCH-Aaes Treatment of Buttock Cellulite in Adult Females

Lead Principal Investigator: Not applicable

Phase of development: 4

Objectives and Endpoints:

Primary Objective	Primary Endpoint
To assess the effect of mitigation treatments on bruising in the buttocks of subjects with cellulite after the first treatment of QWO (CCH-aaes).	• The proportion of subjects by buttock at each level of bruising on the Investigator Assessment of Bruising Severity Scale, at Day 4, 3 days after QWO (CCH-aaes) injection. This 5-level scale ranges from 0 to 4, with 0 indicating no bruising or almost none, and 4 indicating very severe bruising.
Secondary Objectives	**Secondary Endpoints**
To assess investigator assessment of bruising with mitigation treatments in subjects with cellulite after the first treatment of QWO (CCH-aaes).	• The proportion of subjects for whom the investigator reported an improvement of bruising on the mitigation treated buttock on Days 4 and 7 as measured on the Investigator-Bruising Improvement Scale (I-BIS), a 3-point Likert scale, with a score on the higher end of the range indicating improvement with treatment. • The proportion of subjects by buttock with bruising at each level of the Investigator Assessment of Bruising Severity Scale, by visit. This 5-level scale ranges from 0 to 4, with 0 indicating no bruising or almost none, and 4 indicating very severe bruising.
To assess subject assessment of bruising with mitigation treatments in subjects with cellulite after the first treatment of QWO (CCH-aaes).	• The proportion of subjects treated with QWO (CCH-aaes) reporting an improvement of bruising on the mitigation treated buttock on Days 4 and 7 as measured on the Subject-Bruising Improvement Scale (S-BIS), a 3-point Likert scale, with a score on the higher end of the range indicating improvement of bruising with treatment. • The proportion of subjects by buttock bothered by the appearance of bruising on each buttocks on the Patient Bother by Bruising Scale, a 4-point scale, with a score of 1 indicating not bothered at all, and a score of 4, indicating, extremely bothered.

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Marketed Product: QWO™(CCH-aaes)

Name of Active Ingredient: Collagenase clostridium histolyticum (CCH)

Secondary Objectives	Secondary Endpoints
To assess the level of aesthetic improvement of cellulite after treatment of QWO (CCH-aaes) with and/or without bruising mitigation treatment.	• The proportion of subjects with an improved (+1 or better) score on the Investigator-Global Aesthetic Improvement Scale (I-GAIS) for either buttock at the Day 71 Visit compared to Baseline. The I-GAIS is a 7-level scale ranging from +3 (very much improved) to -3 (very much worse).
To assess the safety of QWO (CCH-aaes) with mitigation treatment in subjects with cellulite.	• Percentage of subjects reporting each adverse event (AE) and treatment emergent adverse event (TEAEs).
Exploratory Objective	**Exploratory Endpoint**
[redacted]	• [redacted]

Overall Design:

This is a Phase 4, multicenter, open-label, multiple dose study to assess the effect of mitigation treatments on injection site bruising and safety in adult women with moderate cellulite in the buttocks treated with QWO (CCH-aaes). Approximately 75 subjects will be screened in order to enroll approximately 48 subjects in 6 cohorts.

At the Screening Visit, subjects who meet all inclusion criteria and have no exclusion criteria according to the investigator's assessment will be assigned to 1 of 6 treatment cohorts. Subjects will be allocated to cohorts using a site specific Mitigation Treatment Assignment Table provided by the sponsor.

Pending site capabilities and available mitigation treatments, each site will administer each mitigation treatment, with approximately 1-3 subjects assigned to each mitigation treatment as shown in Table 1. Mitigation treatments will be administered at or after the initial treatment session of QWO (CCH-aaes).

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Marketed Product: QWO™(CCH-aaes)

Name of Active Ingredient: Collagenase clostridium histolyticum (CCH)

Table 1: Distribution of Mitigation Treatments

		QWO (CCH-aaes) [a]		Mitigation Treatment	
	N	Left Buttock	Right Buttock	Left Buttock	Right Buttock
Cohort 1	8	Up to 0.84 mg	Up to 0.84 mg	None	
Cohort 2	8	Up to 0.84 mg	Up to 0.84 mg	Compression garment	
Cohort 3	8	Up to 0.84 mg	Up to 0.84 mg	None	Instant cold packs
Cohort 4	8	Up to 0.84 mg	Up to 0.84 mg	None	Arnica patches
Cohort 5	8	Up to 0.84 mg	Up to 0.84 mg	None	INhance Post-Injection Serum with TriHex Technology
Cohort 6	8	Up to 0.84 mg	Up to 0.84 mg	None	PDL treatment [b]

a. For each subject, an identical dose and injection count of QWO (CCH-aaes) should be administered for the first treatment session to each buttock. The number of injections may differ among subjects.

b. Pulse dye laser (PDL) may be used at the settings selected according to the investigator's discretion.

Eligible subjects will receive up to 0.84 mg of QWO (CCH-aaes) per buttock in both buttocks for a total dose of 1.68 mg per treatment session for 3 treatment sessions (Day 1, Day 21 ±3 days, and Day 43 ±3 days). To reduce variance in the bruising observed on the left and right buttocks after the first treatment session of QWO (CCH-aaes), each buttock should be treated with the same number of QWO (CCH-aaes) injections on Day 1, of up to 12 injections per buttock. The number of injections may differ between treatment sessions; 12 injections per buttock may be administered during the first treatment session followed by fewer injections per buttock during the second and third treatment sessions.

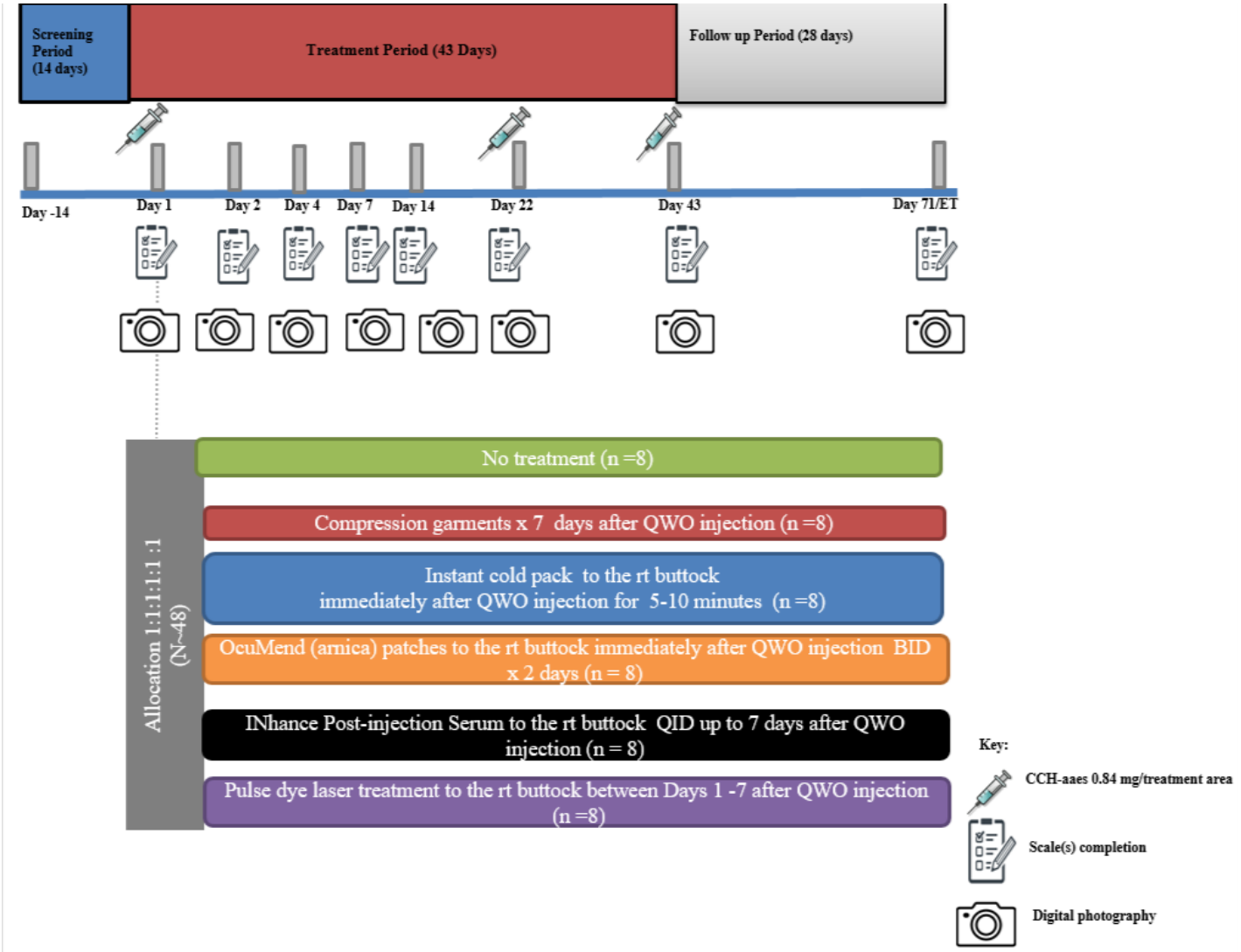
Subjects will return to the site approximately on Days 2, 4, 7, and 14 (ie, 1, 3, 6, and 13 days after injection on Day 1) for additional evaluations and digital photography obtained with standardized parameters. After the first mitigation treatment session, on Days 4 and 7, the effect of mitigation treatments on the severity of bruising will be assessed using the I-BIS and the Investigator Assessment of Bruising Severity Scale. The effect of mitigation treatments on the severity of bruising will be assessed by subjects on the S-BIS and the Patient Bother by Bruising Scale. Safety will be assessed throughout the study by collecting AEs, and TEAEs, and assessing injection site reactions in the buttocks. [redacted]

At the investigator's discretion, for the second and third QWO (CCH-aaes) treatment sessions on Days 22 and 43, subjects will be permitted to receive the same mitigation treatment to the right buttock as received during the first QWO (CCH-aaes) treatment session. The severity of bruising will be assessed at each visit. Subject and investigator assessments of satisfaction, aesthetic improvement, and digital photography will also be conducted on Days 22 (± 3 days) and 43 (±3 days). Subjects will return to the site for last study visit on Day 71 for additional investigator assessments of bruising and digital photography.

Disclosure Statement: This is an interventional open-label, post-marketing study to evaluate the effect of mitigation treatments on the bruising induced by QWO (CCH-aaes). The efficacy of the mitigation treatments in reducing bruising and the safety of QWO (CCH-aaes) with mitigation treatments will also be assessed.

Name of Sponsor/Company: Endo Pharmaceuticals Inc.
Name of Marketed Product: QWO™(CCH-aaes)
Name of Active Ingredient: Collagenase clostridium histolyticum (CCH)
Number of Subjects (planned): A maximum of 75 adult female subjects will be screened in order to enroll 48 adult female subjects into 6 cohorts, such that approximately 45 evaluable subjects complete the study.
Treatment Groups and Duration: It is intended to enroll 6 treatment cohorts of 8 subjects each. Cohort 1, will receive QWO (CCH-aaes) and no mitigation treatment. Cohorts 2-6 will receive QWO (CCH-aaes) with different mitigation treatments. Subjects will complete the study on Day 71. The expected duration of subject participation is up to 92 days.
Data Monitoring Committee: No data monitoring committee will be used for this study.

1.2. Study Schema



BID = twice daily, ET= early termination, rt =right, QID = 4 times daily

1.3. Schedule of Assessments

Procedures	Screening Period	Treatment Period							Follow-up Period
	Day -14	Day 1 (Baseline)	Day 2	Day 4	Day 7	Day 14	Day 22 (±3d)	Day 43 (±3d)	Day 71//ET (+ 7d)
Informed consent	X								
Inclusion/Exclusion criteria	X								
Medical history/surgical history/cellulite history including previous treatments	X								
Prior/Concomitant medications/procedures (including all prior medications/procedures for cellulite)	X	X	X	X	X	X	X	X	X
Physical examination (including height)	X								
Weight	X								X
Fitzpatrick skin type	X[a]								
Vital signs	X	X[b]							
Digital photography[c]		X	X	X	X	X	X[d]	X[d]	X
Cohort assignment	X[e]								
QWO (CCH-aaes) administration		X					X	X	
Subject Assessments									
[redacted]		[redacted]							
Subject-Bruising Improvement Scale (S-BIS)			X	X	X	X	X[d]		
Patient Bother by Bruising Scale[g]				X	X		X[d]		
Investigator Assessments									
Hexsel Cellulite Severity Scale (CSS) Subsection D	X[h]								
Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X[i]								
Selection and marking of dimples to be treated within both buttocks		X[c]					X[d]	X[d]	
Investigator Assessment of Bruising Severity Scale		X	X	X	X	X	X[d]		
Investigator- Bruising Improvement Scale (I-BIS)[j]			X	X	X	X	X[d]		

Procedures	Screening Period	Treatment Period							Follow-up Period
	Day -14	Day 1 (Baseline)	Day 2	Day 4	Day 7	Day 14	Day 22 (±3d)	Day 43 (±3d)	Day 71//ET (+ 7d)
Investigator- Global Aesthetic Improvement Scale (I-GAIS)							X[d]	X	X

Procedures	Screening Period	Treatment Period							Follow-up Period
	Day -14	Day 1 (Baseline)	Day 2	Day 4	Day 7	Day 14	Day 22 (±3d)	Day 43 (±3d)	Day 71//ET (+ 7d)
Mitigation Treatment Cohorts									
Compression garments		X[k,p]							
Instant cold packs to the right buttock only		X[l,p]							
Arnica patches (OcuMend®) to the right buttock only		X[m, p]							
INhance Post-Injection Serum with TriHex Technology® to the right buttock only		X[n,p]							
Pulse dye laser (PDL) treatment to the right buttock only		X[o,p]							
Injection site reactions/local tolerability in each buttock treated		X	X	X	X	X	X	X	X
Adverse events (AEs)		X[q]							

[a] Subjects with a Fitzpatrick skin rating of I-III will be included.
[b] Before injection and approximately 30 minutes after injection. Pulse and blood pressure should be collected after the subject has been sitting for 5 minutes.
[c] Buttocks will be photographed before and after injection site and dimple marking on Days 1, 22, and 43. Buttocks will also be photographed during the Days 2, 4, 7, 14, and 71 visits (ET) (no dimple or injection site markings).
[d.] Before injection.
[e] Subjects will be assigned to 1 of 6 cohorts according to a site specific Mitigation Treatment Assignment Table. Cohort 1 =no mitigation treatment; Cohorts 2-6 = mitigation treatments
[f.] Before QWO (CCH-aaes) injection, and 5 and 15 minutes after injection.
[g] Using mirrors, or photographs captured either by the subject or another person with the subject's imaging device (ie, cell phone, digital camera), or images captured by the investigator or designee using the site's digital photography system.
[h] Baseline Hexsel CSS Subsection D must be '0' (absence of flaccidity or sagging skin) or '1' (slightly draped appearance) on each buttock.
[i] Baseline CR-PCSS rating must be a '3' (moderate) on each buttock.
[j] Based on live assessments while the subject is in front of the investigator.
[k] Compression garments will be worn after QWO (CCH-aaes) injection on Day 1 and worn 24 hours a day for the next 7 days.
[l] Apply instant cold packs immediately after QWO (CCH-aaes) injection for 5-10 minutes immediately after CCH-aaes injection while subject is in a prone position.

[m] Arnica patches applied BID for 2 days immediately after QWO (CCH-aaes) injection on Day 1.
[n] Inhance Post-Injection Serum is applied QID directly on and around the injections site for up to 7 days after QWO (CCH-aaes) injection on Day 1, until resolution of bruising.
[o] PDL treatment between Days 1 (same day of QWO [CCH-aaes) injection) and Day 7 after QWO (CCH-aaes) treatment. PDL settings are according to the investigator's discretion.
[p] For the second and third QWO (CCH-aaes) treatment sessions, at the investigator's discretion, subjects will be allowed to use the same mitigation treatment in the same buttock (as applicable) that received mitigation treatment for the first CCH-aaes treatment session.
[q] AEs will be collected from the time the subject signed the ICF until end of the study or early termination.
BID = twice daily, d = Days, ET = early termination, ICF = informed consent form, QID = Four times daily

2. INTRODUCTION

Collagenase clostridium histolyticum (CCH)-aaes (CCH, EN3835, CCH-aaes, QWO™) is a combination of bacterial collagenases AUX-I and AUX-II, 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 (CCH-aaes) is FDA approved for the treatment of moderate to severe cellulite in the buttocks of adult women.

2.1. Background

The results of the pivotal studies (Studies EN3835-302 and -303) of QWO (CCH-aaes) in edematous fibrosclerotic panniculopathy, otherwise known as cellulite, supported FDA approval of QWO (CCH-aaes) for the treatment of moderate to severe cellulite in the buttocks of adult women. The approved dose of QWO (CCH-aaes) is 0.84 mg per treatment area (buttock) per treatment area for up to 2 treatment areas per treatment session, administered at 3 treatment sessions, approximately 21 days apart. This dose was shown to be an effective treatment of cellulite based on improvement in the severity of cellulite as determined by the investigator and the subject. Overall, the safety profile indicated that QWO (CCH-aaes) was well-tolerated (QWO Prescribing Information). Bruising (injection site bruising) was the most common AE (84%) in the Phase 3 studies. Bruising after the first treatment session was the most robust of the 3 treatment sessions, with the incidence, duration and severity of bruising decreasing with each subsequent treatment session (Endo Clinical Study Reports EN3835-202, EN3835-205, EN3835-302, EN3835-303).

2.2. Rationale

Although QWO (CCH-aaes)-related post-injection bruising generally resolves within 21 days, and before the next treatment session, bruising is bothersome to subjects due to skin discoloration, and associated swelling and pain. This study will investigate treatments that may mitigate bruising after QWO (CCH-aaes) treatment of cellulite in the buttocks.

Mitigation treatments that may potentially reduce bruising after QWO (CCH-aaes) injection were selected collaboratively with aesthetic physicians based on their experience using mitigation treatments when administering other injectable drugs during aesthetic procedures.

A description of the chemistry, pharmacology, efficacy, and safety of QWO (CCH-aaes) is provided in the QWO Prescribing Information.

2.3. Benefit-Risk Assessment

QWO is approved for the treatment of moderate to severe cellulite in the buttocks of adult women.

The selection of the mitigation treatments and their dose/regimen was a consensus based on the collaborative knowledge and experience of the investigators and Endo, the postulated mechanism of bruising of QWO (CCH-aaes) known to date, and/or supportive literature.

The benefit and risk of each mitigation treatment is described in this section.

2.3.1. Compression Garments

Post-operative compression garments can reduce post-operative bruising, edema, and discomfort (Gladfelter, 2007). Bruising is minimized by compression of small blood vessels and capillaries. Ill-fitting compression garments may cause pain.

2.3.2. Instant Cold Packs

Applying cold (cryotherapy) is commonly used treatment for soft tissue injury (Mayo et al, 2013) and after aesthetic procedures (Brennan, 2014; Verner et al, 2019). Cold induces vasoconstriction and minimizes local cellular damage by restricting hemorrhage (Mayo et al, 2013). It also reduces metabolic demand at the site of injury which aids in healing and recovery.

Mayo et al (2013) compared the effect of bruise reduction treatments of either cold compresses, hydrogen peroxide 3%, an over the counter serum containing vitamin E oil, evening primrose oil, glycerin, and pulse dyle laser (PDL) in 17 patients. There was no significant difference among cold compresses, hydrogen peroxide, and over-the-counter serum in reducing time to bruise resolution.

In a meta-analysis conducted by Lee et al (2017), there was a statistically significant reduction in a cold compress group vs a control group in eyelid ecchymosis after rhinoplasty, at 1 hour and 1 day post-operatively.

Nestor et al (2010) evaluated the use of a cooling device in subjects injected with hyaluronic acid dermal fillers. The use of a cooling system was associated with a mean ecchymosis reduction of 88%, 89%, 80%, and 66% compared to control immediately after injection, at 1 hour, 3 hours, and the day after injection, respectively.

Prolonged application of cold at very low temperatures should be avoided, since this may cause frostbite and nerve injuries (Swenson et al, 1996).

2.3.3. Arnica (OcuMend) Patches

Arnica montana is a perennial of the family Asteraceae. The flowers of its various species contain glycosides, terpinoids, amines, coumarins, and volatile oils (Knackstedt and Gatherwright, 2020). It is purported to have anti-inflammatory and tissue healing actions after trauma bruises or tissue injuries (Ianitti et al, 2016; Widegrow et al, 2020). Various homeopathic oral and topical preparations of different dosages are available. A recent literature review evaluated the efficacy of perioperative arnica in reducing edema, ecchymosis and pain after a variety of aesthetic surgeries including rhinoplasty, blepharoplasty, facial cosmetic surgeries, and laser procedures (Knacksted and Gatherwright, 2020). The data on arnica's effect post-laser treatments was equivocal, however there were differences in technique and application.

Three randomized controlled studies of perioperative oral or topical arnica in rhinoplasty demonstrated decreased ecchymosis (Chaiet and Marcus, 2016; Totonchi and Guyuron, 2007; Simsek et al, 2016). In 2 randomized controlled studies of arnica in upper blepharoplasty, there was no difference in the use of oral (500 mg homeopathic dilution 3 times daily) (Kotlus et al, 2010) or topical arnica (10%) applied twice daily (BID) (van Exsel et al, 2016), compared to placebo.

There were 2 randomized controlled studies that evaluated topical arnica in patients undergoing either 585- or 595-nm laser treatment (Leu et al, 2010; Alonso et al, 2002). In the study

conducted by Leu et al (2010), moderate to severe bruises were induced using a 595-nm variable long-pulsed PDL (spot size 7 mm; fluence 9–11 J; pulse duration 1.5 ms; cooling with 30 ms spray, 20 ms delay with dynamic cooling device). Treatment included either topical arnica 20%, 5% vitamin K, 1% vitamin K and 0.3% retinol, 20% arnica, or white petrolatum applied BID, which was then treated under occlusion BID for 2 weeks. There was less ecchymosis with topical arnica compared to controls and similar results with topical vitamin K. However, results of a study conducted by Alonso et al (2002), found no difference between topical arnica and control. The study evaluated topical arnica (1 × tincture; low homeopathic potency) versus placebo applied BID for either 2 weeks before treatment or 2 weeks after treatment of facial telangiectases. PDL was applied at the settings of 585 nm and a 5 mm spot size was treated with 6.3 J/cm^2 fluence for all subjects except 1, for whom a 3 mm spot size with a 6.3 J/cm^2 fluence was used.

In a double-blind placebo-controlled study conducted by Aleshaki and Polich (2020) 18 bruises were mechanically-induced in a single patient by dropping a 3-pound, 2-foot bar of 20 inches onto the skin. Blinded investigators evaluated the extent of bruising after either OcuMend (arnica and ledum palustre patches) or placebo patches were applied. A statistically significant improvement in bruising was observed in the bruises treated with OcuMend compared to placebo. To standardize the strength of arnica and method of application, OcuMend patches will be used in this study.

Use of homeopathic preparations of arnica are generally safe and well tolerated (Ianitti et al, 2016). AEs associated with topical arnica include redness, swelling, and blistering (Leu et al, 2010).

Laser Treatment

Lasers accelerate bruise reduction, by a process known as selective photothermolysis, defined as selectively heating hemoglobin and its breakdown products to accelerate bruise resolution (Mayo et al, 2013; Morton et al, 2013; Verner et al, 2019). PDL, a vascular laser, will be used as a mitigation treatment in this study to reduce bruising after QWO (CCH-aaes) treatment.

The main target chromophore of PDL (585/595 nm) is oxyhemoglobin (absorption peak: 577 nm), which results in its effectiveness in hastening the resolution of ecchymoses. Among its other uses, PDL has been used to treat vascular lesions and post-operative ecchymoses after facial cosmetic procedures (Mayo et al, 2013; Verner et al, 2019).

Defatta et al (2009), used PDL to treat 20 patients with ecchymosis due to facial cosmetic surgeries (ie, cervicofacial rhytidectomy, facial lipocontouring). On post-operative Day 5, half of the bruise was treated. A 10-mm spot size was used, with pulse duration of 6 ms, fluence of 6 J/cm^2, and cryogen spray for 30 ms with a 20-ms delay for 3 passes. The patients returned 48-72 hours later for PDL of the untreated areas under the same parameters, and had a final follow-up assessment 48 hours after. Photographs of the treated areas were obtained before and after PDL treatment. Ecchymoses captured on the photographs was graded on a scale of 0 to 3 (with a score of 3 indicating severe ecchymosis) by 3 blinded independent observers. PDL treatment resulted in a 63% mean improvement in ecchymosis scores within 48 to 72 hours. The authors indicated that in their experience, maximal efficacy of PDL was observed when it was performed between 5 and 10 days post-operatively.

Karen et al (2010), used PDL to treat 10 patients with ecchymosis due to cosmetic procedures or traumatic injury. Each subject served as his or her own control: subjects with 2 ecchymoses had 1 treated; those with a single lesion had half treated. Photographs were taken before treatment and at 24 hours, 48 hours, and 7 days after treatment. Treated bruises were between 24 and 72 hours old. Subjects received a single treatment with the 595-nm V-Beam PDA (Candela Corp, Wayland, Massachusetts) with the following settings: spot size, 10 mm; fluence, 7.5 J/cm^2; and pulse duration, 6 ms. The Dynamic Cooling Device (Candela Corp) was set at 30 ms with a 20 ms delay. Two (2) blinded assessors graded bruise severity from 0 to 10 (0, no bruise; 10, worst bruising). Forty-eight (48) hours after treatment, the average improvement was 76% and 37% for treated and untreated lesions, respectively. One (1) week after treatment, treated and untreated bruises had improved by 87% and 81%, respectively.

Accelerated resolution of the treated bruise was observed within 24 hours. Twenty-four (24) hours after treatment, the average reduction in the size of the ecchymosis was 62% and 13% for treated and untreated bruises, respectively. Forty-eight (48) hours after treatment, the average improvement was 76% and 37% for treated and untreated lesions, respectively. The authors suggested that the most dramatic response occurred when hemoglobin predominates AEs attributed to PDL treatment include mild discomfort and edema (Defatta et al, 2009), transient crusting (Karen et al, 2010), and redness and bruising when used at higher settings intended to induce bruising (Alonso et al 2002; Leu et al, 2010).

2.3.4. INhance Post-Injection Serum with TriHex Technology®

INhance Post-Injection Serum with TriHex Technology is a commercial product containing the following ingredients: Water/Aqua/Eau, Glycerin, Caprylic/Capric Triglyceride, Propanediol, Polyacrylate-13, Lactoferrin, Phosphatidylserine, Palmitoyl Hexapeptide-12, Palmitoyl Tripeptide-1, Hexapeptide-11, Acetyl Hexapeptide-38, Acetyl Tetrapeptide-2, Sodium Hyaluronate Crosspolymer, Tremella Fuciformis Sporocarp (Silver Ear Mushroom) Extract, Peucedanum Graveolens (Dill) Extract, Hydroxymethoxyphenyl Decanone, Dunaliella Salina Extract, Betaine, Ledum Palustre (Labrador Tea) Extract, Arnica Montana Flower Extract, Phospholipids, Xylitylglucoside, Squalane, Caprylyl Glycol, Anhydroxylitol, Polysorbate 20, Xylitol, Butylene Glycol, Sorbitan Isostearate, Ethylhexylglycerin, Caprylhydroxamic Acid, Ascorbyl Palmitate, Xanthan Gum, Pentylene Glycol, Glucose, Helianthus Annuus (Sunflower) Seed Oil, Tocopherol, Potassium Sorbate, Caprylyl Methicone, Polyisobutene, Lecithin, Sodium Hydroxide, Disodium EDTA, Phenoxyethanol.

The effect of INhance Post-Injection Serum vs a moisturizer was evaluated in a randomized, double-blind study of 16 patients who received an induced bruise via mechanical disruption (ie, venipuncture, blood removal and reinjection) (Widegrow et al, 2020). Of the patients treated with INhance Post-Injection Serum, 81% experienced less bruising after their treatment at Days 2 and 3 compared to placebo. AEs were not reported.

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives and Endpoints

Primary Objective	Primary Endpoint
To assess the effect of mitigation treatments on bruising in the buttocks of subjects with cellulite after the first treatment of QWO (CCH-aaes).	• The proportion of subjects by buttock at each level of bruising on the Investigator Assessment of Bruising Severity Scale, at Day 4, 3 days after QWO (CCH-aaes) injection. This 5-level scale ranges from 0 to 4, with 0 indicating no bruising or almost none, and 4 indicating very severe bruising.
Secondary Objectives	**Secondary Endpoints**
To assess investigator assessment of bruising with mitigation treatments in subjects with cellulite after the first treatment of QWO (CCH-aaes)	• The proportion of subjects for whom the investigator reported an improvement of bruising on the mitigation treated buttock on Days 4 and 7 as measured on the Investigator-Bruising Improvement Scale (I-BIS), a 3-point Likert scale, with a score on the higher end of the range indicating improvement with treatment. • The proportion of subjects by buttock with bruising at each level of the Investigator Assessment of Bruising Severity Scale, by visit. This 5-level scale ranges from 0 to 4, with 0 indicating no bruising or almost none, and 4 indicating very severe bruising.
To assess subject assessment of bruising with mitigation treatments in subjects with cellulite after the first treatment of QWO (CCH-aaes).	• The proportion of subjects treated with QWO (CCH-aaes) reporting an improvement of bruising on the mitigation treated buttock on Days 4 and 7 as measured on the Subject-Bruising Improvement Scale (S-BIS), a 3-point Likert scale, with a score on the higher end of the range indicating improvement of bruising with treatment. • The proportion of subjects by buttock bothered by the appearance of bruising on each of their buttocks on the Patient Bother by Bruising Scale, a 4-point scale, with a score of 1 indicating not bothered at all, and a score of 4, indicating, extremely bothered.
To assess the effect of mitigation treatments on bruising in the buttocks of subjects with cellulite after the first treatment of QWO (CCH-aaes).	• The proportion of subjects by buttock with bruising at each level of the Investigator Assessment of Bruising Severity Scale, by visit. This 5-level scale ranges from 0 to 4, with 0 indicating no bruising or almost none, and 4 indicating very severe bruising.

Secondary Objectives	Secondary Endpoints
To assess the level of aesthetic improvement of cellulite after treatment of QWO (CCH-aaes) with and/or without bruising mitigation treatment.	• The proportion of subjects with an improved (+1 or better) score on the Investigator-Global Aesthetic Improvement Scale (I-GAIS) for either buttock at the Day 71 Visit compared to Baseline. The I-GAIS is a 7-level scale ranging from +3 (very much improved) to -3 (very much worse).
To assess the safety of QWO (CCH-aaes) with mitigation treatment in subjects with cellulite.	• Percentage of subjects reporting each adverse event (AE) and treatment emergent adverse event (TEAEs).
Exploratory Objective	**Exploratory Endpoint**
[redacted]	• [redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 4, multicenter, open-label, multiple dose study to assess the effect of mitigation treatments on injection site bruising and safety in adult women with moderate cellulite in the buttocks treated with QWO (CCH-aaes). Approximately 75 subjects will be screened in order to enroll approximately 48 subjects in 6 cohorts.

At the Screening Visit, subjects who meet all inclusion criteria and have no exclusion criteria according to the investigator's assessment will be assigned to 1 of 6 treatment cohorts. Subjects will be allocated to cohorts using a site specific Mitigation Treatment Assignment Table provided by the sponsor.

Pending site capabilities and available mitigation treatments, each site will administer each mitigation treatment, with approximately 1-3 subjects assigned to each mitigation treatment as shown in Table 1. Mitigation treatments will be administered at or after the initial treatment session of QWO (CCH-aaes).

Table 1: Distribution of Mitigation Treatments

		QWO (CCH-aaes)[a]		**Mitigation Treatment**	
	N	Left Buttock	Right Buttock	Left Buttock	Right Buttock
Cohort 1	8	Up to 0.84 mg	Up to 0.84 mg	None	
Cohort 2	8	Up to 0.84 mg	Up to 0.84 mg	Compression garment	
Cohort 3	8	Up to 0.84 mg	Up to 0.84 mg	None	Instant cold packs
Cohort 4	8	Up to 0.84 mg	Up to 0.84 mg	None	Arnica patches
Cohort 5	8	Up to 0.84 mg	Up to 0.84 mg	None	INhance Post-Injection Serum with TriHex Technology
Cohort 6	8	Up to 0.84 mg	Up to 0.84 mg	None	PDL treatment[b]

[a] For each subject, an identical dose and injection count of QWO (CCH-aaes) should be administered for the first treatment session to each buttock. The number of injections may differ among subjects.
[b]Pulse dye laser (PDL) may be used at the settings selected according to the investigator's discretion.

Eligible subjects will receive up to 0.84 mg of QWO (CCH-aaes) per buttock in both buttocks for a total dose of 1.68 mg per treatment session for 3 treatment sessions (Day 1, Day 21 ±3 days, and Day 43 ±3 days). To reduce variance in the bruising observed on the left and right buttock of a subject after the first treatment session of QWO (CCH-aaes), each buttock should be treated with the same number of QWO (CCH-aaes) injections on Day 1, of up to 12 injections per buttock. The number of injections may differ between treatment sessions; 12 injections per buttock may be administered during the first treatment session followed by fewer injections per buttock during the second and third treatment sessions. The number of injections per buttock per subject may differ among subjects.

Subjects will return to the site approximately on Days 2, 4, 7, and 14 (ie, 1, 3, 6, and 13 days after injection on Day 1) for additional evaluations and digital photography obtained with standardized parameters. After the first mitigation treatment session, on Days 4 and 7, the effect of mitigation treatments on the severity of bruising will be assessed using the I-BIS and the Investigator Assessment of Bruising Severity Scale. The effect of mitigation treatments on the severity of bruising will be assessed by subjects on the S-BIS and the Patient Bother by Bruising

Scale. Safety will be assessed by collecting AEs, and TEAEs and assessing injection site reactions in the buttocks throughout the study. [redacted]

At the investigator's discretion, for the second and third QWO (CCH-aaes) treatment sessions on Days 22 and 43, subjects will be permitted to receive the same mitigation treatment to the right buttock as received during the first QWO (CCH-aaes) treatment session. The severity of bruising will be assessed at each visit. Subject and investigator assessments of satisfaction, aesthetic improvement, and digital photography will also be conducted on Days 22 (± 3 days) and 43 (±3 days). Subjects will return to the site for last study visit on Day 71 for additional investigator assessments of bruising and digital photography.

Subjects will participate in the study for approximately 92 days.

4.2. Scientific Rationale for the Study Design

The most common AE in previous studies of QWO (CCH-aaes) was injection site bruising (QWO Prescribing Information). Ecchymosis that occurs after an injury is generally referred to as a bruise (Verner et al, 2019). Bruising after the first treatment of QWO (CCH-aaes) is the most robust (ie, greater frequency, greater severity, longest duration) as compared to the bruising after the second or third treatments (CSR EN3835-205). Bruising typically resolves within 21 days.

The photographic substudy of Study EN3835-205, depicted bruising over time in photocollages, Investigators that participated in the investigational studies of QWO (CCH-aaes), and/or aesthetic medicine specialists who have viewed these photocollages have expressed interest in evaluating the effects of mitigation treatments to reduce QWO (CCH-aaes)-induced bruising. Mitigation treatments supported by the literature or commonly used to reduce bruising either post-injection or procedures in clinical practice have been selected for evaluation in this study.

To ensure a balanced approach in the assessment of bruising among the sites and investigators, a Mitigation Treatment Assignment Table will be used to assign 1-3 subjects per mitigation treatment per site (pending site capabilities, eligible subjects, and available mitigation equipment).

Subjects with Fitzpatrick skin types of I-III are included in this study. This aligns with the approach taken by Widegrow et al (2020) in another study conducted evaluating mitigation treatments on bruising.

The endpoints evaluating the effect of the mitigation treatments on bruising will be limited to the time period after the first injection of QWO (CCH-aaes) when characterization of bruising of the unmitigated buttock is more robust (greater frequency, more severe, and longest duration) than after the second and third injections of QWO (CCH-aaes). This will limit confounding introduced by the decreased bruising observed over subsequent treatments of QWO (CCH-aaes) when interpreting the effects of the mitigation treatments.

At the investigator's discretion, for the second and third QWO (CCH-aaes) treatment sessions, subjects are permitted to use the same mitigation treatment in the same buttock (as applicable) that received mitigation treatment for the first QWO (CCH-aaes) treatment session.

4.2.1. Changes to the Study Design Due to COVID-19

The COVID-19 public health emergency has disrupted the conduct of clinical research throughout the world. At Endo Pharmaceuticals Inc. (Endo), ensuring the safety of clinical study subjects is our primary concern. In addition, the integrity of data obtained from clinical studies must be ensured.

To ensure subject safety and protect data integrity Endo will allow remote visits for certain study and safety assessments. This is aligned with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 21 September 2020),

Additionally, subjects impacted by the health emergency will be allowed to continue in the study and complete assessments when the investigational sites re-open as follows:

- If a subject had received any dose of QWO (CCH-aaes) in the study prior to an interruption will be allowed to continue in the study.

4.3. Justification for Endpoints

The primary endpoint will be the investigator's assessment of bruising based on observed, in-person assessments during the first treatment session. The subject will not be able to directly view the bruised skin (ie, would have to use reflection in the mirror) and lighting may not be standardized. As such subject viewing of the bruise might be less authentic than direct viewing by the investigator.

The effect of mitigation treatments that are bilaterally administered (eg, compression garments) will be evaluated by the investigator by comparing bruising on each buttock (both of which receive mitigation treatment) vs bruising observed in the control arm (Cohort 1) that is not receiving mitigation treatment. Subjects in this group will not be able to compare their bruising to bruising on buttocks with no mitigation.

The effect of unilaterally applied (right buttock only) topical mitigation treatments (ie, arnica patches, INhance, PDL treatment) will be assessed by comparing the bruising in the mitigation-treated buttock to the contralateral buttock that did not receive mitigation treatment. As such, in unilateral mitigation treatment cohorts, subjects will serve as their own control.

4.4. Justification for Dose

The doses of the mitigation treatments selected are based on the published literature and the experience of the collaborative investigators.

During this study, both buttocks will be treated with QWO (CCH-aaes) at the doses described in the QWO Prescribing Information. Subjects can receive up to 12 injections of QWO (CCH-aaes) to each buttock. For the first treatment session, the number of injections and dose of QWO (CCH-aaes) administered to each buttock should be identical.

4.5. End of Study Definition

A subject is considered to have completed the study if the subject has completed the Day 71 visit. The end of the study is defined as the completion of the final assessment for the last subject enrolled in the study.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Subject Inclusion Criteria

In order to be eligible to participate in the study, on Screening and/or Day 1, subjects must:

1. Voluntarily sign and date an informed consent agreement.
2. Be a female between ≥18 years of age and ≤ 50 years old.
3. Have both buttocks with:
    a. a CR-PCSS score of 3 (moderate) as reported by the Investigator, and
    b. a Hexsel 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).
4. Have a body mass index between ≥18 and ≤30 kg/m^2, and intends to maintain stable body weight throughout the duration of the study (a variation of ≤10% from baseline body weight is permitted).
5. Have a Fitzpatrick skin rating of I-III.
6. Be willing to apply sunscreen before each exposure to the sun while participating in the study (ie, Baseline through end of study).
7. Be judged to be in good health, based upon the investigator's medical judgement and the results of a medical history and physical examination at Screening.
8. Be willing and able to cooperate with the requirements of the study.
9. Have ability to read, complete and understand the patient-reported outcomes rating instruments in English.

5.2. Subject Exclusion Criteria

A subject will be excluded from study participation if the subject:

1. Has any of the following systemic conditions:
    a. Coagulation disorder including but not limited to a Factor II, V, VII, or X deficiency.
    b. Skin pigmentation disorder.
    c. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years.
    d. History of keloidal scarring or abnormal wound healing.
    e. 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 including but not limited to rheumatoid arthritis and/or other rheumatoid disease(s), Vitamin K deficiency, or liver diseases. Any questions about concurrent diseases should be discussed with the Medical Monitor.
    f. Evidence of clinically significant abnormalities on physical examination or vital signs.
2. Has any of the following local conditions in the buttocks:
    a. History of lower extremity thrombosis or post-thrombosis syndrome.
    b. Vascular disorder (eg, varicose veins, telangiectasia, vasculitis) in area to be treated.

c. Inflammation or active infection in the buttocks.
d. Active cutaneous alteration including rash, eczema, or psoriasis.
e. Has a tattoo in the buttocks, visible in clinical photographs.

3. Has skin laxity or linear undulations on either buttock that can be effaced by lifting skin.
4. Requires the following concomitant medications during the study and cannot discontinue these medications within the time specified before QWO (CCH-aaes) treatment.
   a. Antiplatelet medication (clopidogrel [Plavix®] including aspirin at any dose within 14 days of treatment.
   b. Anticoagulants, such as warfarin (Coumadin®); heparin analogues within 14 days of treatment.
   c. Non-steroidal anti-inflammatory drugs (NSAIDS), such as ibuprofen (Motrin®, Advil®) and naproxen (Aleve®) 7 days before the study.
   d. Any medications (eg, corticosteroids, certain antidepressants [eg, citalopram, fluoxetine], nutritional/homeopathic supplements [eg, fish oil, Vitamin E, omega 3, ginko biloba, ginger, St John's Wart, green tea, ginseng, feverfew, saw palmetto, turmeric, bromelain]) or foods (eg, pineapple) that have, or have been reported to have anticoagulant effects within 14 days of treatment.
   e. Antibiotics, such as penicillin and cephalosporin within 48 hours of treatment.
5. Used any of the following for the treatment of cellulite on a buttock within the timelines identified below or intends to use any of the following at any time during the study:
   a. Liposuction in a buttock during the 12-month period before injection of QWO (CCH-aaes).
   b. Injections (eg, mesotherapy, dermal fillers, biostimulatory fillers); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock during the 12-month period before QWO (CCH-aaes) injection.
   c. Any investigational treatment for cellulite on a buttock during the 12-month period before injection of QWO (CCH-aaes).
   d. Endermologie™ or similar treatments in a buttock during the 6-month period before injection of QWO (CCH-aaes).
   e. Massage therapy for cellulite within a buttock during the 3-month period before injection of QWO (CCH-aaes).
   f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate cellulite within a buttock during the 2-week period before QWO (CCH-aaes) injection.
6. Is presently nursing or providing breast milk or intends to do so during the study.
7. Intends to become pregnant during the study.
8. Intends to initiate an intensive sport program regimen, exercise program regimen, or intensive weight reduction program during the study.
9. Has recently tanned or intends to use any tanning spray or tanning booths during the study.

10. Intends to engage in strenuous activity within 48 hours after the first injection of QWO (CCH-aaes).
11. Has received an investigational drug or treatment within 30 days prior to injection of QWO (CCH-aaes).
12. Has a known systemic allergy to collagenase or any other excipient of QWO (CCH-aaes).
13. Has a known systemic allergy or local sensitivity to any of the mitigation treatments or included excipients (ie, arnica patches, INhance Post-injection Serum).
14. Has received any collagenase treatments at any time prior to treatment in this study.
15. Was a subject in a previous cellulite clinical study of CCH (EN3835, QWO [CCH-aaes]).
16. For subjects allocated to PDL treatment

    Subjects will be excluded from PDL treatment if they have any contraindications to PDL as indicated in the manufacturer's documentation, for example but not limited to:

    a. previous exposure to photosensitizing medications, food and/or supplements or other photosensitizing agents within 2 weeks of QWO (CCH-aaes) treatment
    b. exposure to Accutane® (isotretinoin) within 6 months of QWO (CCH-aaes) treatment.

5.3. Lifestyle Considerations

Subjects will be instructed to refrain from strenuous exercise for 48 hours after the first treatment with QWO (CCH-aaes).

Subjects should avoid medications, homeopathic supplements, or foods as advised by the physician prior to QWO (CCH-aaes) treatment.

Subjects should not use any tanning spray or tanning booths during the study.

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in this study but do not subsequently receive an injection of QWO (CCH-aaes). Screening procedures will be conducted on Day -14, prior to receiving QWO (CCH-aaes) injection. If mitigation treatments could not be procured within the 14-day Screening Period, subjects can be rescreened after the Screening Period.

Subjects who do not meet all of the eligibility criteria 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.
- Any AEs (including serious adverse events [SAEs]) experienced by the subject.

6. STUDY TREATMENT

Study treatment comprises QWO (CCH-aaes) and mitigation treatments.

6.1. Selection and Marking of Dimples

To ensure that the contralateral buttock that does not receive mitigation treatment can serve as its own control, and that a similar level of injection site bruising will be induced, subjects should have a similar number of dimples requiring treatment. Subjects can be treated with up to 12 injections of QWO (CCH-aaes) on each buttock. The number of injections of QWO (CCH-aaes) administered to the right and left buttocks should be identical on Day 1. The number of injections may differ between treatment sessions, eg, 12 injections in each buttock in the first treatment session followed by fewer injections per buttock at the second and third treatment sessions as dimples improve.

For treatment, the investigator or qualified designee will select up to 12 dimples within each treatment area (each buttock) that are well-defined, evident when the subject is standing, and suitable for treatment.

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 1 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.

6.2. Treatment Administration

6.2.1. QWO (CCH-Aaes)

QWO will be provided by Endo Pharmaceuticals Inc.

Dosage and Mode of Administration: QWO (CCH-aaes), 0.84 mg, injected subcutaneously per buttock with both buttocks treated for a total dose of 1.68 mg. For each buttock, a dose of up to 0.84 mg of QWO (CCH-aaes) in 3.6 mL will be administered as up to 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection). There will be 3 treatment visits at intervals of approximately 21 days as described in schedule of assessments.

To induce a similar extent and severity of bruising in each buttock, approximately the same number of injections should be administered to the left and to the right buttock. However, the number of injections per buttock may differ among treatments. The number of injections administered to each buttock on Day 1 must be recorded. The volume and dose of injection at each treatment visit will be injected per the QWO Prescribing Information. QWO will be provided in cartons containing 1 QWO 1.84-mg single-dose vial and 1 diluent for QWO 8-mL single-dose vial.

6.2.2. Mitigation Treatments

Mitigation treatments will be provided locally by each investigator/subject.

At the investigator's discretion and with consent of the subject, mitigation treatments provided after the first treatment session of QWO (CCH-aaes), can be administered after the second and third QWO (CCH-aaes) treatment sessions. Mitigation treatments administered after each treatment session with QWO (CCH-aaes) will be recorded as concomitant medications (Section 6.4).

Cohort 1 will serve as a control and no mitigation treatment will be administered.

Compression Garments (Cohort 2)

Subjects will be instructed to wear a commercially available compression garment (ie, SPANX Grade 3) after the injection on Day 1, for 24 hours per day for 7 days after the injection (Day 1 – 8). Garments may be removed for personal hygiene and when the subject is being evaluated at the investigator's office during study visits. Subjects should be informed that ill-fitting compression garments may contribute to pain.

Instant cold packs (Cohort 3)

Instant cold packs should be applied **to the right buttock only** for 5-10 minutes immediately after the injection of QWO (CCH-aaes) while the subject is lying in prone position.

Arnica Gel Patches (OcuMend) (Cohort 4)

Subjects will be instructed to apply OcuMend gel patches (arnica montana 50% and ledum palustre) immediately after the CCH-aaes injection **to the right buttock only** BID on Days 1 and 2 for a total of 4 doses. One or 2 patches per application may be required depending on the extent of the bruising.

INhance Post-Injection Serum with TriHex Technology® (Cohort 5)

INhance Post-injection Serum will be applied by investigators at the site of injections on Day 1 **on the right buttock only** and then by the subject or subject's associate QID for up to 7 days after injection or until resolution of bruising according to the product instructions. The serum is available in a small 10-mL tube with a chilled tip. A small amount of the serum will be applied on the skin and around the injection site and gently rubbed in using the cooling applicator.

Pulse Dye Laser Treatment (Cohort 6)

Investigators will apply laser treatment with PDL to the bruising observed **on the right buttock only** as a single treatment between Days 1 (same day of QWO [CCH-aaes) injection) and Day 7 after QWO (CCH-aaes) treatment.

The investigator can adjust laser settings at his/her discretion. Laser settings will be recorded in detail to allow comparability across sites. Only select sites will be administering laser treatment.

6.2.3. QWO (CCH-Aaes) Preparation/Handling/Storage

Vials of 1.84 mg QWO (CCH-aaes) and its diluent (8 mL) will be supplied in the approved commercial packaging. QWO (CCH-aaes) and the diluent must be kept in a temperature-monitored refrigerator (2°C to 8°C).

Please refer to the QWO Prescribing Information for complete information regarding preparation, handling, and storage.

6.3. Measures to Minimize Bias

This is an open label study, however, the mitigation treatment for each subject will be assigned in a 1:1:1:1:1:1 ratio using a Mitigation Treatment Assignment Table. To ensure a balanced approach in the application of mitigation treatments and the assessment of bruising among the sites and investigators, 1-3 subjects per site will be assigned to each mitigation treatment (pending site capabilities, subjects available, and available mitigation equipment).

6.3.1. Mitigation Treatment Assignment Table

At Screening, the investigator or designee will refer to the Mitigation Treatment Assignment Table to determine which mitigation treatment should be administered.

The investigator must maintain a subject master log linking the subject identification number to the subject's name. The subject identification number will not be reassigned to another subject in this study in the case of study withdrawal. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality. Information that could identify a subject will be masked on material sent to and/or received by the sponsor.

6.4. Study Treatment Compliance

All subjects will receive study treatment (QWO [CCH-aaes] and mitigation treatments) 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 applicable study records for each site. Used drug and diluent vials will be disposed of according to site procedures. Unused/unopened drug and diluent vials 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).

6.5. 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 30 days prior to the Baseline Visit) and concomitant (taken from the Baseline Visit through the Day 71 Visit) medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) received will be recorded. Mitigation treatments administered after each treatment session of QWO (CCH-aaes) will be recorded as concomitant medications.

6.5.1. Prohibited Medications

During the study, the following treatments are prohibited:

- Anticoagulants (ie, warfarin [Coumadin] heparin analogues).
- Antiplatelet medications (eg, clopidogrel [Plavix], aspirin).

If a 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.

6.5.2. Suggested Concomitant Medications and Procedures

During the study, acetaminophen will be permitted to treat pain at the injection site as needed.

Other required concomitant medications may be administered at the investigator's discretion.

6.5.3. COVID-19 Related Protocol Deviations

All study assessments conducted outside of the allowed windows outlined in the schedule of assessments due to a COVID-19 interruption will be documented as a protocol deviation. COVID-19 will be recorded as the reason for these out-of-window assessments.

7. DISCONTINUATION FROM STUDY TREATMENT AND STUDY WITHDRAWAL

7.1. Discontinuation of Study Treatment

Subjects who discontinue study treatment (QWO [CCH-aaes], or mitigation treatment) or are withdrawn from the study for any reason, 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 any of the following:

- The subject becomes pregnant during the study.

Subjects who discontinue from study treatment at any time after the first dose of study treatment (QWO [CCH-aaes] and mitigation treatments) will not be replaced.

7.2. 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 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 tested and 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).
- An AE.
- Death.
- A protocol deviation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, etc).
- Lost to follow-up.
- Other reasons (reason must be specified, for example: the subject moved, pregnancy, investigator decision, sponsor decision to terminate the study, etc).

If a subject withdraws from the study, all early termination (ET) procedures should be conducted as detailed in schedule of assessments. The date a subject withdraws and the reason for withdrawal will be recorded in 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 treatment (QWO [CCH-aaes], mitigation treatments) will not be replaced.

7.3. 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.

Subjects lost to follow-up at any time after the first dose of study treatment (QWO [CCH-aaes]) and mitigation treatment) will not be replaced.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the schedule of assessments (Section 1.3). Adherence to the study design requirements, including those specified in the schedule of assessments, is essential and required for study conduct. Protocol waivers or exemptions are not allowed.

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 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 assessments.

8.1. Screening Assessments

8.1.1. Medical History

Medical history and cellulite history, including all prior procedures to treat cellulite 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 for 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.

8.1.2. Physical Examination

A limited physical examination will include evaluation of height, weight, lungs, heart, abdomen, and extremities will be conducted at the Screening Visit. Weight will also be recorded at the Day 71/ET visit.

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 examination finding meeting the investigator's criteria for clinical significance will be recorded as an AE or SAE as appropriate.

8.1.1. Vital Signs

Temperature, pulse, systolic blood pressure, and diastolic blood pressures will be collected at the Screening Visit and before the first QWO (CCH-aaes) injection and approximately 30 minutes after injection. Pulse and blood pressure will be collected after the subject has been sitting for 5 minutes.

The investigator will review all vital sign values for clinical significance. Any vital sign value meeting the investigator's criteria for clinical significance will be recorded as an AE (or SAE, if appropriate).

8.1.2. 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 on Day 1.

Only subjects with a Fitzpatrick skin rating of I-III at the Screening Visit will be included in the study. This aligns with the approach taken by Widegrow et al (2020) in another study conducted evaluating mitigation treatments.

8.1.3. Hexsel Cellulite Scale Severity

The Hexsel CSS is a photonumeric scale used to assess 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. For this study, only (D) laxity, flaccidity, or sagging skin will be assessed.

To participate in the study, for each buttock, subjects must have a Baseline Hexsel CSS Subsection D must be '0' (absence of flaccidity or sagging skin) or 1 (slightly draped appearance) at the Screening Visit.

8.1.4. Clinician Reported Photonumeric Cellulite Severity Scale

The Clinician Reported Photonumeric Cellulite Severity Scale (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 investigators 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-prior to assessing any subjects.

Subjects must have a baseline CR-PCSS rating of '3' (moderate) on each buttock at the Screening Visit to be included in the study.

8.2. Efficacy Assessments

Efficacy assessments will be evaluated at times specified in the schedule of assessments. 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.

To ensure subject safety and protect data integrity, Endo, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 21 September 2020), will allow remote visits for certain efficacy

assessments. Additionally, subjects impacted by the health emergency will be allowed to continue in the study and complete remaining assessments when the investigational sites re-open.

8.2.1. Digital Photography

At the time points indicated on the schedule of assessments, the investigator or qualified designee will photograph bilateral buttocks in a single photograph while the subjects is standing in a consistent, standard relaxed pose, with relaxed gluteus muscles using the investigator's digital camera. Photographs of bilateral buttocks will be obtained

- Before and after marking dimples and injection sites (prior to injections) on Days 1, 22, and 43.
- During the Days 2, 4, 7, 14, and 71 visits (end of study/ET) (no dimple or injection site markings).

All photographs taken by the investigator or qualified designee during 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.

Digital photographs captured by the investigator will be uploaded to a central repository. Further information is provided in the Study Operations Manual.

Photographs captured by the subject to assess bruising will not be uploaded to a central repository and are not the property of Endo.

8.2.2. Investigator Assessment of Bruising Severity Scale

At the time points indicated on the schedule of assessments, the severity of bruising for each buttock will be documented on the Investigator Assessment of Bruising Severity Scale, a 5-point photonumeric scale with

0 = None or almost no bruising

1 = Mild bruising

2 = Moderate bruising

3 = Severe bruising

4 = Very severe bruising

The severity of bruising will be documented on the bruising page of the eCRF.

8.2.3. Investigator-Bruising Improvement Scale

Before and after the first treatment session with QWO (CCH-aaes), at the time points indicated on the schedule of assessments, Investigators will complete the I-BIS, a 3-point Likert scale with scores on the higher end of the range indicating greater improvement with mitigation treatment.

Investigators will rate the bruising of the mitigation-treated buttock when compared to the untreated (with mitigation treatment) buttock as either:

1 = Worse (more bruising)

2 = Similar

3 = Improved (less bruising)

Note: The I-BIS assessment cannot be completed in subjects that either do not receive mitigation treatment (Cohort 1) or subjects that receive bilateral mitigation treatment (eg, Cohort 2 – compression garments). These subjects do not have only 1 untreated buttock as a comparator.

8.2.4. Investigator-Global Aesthetic Improvement Scale

The investigator will determine the degree of improvement of each buttock by comparing the cellulite from the Day 1 pre-treatment (Baseline) digital image of each buttock to the cellulite seen in a live assessment (Table 2). For each buttock, the investigator will provide the rating from those below that best represents his/her answer.

Table 2: Investigator-Global Aesthetic Improvement Scale

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

8.2.5. [redacted]

[redacted]

8.2.6. Subject-Bruising Improvement Scale

Before and after the first treatment session with QWO (CCH-aaes), at the time points indicated on the schedule of assessments, subjects will complete the S-BIS, a 3-point Likert scale with scores on the higher end of the range indicating greater improvement of bruising with treatment.

Subjects will rate the bruising of the QWO (CCH-aaes) mitigation-treated buttock when compared to the untreated (ie, meaning the buttock that was not treated with mitigation treatment) buttock as either:

1 = Worse (more bruising)

2 = Similar

3 = Improved (less bruising)

Note: The S-BIS assessment cannot be completed in either subjects that do not receive mitigation treatment (Cohort 1) or subjects that receive bilateral mitigation treatment (eg, Cohort 2 – compression garments). These subjects do not have only 1 untreated buttock as a comparator.

8.2.7. Patient Bother by Bruising Scale

At the time points indicated on the schedule of assessments, for each buttock, subjects will indicate their level of bother by bruising, on a 4-point scale as follows:

Thinking about the bruising on your left/right buttock, how bothered are you with the appearance of the bruising on your left/right buttock, as either:

1 = Not at all bothered

2 = A little bothered

3 = Moderately bothered

4 = Extremely bothered

Subjects may use either a mirror, or photographs captured by the subject or another person with the subject's imaging device (ie, cell phone, digital cameras), or images captured by the investigator or designee using the site's digital photography system.

Images captured by the investigator or designee using the site's digital photography system are the property of Endo (Section 8.2.1). Photographs taken by the subject will not be uploaded to the central repository and are not considered source documentation.

8.3. Safety Assessments

All safety assessments will be performed at the time points outlined in the schedule of assessments. Additional (unscheduled) safety assessments may be performed as needed.

To ensure subject safety and protect data integrity, Endo, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 21 September 2020), will allow remote visits for certain safety assessments. Additionally, subjects impacted by the health emergency will be allowed to continue in the study and complete remaining assessments when the investigational sites re-open.

8.4. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.2.

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. Study treatment includes QWO (CCH-aaes) and mitigation treatments. 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.

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All SAEs and AEs will be collected by the investigator from the time of signing the ICF through the Day 71 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.

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 notify the sponsor within 24 hours as described in Section 10.2.4.1.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. 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 10.2.

8.4.2. Method of Detecting Adverse Events and Serious Adverse Events

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 treatment compliance record should also be reviewed to detect potential intentional or unintentional overdoses.

In addition, investigators will document observed and elicited AE.

8.4.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All ongoing AEs must be followed until they have resolved or for 28 days after the subject’s last study treatment, whichever comes first. All SAEs will be followed until they have resolved or the condition stabilizes, the event is otherwise explained, or until follow-up is no longer possible. Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of an SAE due to QWO (CCH-aaes) or mitigation treatment 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, 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 a SUSAR IND 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 their study documentation, and will notify the IRB, if appropriate according to local requirements.

8.4.5. Pregnancy

All pregnancies in subjects identified during or after this study, where the estimated date of conception is determined to have occurred during the study or within 28 days of the last study treatment in subjects who terminate from the study early, must be reported, followed to conclusion, and the outcome reported, even if the subject is discontinued from the study. The investigator should report (as outlined above) all pregnancies within 24 hours using the Pregnancy Form. Monitoring of the pregnancy should continue until conclusion and follow-up information detailing the progress and outcome must be submitted on 1 or more Pregnancy Form(s). A Two-Month Follow-up Pregnancy Form detailing the status of the infant should also 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 10.2). 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 be withdrawn from the study. Should a subject discontinue treatment due to pregnancy, alternative treatment (if available) should be arranged according to standard of care, as determined by the investigator. Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary even if a subject discontinues treatment because of pregnancy.

8.4.6. Adverse Events/Serious Adverse Events 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 the Endo Pharmacovigilance and Risk Management Department 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

treatment will be processed within the same SAE reporting timelines as described in Section 10.2. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

8.5. 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 treatment eCRF.

An overdose is not an AE per se, however all AEs associated with an overdose should both be entered on the AE eCRF and reported using the procedures detailed in Section 10.2, 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 AE eCRF.

8.5.1. Treatment Abuse/Misuse

AEs associated with misuse or abuse will be appropriately reported as AEs or SAEs, and monitored per Section 10.2.

9. STATISTICAL CONSIDERATIONS AND METHODS

9.1. Sample Size Determination

The proposed sample size is approximately 48 subjects. The sample size is based on evaluation of mitigation treatment in 6 cohorts of approximately 8 subjects each. Five (5) treatment cohorts will receive mitigation treatments and 1 treatment cohort will not receiving mitigation treatment.

9.2. Populations for Analysis

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

Safety Population - The Safety Population is defined as all allocated subjects who have received at least 1 injection of QWO (CCH-aaes) with or without mitigation treatment. All demographic and baseline characteristic summaries and safety analyses will be based on this population. The safety parameters will be summarized using this population.

Evaluable Population - The Evaluable Population is defined as all allocated subjects who have received at least 1 injection of QWO (CCH-aaes) and have at least 1 bruising assessment after the first dose of QWO (CCH-aaes). Analyses of the primary and secondary endpoints will be summarized using this population.

9.3. 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 (SAP) will be developed and finalized prior to database lock.

9.3.1. Efficacy Analysis

The primary efficacy and secondary endpoints will be summarized as count and percentage by mitigation group.

In addition, the severity of bruising will be displayed by visit and mitigation group using count and percent. [redacted]

9.3.2. Safety Analyses

All subjects who receive at least 1 dose of QWO [CCH-aaes] with or without mitigation treatment will be included in the safety analyses. Subjects will be included in the safety analyses based on the actual mitigation received.

9.3.2.1. Adverse Events

AEs will be coded using MedDRA by preferred term within each system organ class. The number of AEs and the number of subjects reporting AEs will be listed and summarized descriptively by system organ class, preferred term, severity, and causality for each mitigation group. Only TEAEs will be included in all summaries. SAEs including death, will be listed.

9.4. Interim Analysis

An interim analysis will be conducted at a time point to be determined after at least 25% of subjects of the count of total planned subjects have received treatment and completed Day 22 Visit assessments.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This clinical study is designed to comply with the International Council for Harmonisation (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 good clinical practice 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 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 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 informed consent form (ICF), advertisements, materials being provided to subjects, and amendments (if any) will be approved to IRBs 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 with a copy of the current QWO Prescribing Information. During the course of the study, the investigator will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB of SAEs or other significant safety findings, per the policy of the IRB. At the conclusion of the study, the investigator will submit a final report or close out report to the IRB 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 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 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.

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

10.1.2. Financial Disclosure

Investigators and subinvestigators 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.

10.1.3. Informed Consent Process

The ICF must be approved by the sponsor and the IRB before any subject provides consent. The investigator will provide the sponsor with a copy of the IRB-approved ICF and a copy of the IRB'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.

If appropriate, the ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

At Baseline (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 Good Clinical Practice 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.

10.1.4. 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 members, and by inspectors from regulatory authorities.

10.1.5. 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 regulations.

10.1.6. 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.

10.1.7. Source Documents

All subject information will be documented on source documentation (ie, paper or eCRF). Further information regarding documentation will be provided in the Study Operations Manual.

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.

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 Good Clinical Practice as essential.

10.1.8. 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.

10.1.9. Publication 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.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

10.2.1. Definitions

An AE is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, electrocardiogram, X-ray, etc), or worsening of a pre-existing condition associated temporally with the use of the study treatment (QWO [CCH-aaes]) or mitigation treatments) whether or not considered related to the study treatment. 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 treatment 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).

An 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 treatment 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 any cancer, 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.

10.2.2. Relationship to Study Treatment

In this study, study treatment will comprise QWO (CCH-aaes), and mitigation treatments.

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

- **Not related** indicates that the AE is definitely not related to the study treatment.
- **Unlikely related** indicates that there are other, more likely causes and study treatment is not suspected as a cause.
- **Possibly related** indicates that a direct cause and effect relationship between study treatment 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 treatment.

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.

10.2.3. 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.

10.2.4. Reporting Adverse Events and Serious Adverse Events

10.2.4.1. Reporting Adverse Events

Throughout the study, AEs will be documented in existing medical records at the site either in paper or electronic format 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 treatment; relationship will be classified as not related, unlikely related, possibly related, or probably related.

10.2.4.2. 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. 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 Endo Serious Adverse Event (SAE)/Reportable Event Forms should be sent to [redacted] or faxed to [redacted].

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

10.2.4.3. 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 treatment. All events determined to be nonserious should be reported on the eCRF.

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

See Section 5, and Section 8.4.5.

10.4. Abbreviations

Abbreviation	Explanation
AE	Adverse event
BID	Twice daily
CCH	Collagenase clostridium histolyticum
CSS	Cellulite Severity Scale
CR-PCSS	Clinician Reported Photonumeric Cellulite Severity Scale
eCRF	Electronic case report form
ET	Early termination
HIPAA	Health Insurance Portability and Accountability Act
I-BIS	Investigator-Bruising Improvement Scale
I-GAIS	Investigator-Global Aesthetic Improvement Scale
ICF	Informed consent form
	International Council on Harmonisation
ICH	Institutional Review Board
PDL	Pulse dye laser
QID	Four times daily

Abbreviation	Explanation
SAE	Serious adverse event
S-BIS	Subject-Bruising Improvement Scale
SUSAR	Suspected, unexpected serious adverse reactions
TEAE	Treatment emergent adverse event

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

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