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

EN3835-226 CEL

APHRODITE-1: A PHASE 2, OPEN-LABEL, SELF-CONTROLLED STUDY OF DIFFERENT INTERVENTIONS TO REDUCE BRUISING FOLLOWING CCH-AAES TREATMENT FOR CELLULITE OF THE BUTTOCKS 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

Date:

Original Protocol**:** 31 March 2022

Amendment 01: 13 May 2022

Amendment 02: 12 August 2022

The sponsor of the IND is Endo Global Aesthetics Limited (EGAL); however, Endo Pharmaceuticals Inc. (Endo) is authorized to act and to communicate on behalf of EGAL. The sponsor is responsible for the conduct of the study, analysis of the data, and preparation of the clinical study report.

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SUMMARY OF CHANGES

Amendment 02

The primary reason for Amendment 02 was to add Cohort 7 as a new investigation. The major changes to the protocol are outlined below. Revisions in style, minor corrections (such as spelling errors, etc), and other minor changes that do not impact content may also have been made.

Section	Reason for Change/ Original Text	Revision
Global	Identified additional methods for preventing bruising	Change the total number of cohorts in the study from 6 to 7.
Section 2.1, Synopsis, Overall Design Section 5.1, Overall Design Section 10.1, Sample Size Determination	Added an additional cohort (Cohort 7).	Change sample size from 180 to 210 participants with 168 completers.
Section 2.1, Synopsis, Overall Design Section 2.2 and Section 2.3, Study Schemas for Cohorts 1-5 and Cohort 6 Section 2.6 and Section 2.7, Schedules of Assessment for Cohorts 1-5 and Cohort 6 Section 5.1, Overall Design	Added an additional cohort (Cohort 7).	Modify duration of the Treatment Period from 56 to 90 days for Cohorts 1-6 and Cohorts 7a and 7b.
Section 2.1, Synopsis, Overall Design Section 5.1, Overall Design	Added an additional cohort (Cohort 7).	Included method of administration of QWO and tranexamic acid in Cohort 7.
Section 2.4 and Section 2.5, Study Schemas for Cohort 7a and Cohort 7b	Added an additional cohort (Cohort 7).	Added study schematic diagrams for Cohorts 7a and 7b.
Section 2.8 and Section 2.9, Schedules of Assessments for Cohort 7a and Cohort 7b	Added an additional cohort (Cohort 7).	Added schedule of assessments to account for the addition of Cohort 7a and 7b.
Section 3.3.6, Tranexamic Acid	Added an additional cohort (Cohort 7).	Added the risks and benefits of tranexamic acid to account for the addition of Cohort 7.

Section	Reason for Change/ Original Text	Revision
Section 4.1, Objective and Endpoints and Study Synopsis	Added an additional cohort (Cohort 7).	Added a new primary endpoint for Cohorts 7a and 7b and specified that the previous endpoint was for Cohorts 1-6. Added additional secondary and exploratory endpoints for Cohort 7. Modified secondary endpoint for the I-GAIS assessments to add the visit at Day 64 in Cohort 7.
Section 5.2, Scientific Rationale for Study Design	Added an additional cohort (Cohort 7).	Added rationale for additional visits and asynchronous administration of QWO (CCH-aaes) and tranexamic acid in Cohort 7.
Section 5.3, Justification of Endpoints	Added an additional cohort (Cohort 7).	Added rationale for modification of primary endpoint in Cohort 7, during which the first treatment for the investigational cohort will be staggered.
Section 5.4, Justification for Dose	Added an additional cohort (Cohort 7).	Added justification for the dose of tranexamic acid.
Section 6.1, Participant Inclusion Criteria	Account for risk of thrombosis with tranexamic acid	Modified inclusion criterion #6 to exclude oral contraceptive use as an acceptable method of contraception, specific to Cohort 7.
Section 6.2, Participant Exclusion Criteria	Account for the exclusion criteria to tranexamic acid	For all cohorts, added additional exclusion criteria to exclude participants taking tranexamic acid before treatment. Added additional exclusion criteria for Cohort 7.
Section 6.3, Lifestyle Considerations	Account for risk of thrombosis with tranexamic acid	For Cohort 7, added that participants should not smoke during the study.
Section 7.1, Selection and Marking of Dimples	Added an additional cohort (Cohort 7).	Added the timepoints for selection and marking of dimples for Cohort 7.
Section 7.2.1, Table 2, Study Intervention (QWO -CCH-aaes) by Buttock	Added an additional cohort (Cohort 7).	Added QWO (CCH-aaes) for Cohort 7 and clarified in title for QWO (CCH-aaes).

Section	Reason for Change/ Original Text	Revision
Section 7.2.1, Table 3, Study Intervention (Tranexamic Acid) in Cohort 7	Added an additional cohort (Cohort 7).	Added tranexamic acid for Cohort 7.
Section 7.2.9, Cohort 6, Control Side Only, QWO (CCH-aaes) – Half of the Labeled Dose (0.42 mg/control side) Using the Labeled Concentration (0.23 mg/mL) at Approximately 42 Days between Visits		Added details of treatment administration for the control side. Previously only the investigational side was delineated.
Section 7.2.10, Labeled dose and concentration of QWO (CCH-aaes) and Tranexamic Acid	Added an additional cohort (Cohort 7).	Added details of study intervention for Cohort 7.
Section 7.2.12, Preparation/ Handling/Storage/Accountability	Added an additional cohort (Cohort 7).	Added details of study intervention for Cohort 7.
Section 7.3, Measures to Minimize Bias, Global	Added an additional cohort (Cohort 7).	Updated the number of cohorts for randomization.
Section 7.4, Study Intervention Compliance	Added an additional cohort (Cohort 7).	Added text to account for compliance checks with tranexamic acid use.
Section 7.5.1, Prohibited Medications/Procedures	Added an additional cohort (Cohort 7).	For all participants, added prohibited medication of tranexamic acid 30 days before treatment. Added prohibited medications (eg, combination hormonal contraceptives) for Cohort 7.
Section 9.2.1, Digital Photography	Added an additional cohort (Cohort 7).	Add additional timepoint of Day 64 for Cohort 7.
Section 9.3.1, Vital Signs	Added an additional cohort (Cohort 7).	Add additional timepoint of Day 64 for Cohort 7.
Section 11.1.1, Regulatory Considerations	Added an additional cohort (Cohort 7).	Added reference to providing the Tranexamic Acid Prescribing Information to the local IRBs.
Section 11.5, Appendix 5: Amendment 01	Formatting change	Moved summary of changes for Amendment 01 to the end of the protocol.

2. PROTOCOL SUMMARY

2.1. 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: APHRODITE-1: A PHase 2, Open Label, Self-ContROlled Study of DIfferent Interventions to Reduce Bruising Following CCH-Aaes TrEatment for Cellulite of the Buttocks in Adult Females

Lead Principal Investigator: Not applicable

Phase of development: 2

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the effects of interventions on bruising of the buttocks of participants with cellulite after the first treatment with QWO (CCH-aaes).	• Cohorts 1 to 6: The proportion of participants whose left buttock (investigational side) demonstrates at least 1-level lower score versus the right buttock (control side) on the Investigator Assessment of Bruising Severity Scale (IABSS), at Visit 3, three to 5 days after initial QWO (CCH-aaes) injection. The IABSS is a 5-point scale ranging from 0-4, with 0 indicating no bruising or almost none, and 4 indicating very severe bruising. • Cohort 7a: The proportion of participants whose left buttock (investigational side), at Visit 3, demonstrates at least 1-level lower score versus the right buttock (control side), at Visit 8 on the Investigator Assessment of Bruising Severity Scale (IABSS). These visits are three to 5 days after initial QWO (CCH-aaes) injection for each respective buttock. • Cohort 7b: The proportion of participants whose left buttock (investigational side), at Visit 8, demonstrates at least 1-level lower score versus the right buttock (control side), at Visit 3, on the Investigator Assessment of Bruising Severity Scale (IABSS). These visits are three to 5 days after initial QWO (CCH-aaes) injection for each respective buttock.
Secondary	
• To assess the effects of interventions on bruising of the buttocks of participants with cellulite after each treatment with QWO (CCH-aaes).	• The proportion of participants whose left buttock (investigational side) demonstrates at least 1 level lower score versus the right buttock (control side) on the IABSS, by visit. The IABSS is a 5-point scale ranging from 0-4, with 0 indicating no

Name of Sponsor/Company: Endo Pharmaceuticals Inc.	
Name of Marketed Product: QWO (CCH-aaes)	
Name of Active Ingredient: Collagenase clostridium histolyticum (CCH)	
	bruising or almost none, and 4 indicating very severe bruising. • Cohorts 7a and 7b: The proportion of participants within each cohort (i.e. 7a and 7b) whose left buttock (investigational side) demonstrates at least 1-level lower score versus the right buttock (control side), on the IABSS, by corresponding treatment visit by buttock (first dose of QWO [CCH-aaes] on the investigational buttock with tranexamic acid vs the first dose of QWO [CCH-aaes] without tranexamic acid on the control side; second dose of QWO [CCH-aaes] on the investigational buttock vs second dose of QWO [CCH-aaes] on the control side; third dose of QWO [CCH-aaes] on the investigational side vs third dose of QWO [CCH-aaes] on the control side); and at each follow up visit thereafter.
• To assess the level of aesthetic improvement of cellulite after treatment with QWO (CCH-aaes).	• The proportion of participants with an improved (+1 or better) score on the Investigator-Global Aesthetic Improvement Scale (I-GAIS) by treatment area at Days 22, 43, 64, 90, 135 and 180 Visits. The I-GAIS is a 7-point scale ranging from +3 (very much improved) to -3 (very much worse).
• To assess the safety of QWO (CCH-aaes) for each study intervention in participants with cellulite.	• Proportion of participants reporting each treatment-emergent adverse events (TEAEs) throughout the study.
• To assess the safety of QWO (CCH-aaes) in participants for each study intervention in participants with cellulite.	• Proportion of participants reporting TEAEs of injection site reactions in the left buttock (investigational side) vs the right buttock (control side).
Exploratory	
• [redacted]	• [redacted] • [redacted]

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Marketed Product: QWO (CCH-aaes)

Name of Active Ingredient: Collagenase clostridium histolyticum (CCH)

Overall Design: This is a Phase 2 open-label, self-controlled study to assess different interventions designed to reduce bruising following QWO (CCH-aaes) treatment of moderate to severe cellulite of the buttocks in adult females. The study is expected to enroll approximately 210 participants, with up to 30 participants allocated to each of 7 cohorts.

The study will comprise a Screening Period, a Treatment Period, and a Follow-up Period. After the Screening Period on Day 1, participants who meet study criteria will be assigned to 1 of 7 study intervention cohorts using an interactive response technology (IRT) system (table below). Participants will receive QWO (CCH-aaes) in different doses, concentrations, diluent additives, depths of injection, and methods of injection in a split buttock arrangement, with the right buttock serving as the control, and the left buttock (investigational side) receiving a study intervention.

Study Intervention Cohorts

Cohort	N	Study Interventions Tested	Left Buttock – Investigational Side	Right Buttock – Control Side
Cohort 1	30	Labeled dose (0.84 mg/control side) of QWO (CCH-aaes) vs half the labeled dose (0.42 mg/investigational side)	Labeled injection technique (3 aliquots) using half the labeled dose (0.42 mg/investigational side) but maintaining the labeled concentration (0.23 mg/mL).	Labeled injection technique (3 aliquots) using the labeled dose (0.84 mg/control side) and concentration (0.23 mg/mL).
Cohort 2	30	Labeled dose (0.84 mg/buttock) and concentration of QWO (CCH-aaes) vs an ~5-fold dilution of the labeled concentration	Labeled injection technique (3 aliquots) using the labeled dose (0.84 mg/investigational side) but using a ~ 5-fold dilution (0.05 mg/mL) of the labeled concentration (0.23 mg/mL)	Labeled injection technique (3 aliquots) using the labeled dose (0.84 mg/control side) and concentration (0.23 mg/mL).
Cohort 3	30	Labeled dose (0.84 mg/buttock) and concentration of QWO (CCH-aaes) at an injection depth of ½ inch vs ¼ inch	Labeled injection technique (3 aliquots) using the labeled dose (0.84 mg/investigational side) and concentration (0.23 mg/mL) but with an injection depth of ¼ inch.	Labeled injection technique (3 aliquots) using the labeled dose (0.84 mg/area) and concentration (0.23 mg/mL). Labeled injection at labeled depth of ½ inch.
Cohort 4	30	Labeled dose (0.84 mg/buttock) and concentration of QWO (CCH-aaes) vs. an ~2.5-fold dilution of the labeled concentration AND a single aliquot at ¼-inch depth of injection (both buttocks)	Labeled dose (0.84 mg/ investigational side) using an ~2.5-fold dilution (0.09 mg/mL) of the labeled concentration but administering only a single aliquot at ¼-inch depth per injection administered as up to 30 injections.	Labeled dose (0.84 mg/control side) and concentration (0.23 mg/mL) but administering only a single aliquot at ¼-inch depth per injection administered as up to 12 injections.
Cohort 5	30	Labeled dose (0.84 mg/control side) and concentration of QWO (CCH-aaes) vs half the labeled dose (0.42 mg/investigational side) of QWO (CCH-aaes) with lidocaine 2% and epinephrine 1:200,000 utilized as diluent additive.	Labeled injection technique (3 aliquots) using half the labeled dose (0.42 mg/investigational side) with lidocaine 2% and epinephrine 1:200,000 as diluent additive.	Labeled injection technique (3 aliquots) using the labeled dose (0.84 mg/control side) and concentration (0.23 mg/mL).

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Marketed Product: QWO (CCH-aaes)

Name of Active Ingredient: Collagenase clostridium histolyticum (CCH)

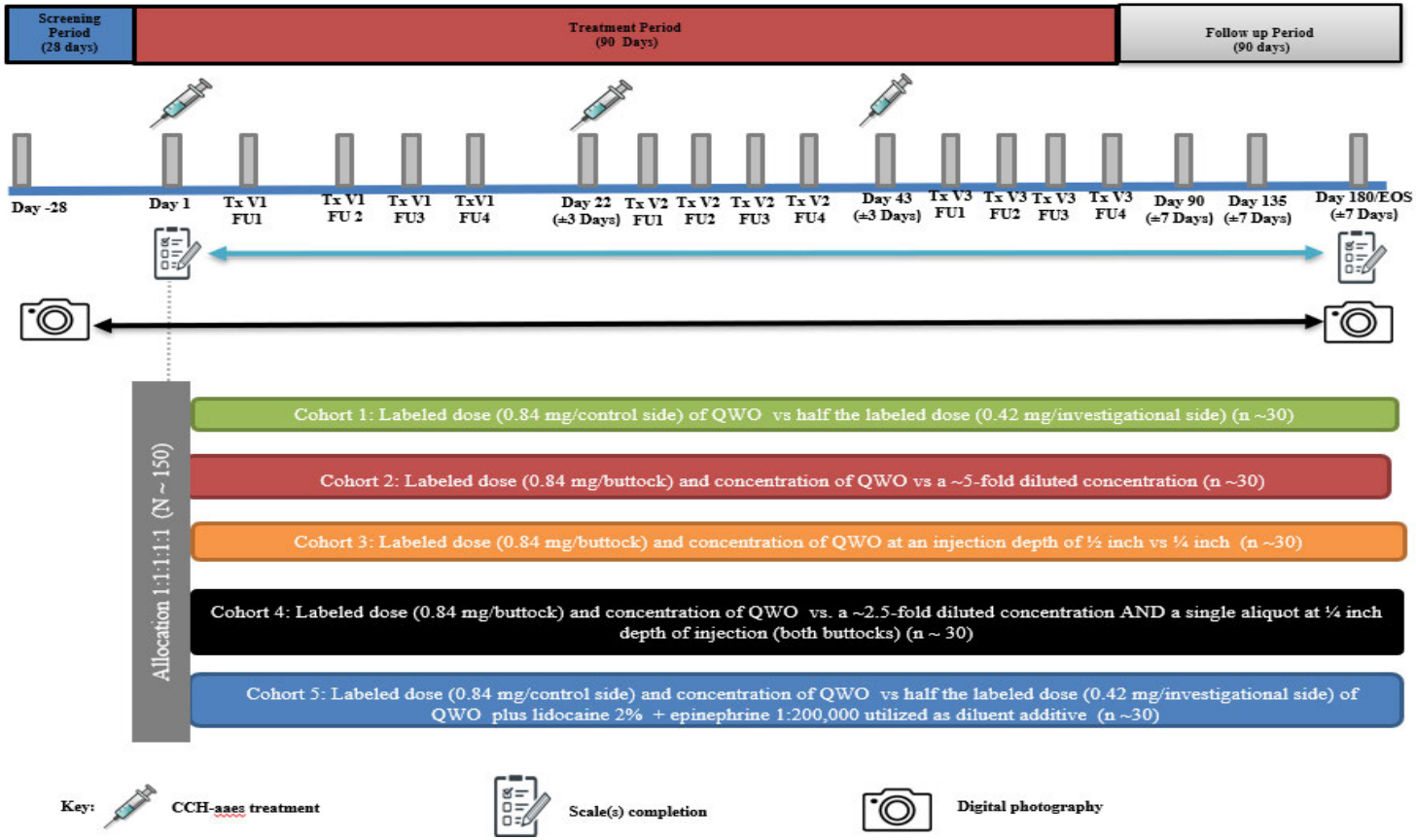
Cohort 6	30	Half of the labeled dose (0.42 mg/control side) while maintaining the labeled concentration (0.23 mg/mL) of QWO (CCH-aaes) vs one-quarter of the labeled dose (0.21 mg/investigational side) at -one-half the labeled concentration (0.12 mg/mL) with both the control and investigational sides receiving only 2 treatment sessions administered 6 weeks apart.	Labeled injection technique (3 aliquots) using one-quarter of the labeled dose (0.21 mg/investigational side) at one-half the labeled concentration (0.12 mg/mL). Treatment sessions will be administered 6 weeks apart.	Labeled injection technique (3 aliquots) using one-half the labeled dose (0.42 mg/control side) but maintaining the labeled concentration (0.23 mg/mL). Treatment sessions will be administered 6 weeks apart.
Cohort 7a	15	Labeled dose (0.84 mg/side) and concentration (0.23 mg/mL) of QWO (CCH-aaes) with oral tranexamic acid.	Labeled dose (0.84 mg/side), injection technique, and concentration (0.23 mg/mL) of QWO (CCH-aaes) to both the investigational and control buttocks. Participants will be receiving tranexamic acid 1300 mg orally three times a day (TID) for 5 days (on Day -1, prior to the day of the first injection on Day 1 and for the 3 days after the first injection of QWO (CCH-aaes) to the investigational side on Days 2-4, during the first treatment session.	
Cohort 7b	15	Labeled dose (0.84 mg/side) and concentration (0.23 mg/mL) of QWO (CCH-aaes) with oral tranexamic acid.	Labeled dose (0.84 mg/side), injection technique, and concentration (0.23 mg/mL) of QWO (CCH-aaes) to both the investigational and control buttocks. Participants will be receiving tranexamic acid 1300 mg orally TID for 5 days (prior to the day of the first injection on Day 21, the day of the first injection, Day 22, and for the 3 days following the first injection on Days 23-25) during the second treatment session. Investigational side will not receive QWO (CCH-aaes) during the first treatment session.	

All participants will receive QWO (CCH-aaes) throughout the study to both the investigational and the control sides. Enrolled participants assigned to Cohorts 1 and 5 will receive a maximum dose of up to 0.84 mg of QWO (CCH-aaes) on the control side and a maximum dose of up to 0.42 mg of QWO (CCH-aaes) to the investigational side per treatment session (Days 1, 22, and 43) for a maximum total dose of 3.78 mg. Participants assigned to Cohorts 2, 3, and 4 will receive a maximum dose of up to 0.84 mg of QWO (CCH-aaes) per treatment area (to the control and investigational sides) per treatment session (total maximum dose of 1.68 mg per treatment session × 3 treatment sessions [Days 1, 22, and 43] for a maximum total dose of 5.04 mg). Participants in Cohort 6 will receive a maximum dose of up to 0.42 mg of QWO (CCH-aaes) on the control side and a maximum dose of up to 0.21 mg of QWO (CCH-aaes) to the investigational side per treatment session×2 treatment sessions (Days 1 and 43) for a maximum total dose of 1.26 mg. Participants in Cohorts 1-6 have their final, scheduled treatment visit on Day 43.

All participants in Cohort 7 will receive a maximum dose of up to 0.84 mg of QWO (CCH-aaes) on the control side and a maximum dose of up to 0.84 mg of QWO (CCH-aaes) to the investigational side per treatment session×3 treatment sessions for a maximum total dose of 5.04 mg. Participants in Cohort 7a will have the investigational side treated on Days 1, 22, and 43 with the control side treated on Days 22, 43 and 64. Treatment will be staggered for participants in Cohort 7b vs Cohort 7a; the investigational side treated on Days 22, 43, and 64 and the control side treated on Days 1, 22, and 43. Tranexamic acid will be provided by the sponsor and self-administered by all participants enrolled in Cohort 7. Participants in Cohort 7a will take tranexamic acid 1300 mg orally TID for 5 days (prior to the day of the

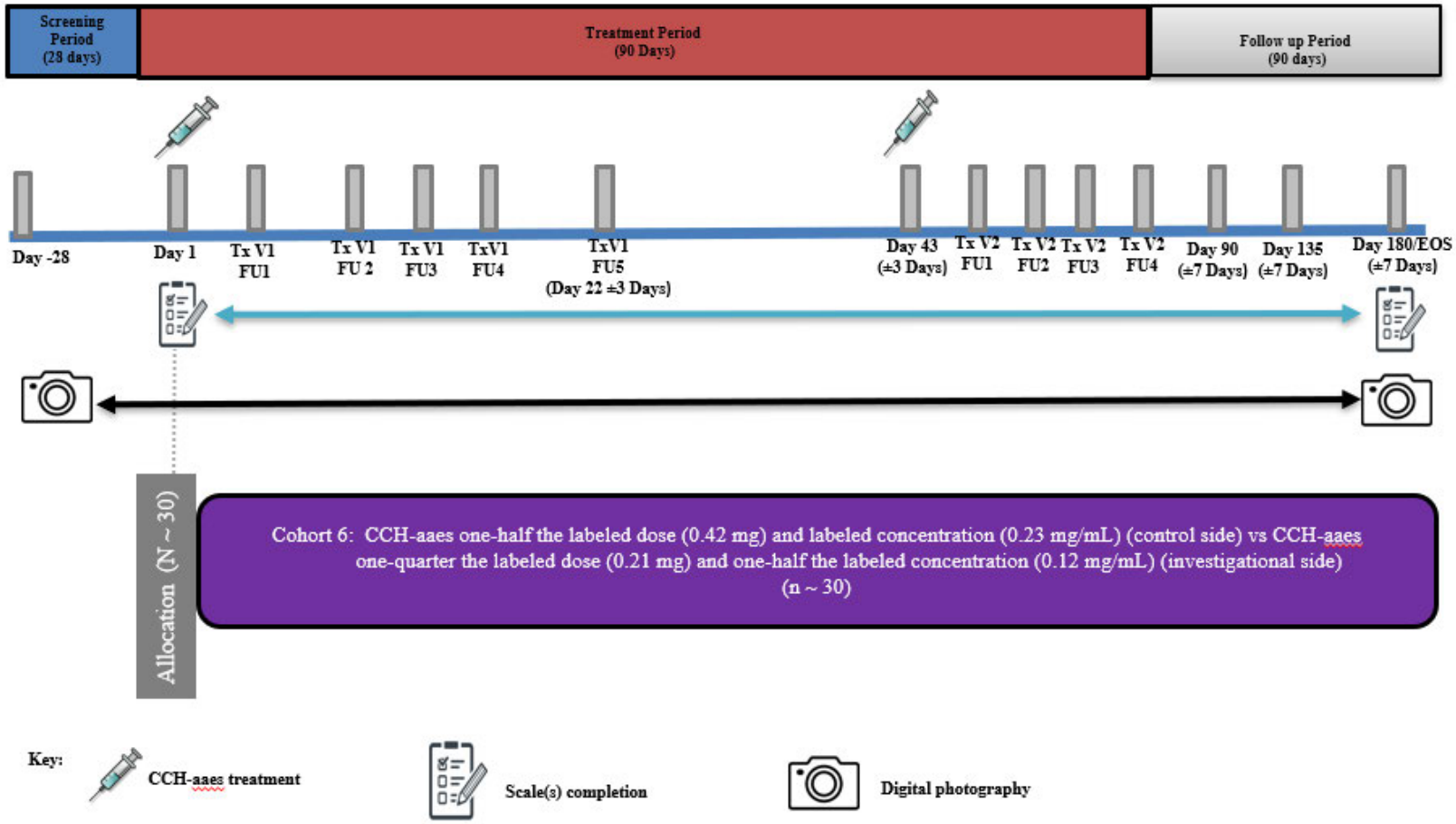
Name of Sponsor/Company: Endo Pharmaceuticals Inc.
Name of Marketed Product: QWO (CCH-aaes)
Name of Active Ingredient: Collagenase clostridium histolyticum (CCH)
first injection of QWO (CCH-aaes) of the investigational buttock (Day -1) , the day of the first injection (Day 1) and for the 3 days following the first injection (Days 2 to 4). Participants in Cohort 7b will take tranexamic acid orally TID for 5 days (prior to the day of the second injection on Day 21, the day of the second injection (Day 22) and for the 3 days following the second injection (Day 23 to Day 25). All participants in Cohort 7, will have an additional treatment visit on Day 64. Bruising will be observed throughout the study. In an effort to standardize the risk and scope of bruising, the investigational and control sides in Cohorts 1 and 5 should be treated with the same concentration and number of injections and same number of aliquots per injection, but at different doses per injection or addition of diluent additive. In Cohort 2, the investigational and control sides will be treated with the same dose and number of injections, but the concentration will vary. In Cohort 3, the investigational and control sides will be treated with the same dose, aliquots per injection, and number of injections but at different injection depths. In Cohort 4, the dose will remain consistent between buttocks, but the number of injections and concentration will vary between the investigational and control sides. In Cohort 6, the investigational and control sides will be treated with the same number of injections, the same number of aliquots per injection, and an extended treatment interval, but at different doses and concentrations. In Cohort 7, the investigational and control sides should be treated with the labeled dose, injection technique and concentration of QWO (CCH-aaes) during each treatment visit, but oral tranexamic acid will be given before and after the first treatment with QWO (CCH-aaes) for the investigational buttock. Participants will return to the site for 4 follow-up visits (1 to 2 days, 3 to 5 days, 6 to 9 days, and 10 to 14 days) after each treatment of QWO (CCH-aaes), for additional evaluations and digital photography to monitor the severity of bruising. Digital photographs will be obtained using a standardized method at each visit throughout the study. The effect of the different QWO (CCH-aaes) doses, strengths (concentrations), diluent additives, depths of injection, and methods of injection on the severity of bruising will be assessed by the Investigator using the IABSS. The investigators will be evaluating the left (investigational) and right (control) buttocks separately with the IABSS. To assess the effect of QWO (CCH-aaes) on the severity of cellulite, the investigator will complete the I-GAIS. Each buttock will be evaluated separately. After completing the Treatment Period, participants will return for 3 follow-up visits at Days 90, 135, and Day 180 (EOS Visit). At the EOS visit, the investigator will complete the I-GAIS, and safety assessments will be evaluated. The total duration of study participation, including the Screening (28 days), Treatment (90 days), and Follow-up Periods (90 days), is approximately 208 days.
Disclosure Statement: This is an interventional open-label, Phase 2 study to evaluate the effect of different doses, strengths (concentrations), diluent additives, depths of injection, and methods of injection on the severity of bruising potentially induced by QWO (CCH-aaes).
Number of Participants (planned): Adult females will be screened to enroll approximately 210 participants into 7 treatment cohorts of up to 30 participants each, such that up to 168 participants complete the study.
Treatment Groups and Duration: It is intended to enroll 7 treatment cohorts of up to 30 participants each. See the Study Intervention Cohorts table above for further details regarding the treatment cohorts. Duration: The total duration of study participation, including the Screening (28 days), Treatment (90 days), and Follow-up Periods (90 days), is approximately 208 days.
Data Monitoring Committee: No data monitoring committee will be used for this study.

2.2. Study Schema for Cohorts 1 to 5



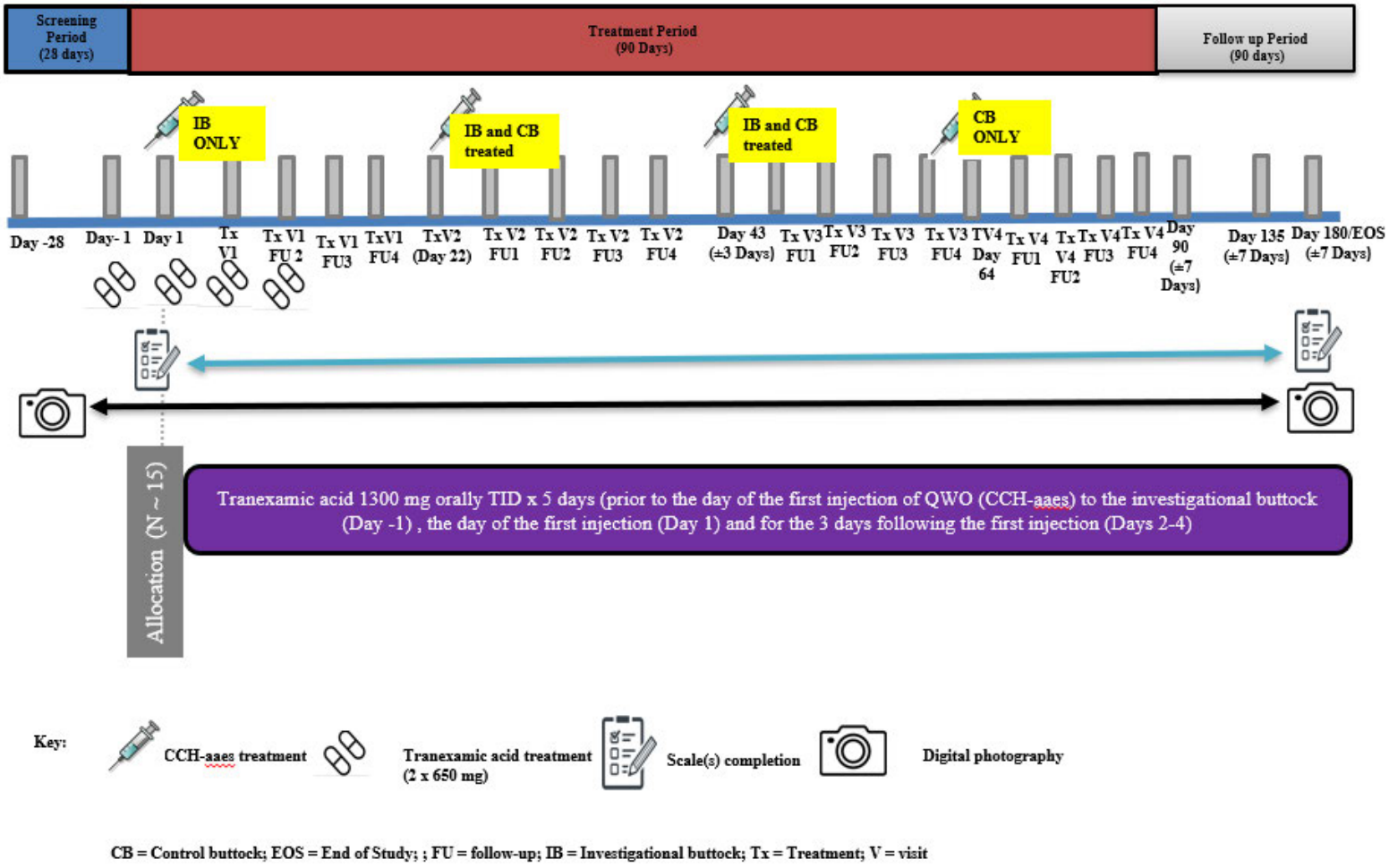
EOS = End of Study; FU = follow-up; Tx = Treatment; V = visit

2.3. Study Schema for Cohort 6



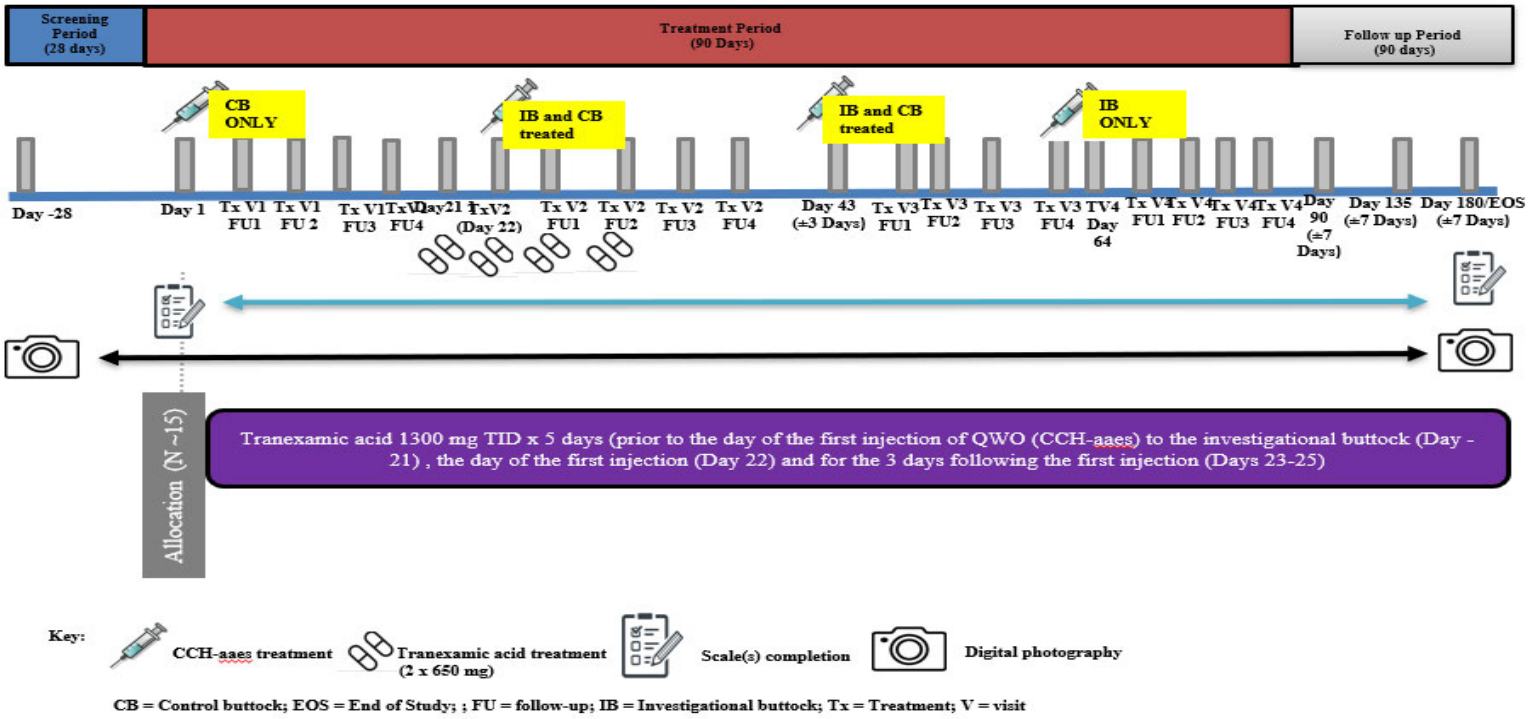
EOS = End of Study; FU = follow-up; Tx = Treatment; V = visit

2.4. Study Schema for Cohort 7a



CB = Control buttock; EOS = End of Study; ; FU = follow-up; IB = Investigational buttock; Tx = Treatment; V = visit

2.5. Study Schema for Cohort 7b



CB = Control buttock; EOS = End of Study; ; FU = follow-up; IB = Investigational buttock; Tx = Treatment; V = visit

2.6. Schedule of Assessments for Cohorts 1 to 5

Activities	Screening 28 days	Treatment Period 90 days															Follow-Up Period 90 days		
Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Visit	**Screening**	**Tx Visit 1**	**Tx V1 FU1**	**Tx V1 FU2**	**Tx V1 FU3**	**Tx V1 FU4**	**Tx Visit 2**	**Tx V2 FU1**	**Tx V2 FU2**	**Tx V2 FU3**	**Tx V2 FU4**	**Tx Visit 3**	**Tx V3 FU1**	**Tx V3 FU2**	**Tx V3 FU3**	**Tx V3 FU4**	**90 Day Follow-Up Visit**	**135 Day Follow-Up Visit**	**EOS / ET Visit[o]**
Visit Windows (Days)	**(Day -28 to Day -1)**	**Day 1**	**1 to 2 Days After TV1**	**3 to 5 Days After TV1**	**6 to 9 Days After TV1**	**10 to 14 Days After TV1**	**Day 22 (±3 Days)**	**1 to 2 Days After TV2**	**3 to 5 Days After TV2**	**6 to 9 Days After TV2**	**10 to 14 Days After TV2**	**Day 43 (±3 Days)**	**1 to 2 Days After TV3**	**3 to 5 Days After TV3**	**6 to 9 Days After TV3**	**10 to 14 Days After TV3**	**Day 90 (±7 Days)**	**Day 135 (±7 Days)**	**Day 180 (±7 Days)**
Informed consent[a]	X																		
Inclusion/Exclusion criteria review	X	X[b]																	
Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)[c,d]	X	X[b]																	
Hexsel Cellulite Severity Scale (CSS)[c,d]	X	X[b]																	
Cohort assignment[e]		X																	
Medical and surgical history[f]	X																		
Cellulite history	X																		
Physical examination (including height)	X																		
Weight	X	X																	X
Fitzpatrick Skin Type[d]	X																		
Vital signs	X	X[g]					X[g]					X[g]							X
Clinical laboratory tests (chemistry, hematology, urinalysis)	X																		X
Serum pregnancy test	X																		X
Urine pregnancy test		X[h]					X[h]					X[h]							

Activities	Screening 28 days	Treatment Period 90 days															Follow-Up Period 90 days		
Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Visit	**Screening**	**Tx Visit 1**	**Tx V1 FU1**	**Tx V1 FU2**	**Tx V1 FU3**	**Tx V1 FU4**	**Tx Visit 2**	**Tx V2 FU1**	**Tx V2 FU2**	**Tx V2 FU3**	**Tx V2 FU4**	**Tx Visit 3**	**Tx V3 FU1**	**Tx V3 FU2**	**Tx V3 FU3**	**Tx V3 FU4**	**90 Day Follow-Up Visit**	**135 Day Follow-Up Visit**	**EOS / ET Visit[o]**
Visit Windows (Days)	**(Day -28 to Day -1)**	**Day 1**	**1 to 2 Days After TV1**	**3 to 5 Days After TV1**	**6 to 9 Days After TV1**	**10 to 14 Days After TV1**	**Day 22 (±3 Days)**	**1 to 2 Days After TV2**	**3 to 5 Days After TV2**	**6 to 9 Days After TV2**	**10 to 14 Days After TV2**	**Day 43 (±3 Days)**	**1 to 2 Days After TV3**	**3 to 5 Days After TV3**	**6 to 9 Days After TV3**	**10 to 14 Days After TV3**	**Day 90 (±7 Days)**	**Day 135 (±7 Days)**	**Day 180 (±7 Days)**
Selection and marking of dimples to be treated within both buttocks		X[h]					X[h]					X[h]							
Digital photography[i]	X	X[j]	X	X	X	X	X[j]	X	X	X	X	X[j]	X	X	X	X	X	X	X
QWO (CCH-aaes) administration[d] (Investigational and Control Buttocks)		X					X					X							
Investigator Assessment of Bruising Severity Scale (IABSS) [d,k]		X[h]	X	X	X	X	X[h]	X	X	X	X	X[h]	X	X	X	X			
Investigator-Global Aesthetic Improvement Scale (I-GAIS) [d,k,l]							X[h]					X[h]					X	X	X
Prior medications[m]	X	X																	
Concomitant medications/procedures	Collect throughout the study																		
Adverse events[n]	Collect throughout the study																		

[a] Performed prior to any study-required assessments.
[b] Reassessed and verified prior to dosing.
[c] CR-PCSS rating must be a '3' (moderate) or '4' (severe) on each buttock and the Hexsel CSS total score must be ≤ 12.
[d] To be performed by a qualified designated physician.
[e] Participants will be assigned to 1 of 7 cohorts using an interactive response technology (IRT) system.

[f] Medical and surgical history will include a review of all medical history and surgical procedures completed in the prior 10 years and any surgery completed at any time in the treatment area. Tobacco and ethanol (EtOH) use will also be collected.
[g] Vital signs (temperature, pulse, systolic blood pressure, and diastolic blood pressures) will be collected up to 2 hours prior to, and at 15 and 30 minutes after, QWO (CCH-aaes) administration on the days of treatment. Pulse and blood pressure will be collected after the participant has been sitting for 5 minutes.
[h] Prior to treatment with QWO (CCH-aaes).
[i] No manipulation of the treatment area should be done prior to any "before" images.
[j] On the days of treatment, the buttocks will be photographed before and after injection site and dimple marking.
[k] Based on live assessments while the participant is in front of the investigator. Assessments will be performed for each buttock separately.
[l] 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 during the live assessment.
[m] Prior medications (other than QWO [CCH-aaes]) include medications taken 90 days before Screening. All prior QWO (CCH-aaes) use should be captured.
[n] Serious adverse events (SAEs) and adverse events (AEs) will be collected by the investigator from the time of signing the informed consent through the Day 180 EOS/ET Visit. All ongoing AEs must be followed until they have resolved or for 28 days after the participant's last treatment visit, whichever comes first. For participants who withdraw from the study early, SAEs and AEs will be collected for 28 days after the last dose of QWO (CCH-aaes).
[o] Participants are encouraged to remain in the study for follow-up until the Day 180 Visit. Participants who discontinue from the study or study intervention and do not agree to remain in the study for follow-up until Day 180, will be asked to complete an early termination (ET) visit and a 28-day post-treatment Safety Follow-up Visit (or phone call if a visit is not possible) if applicable. The status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs will be assessed.

EOS = end of study; FU = follow-up; Tx = Treatment; V = visit

2.7. Schedule of Assessments for Cohort 6

Activities	Screening 28 days	Treatment Period 90 days											Follow-Up Period 90 days		
Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Visit	**Screening**	**Tx Visit 1**	**Tx V1 FU1**	**Tx V1 FU2**	**Tx V1 FU3**	**Tx V1 FU4**	**Tx V1 FU5**	**Tx Visit 2**	**Tx V2 FU1**	**Tx V2 FU2**	**Tx V2 FU3**	**Tx V2 FU4**	**90 Day Follow-Up Visit**	**135 Day Follow-Up Visit**	**EOS / ET Visit[o]**
Visit Windows (Days)	**(Day -28 to Day -1)**	**Day 1**	**1 to 2 Days After TV1**	**3 to 5 Days After TV1**	**6 to 9 Days After TV1**	**10 to 14 Days After TV1**	**18 to 24 Days After TV1 (Day 22 ± 3 Days)**	**Day 43 (±3 Days)**	**1 to 2 Days After TV2**	**3 to 5 Days After TV2**	**6 to 9 Days After TV2**	**10 to 14 Days After TV2**	**Day 90 (±7 Days)**	**Day 135 (±7 Days)**	**Day 180 (±7 Days)**
Informed consent[a]	X														
Inclusion/Exclusion criteria review	X	X[b]													
Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)[c,d]	X	X[b]													
Hexsel Cellulite Severity Scale (CSS)[c,d]	X	X[b]													
Cohort assignment[e]		X													
Medical and surgical history[f]	X														
Cellulite history	X														
Physical examination (including height)	X														
Weight	X	X													X
Fitzpatrick Skin Type[d]	X														
Vital signs	X	X[g]						X[g]							X
Clinical laboratory tests (chemistry, hematology, urinalysis)	X														X

Activities	Screening 28 days	Treatment Period 90 days											Follow-Up Period 90 days		
Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Visit	**Screening**	**Tx Visit 1**	**Tx V1 FU1**	**Tx V1 FU2**	**Tx V1 FU3**	**Tx V1 FU4**	**Tx V1 FU5**	**Tx Visit 2**	**Tx V2 FU1**	**Tx V2 FU2**	**Tx V2 FU3**	**Tx V2 FU4**	**90 Day Follow-Up Visit**	**135 Day Follow-Up Visit**	**EOS / ET Visit[o]**
Visit Windows (Days)	**(Day -28 to Day -1)**	**Day 1**	**1 to 2 Days After TV1**	**3 to 5 Days After TV1**	**6 to 9 Days After TV1**	**10 to 14 Days After TV1**	**18 to 24 Days After TV1 (Day 22 ± 3 Days)**	**Day 43 (±3 Days)**	**1 to 2 Days After TV2**	**3 to 5 Days After TV2**	**6 to 9 Days After TV2**	**10 to 14 Days After TV2**	**Day 90 (±7 Days)**	**Day 135 (±7 Days)**	**Day 180 (±7 Days)**
Serum pregnancy test	X														X
Urine pregnancy test		X[h]						X[h]							
Selection and marking of dimples to be treated within both buttocks		X[h]						X[h]							
Digital photography[i]	X	X[j]	X	X	X	X	X	X[j]	X	X	X	X	X	X	X
QWO (CCH-aaes) administration[d] (Investigational and Control Buttocks)		X						X							
Investigator Assessment of Bruising Severity Scale (IABSS)[d,k]		X[h]	X	X	X	X	X	X[h]	X	X	X	X			
Investigator-Global Aesthetic Improvement Scale (I-GAIS)[d,k,l]								X[h]					X	X	X
Prior Medications[m]	X	X													
Concomitant medications/procedures	Collect throughout the study														
Adverse Events[n]	Collect throughout the study														

[a] Performed prior to any study-required assessments.
[b] Reassessed and verified prior to dosing.

[c] CR-PCSS rating must be a '3' (moderate) or '4' (severe) on each buttock and the Hexsel CSS total score must be ≤ 12.
[d] [e] To be performed by a qualified designated physician.
Participants will be assigned to 1 of 7 cohorts using an interactive response technology (IRT) system.
[f] Medical and surgical history will include a review of all medical history and surgical procedures completed in the prior 10 years and any surgery completed at any time in the treatment area. Tobacco and ethanol (EtOH) use will also be collected.
[g] Vital signs (temperature, pulse, systolic blood pressure, and diastolic blood pressures) will be collected up to 2 hours prior to, and at 15 and 30 minutes after, QWO (CCH-aaes) administration on Treatment Visit Days. Pulse and blood pressure will be collected after the participant has been sitting for 5 minutes.
[h] Prior to treatment with QWO (CCH-aaes).
[i] No manipulation of the treatment area should be done prior to any "before" images.
[j] On Treatment Visit Days, the buttocks will be photographed before and after injection site and dimple marking.
[k] Based on live assessments while the participant is in front of the investigator. Assessments will be performed for each buttock separately.
[l] 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 during the live assessment.
[m] Prior medications (other than QWO [CCH-aaes]) include medications taken 90 days before Screening. All prior QWO (CCH-aaes) use should be captured.
[n] Serious adverse events (SAEs) and adverse events (AEs) will be collected by the investigator from the time of signing the informed consent through the Day 180 EOS/ET Visit. All ongoing AEs must be followed until they have resolved or for 28 days after the participant's last treatment visit, whichever comes first. For participants who withdraw from the study early, SAEs and AEs will be collected for 28 days after the last dose of QWO (CCH-aaes).
[o] Participants are encouraged to remain in the study for follow-up until the Day 180 Visit. Participants who discontinue from the study or study intervention and do not agree to remain in the study for follow-up until Day 180, will be asked to complete an early termination (ET) visit and a 28-day post-treatment Safety Follow-up Visit (or phone call if a visit is not possible) if applicable. The status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs will be assessed.

EOS = end of study; FU = follow-up; Tx = Treatment; V = Visit

2.8. Schedule of Assessments for Cohort 7a

Activities	Screening 28 days	Treatment Period 90 days																			Follow-Up Period 90 days		
Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
Visit	**Screening**	**Tx Visit 1**	**Tx V1 FU1**	**Tx V1 FU2**	**Tx V1 FU3**	**Tx V1 FU4**	**Tx Visit 2**	**Tx V2 FU1**	**Tx V2 FU2**	**Tx V2 FU3**	**Tx V2 FU4**	**Tx Visit 3**	**Tx V3 FU1**	**Tx V3 FU2**	**Tx V3 FU3**	**Tx V3 FU4**	**Tx Visit 4**	**Tx V4 FU1**	**Tx V4 FU2**	**Tx V4 FU3**	**Tx V4 FU4**	**90 Day Follow-up Visit**	**135 Day Follow-up Visit**	**EOS / ET Visit[p]**
Visit Windows (Days)	**(Day -28 to Day -1)**	**Day 1**	**1 to 2 Days After TV1**	**3 to 5 Days After TV1**	**6 to 9 Days After TV1**	**10 to 14 Days After TV1**	**Day 22 (±3 Days)**	**1 to 2 Days After TV2**	**3 to 5 Days After TV2**	**6 to 9 Days After TV2**	**10 to 14 Days After TV2**	**Day 43 (±3 Days)**	**1 to 2 Days After TV3**	**3 to 5 Days After TV3**	**6 to 9 Days After TV3**	**10 to 14 Days After TV3**	**Day 64 (±3 Days)**	**1 to 2 Days After TV4**	**3 to 5 Days After TV4**	**6 to 9 Days After TV4**	**10 to 14 Days After TV4**	**Day 90 (±7 Days)**	**Day 135 (±7 Days)**	**Day 180 (±7 Days)**
Informed consent[a]	X																							
Inclusion/Exclusion criteria review	X	X[b]																						
Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)[c,d]	X	X[b]																						
Hexsel Cellulite Severity Scale (CSS)[c,d]	X	X[b]																						
Cohort assignment[e]		X																						
Medical and surgical history[f]	X																							
Cellulite history	X																							
Physical examination (including height)	X																							
Weight	X	X																						X
Fitzpatrick Skin Type [d]	X																							
Vital signs	X	X[g]					X[g]					X[g]					X[g]							X
Clinical laboratory tests (chemistry, hematology, urinalysis)	X																							X
Serum pregnancy test	X																							X
Urine pregnancy test		X[h]					X[h]					X[h]					X[h]							

Activities	Screening 28 days	Treatment Period 90 days																			Follow-Up Period 90 days		
Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
Visit	**Screening**	**Tx Visit 1**	**Tx V1 FU1**	**Tx V1 FU2**	**Tx V1 FU3**	**Tx V1 FU4**	**Tx Visit 2**	**Tx V2 FU1**	**Tx V2 FU2**	**Tx V2 FU3**	**Tx V2 FU4**	**Tx Visit 3**	**Tx V3 FU1**	**Tx V3 FU2**	**Tx V3 FU3**	**Tx V3 FU4**	**Tx Visit 4**	**Tx V4 FU1**	**Tx V4 FU2**	**Tx V4 FU3**	**Tx V4 FU4**	**90 Day Follow-up Visit**	**135 Day Follow-up Visit**	**EOS / ET Visit[p]**
Visit Windows (Days)	**(Day -28 to Day -1)**	**Day 1**	**1 to 2 Days After TV1**	**3 to 5 Days After TV1**	**6 to 9 Days After TV1**	**10 to 14 Days After TV1**	**Day 22 (±3 Days)**	**1 to 2 Days After TV2**	**3 to 5 Days After TV2**	**6 to 9 Days After TV2**	**10 to 14 Days After TV2**	**Day 43 (±3 Days)**	**1 to 2 Days After TV3**	**3 to 5 Days After TV3**	**6 to 9 Days After TV3**	**10 to 14 Days After TV3**	**Day 64 (±3 Days)**	**1 to 2 Days After TV4**	**3 to 5 Days After TV4**	**6 to 9 Days After TV4**	**10 to 14 Days After TV4**	**Day 90 (±7 Days)**	**Day 135 (±7 Days)**	**Day 180 (±7 Days)**
Selection and marking of dimples to be treated within both buttocks		X[h]					X[h]					X[h]					X[h]							
Digital photography[i]	X	X[j]	X	X	X	X	X[j]	X	X	X	X	X[j]	X	X	X	X	X[j]	X	X	X	X	X	X	X
QWO (CCH-aaes) administration[d] (Investigational Buttock)		X[k]					X					X												
QWO (CCH-aaes) administration[d] (Control Buttock)							X					X					X							
Dispensing of tranexamic acid	X																							
Tranexamic acid use		← D-1, D1, D2, D3, D4 →																						
Compliance check for tranexamic acid			X	X																				
Collection of tranexamic acid					X																			
Investigator Assessment of Bruising Severity Scale (IABSS) [d,l]		X[h]	X	X	X	X	X[h]	X	X	X	X	X[h]	X	X	X	X	X[h]	X	X	X	X			
Investigator-Global Aesthetic Improvement Scale (I-GAIS) (Investigational Buttock) [d,l,m]							X[h]					X[h]					X[h]					X	X	X

Activities	Screening 28 days	Treatment Period 90 days																			Follow-Up Period 90 days		
Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
Visit	**Screening**	**Tx Visit 1**	**Tx V1 FU1**	**Tx V1 FU2**	**Tx V1 FU3**	**Tx V1 FU4**	**Tx Visit 2**	**Tx V2 FU1**	**Tx V2 FU2**	**Tx V2 FU3**	**Tx V2 FU4**	**Tx Visit 3**	**Tx V3 FU1**	**Tx V3 FU2**	**Tx V3 FU3**	**Tx V3 FU4**	**Tx Visit 4**	**Tx V4 FU1**	**Tx V4 FU2**	**Tx V4 FU3**	**Tx V4 FU4**	**90 Day Follow-up Visit**	**135 Day Follow-up Visit**	**EOS / ET Visit[p]**
Visit Windows (Days)	**(Day -28 to Day -1)**	**Day 1**	**1 to 2 Days After TV1**	**3 to 5 Days After TV1**	**6 to 9 Days After TV1**	**10 to 14 Days After TV1**	**Day 22 (±3 Days)**	**1 to 2 Days After TV2**	**3 to 5 Days After TV2**	**6 to 9 Days After TV2**	**10 to 14 Days After TV2**	**Day 43 (±3 Days)**	**1 to 2 Days After TV3**	**3 to 5 Days After TV3**	**6 to 9 Days After TV3**	**10 to 14 Days After TV3**	**Day 64 (±3 Days)**	**1 to 2 Days After TV4**	**3 to 5 Days After TV4**	**6 to 9 Days After TV4**	**10 to 14 Days After TV4**	**Day 90 (±7 Days)**	**Day 135 (±7 Days)**	**Day 180 (±7 Days)**
Investigator-Global Aesthetic Improvement Scale (I-GAIS) (Control Buttock)																								
Prior medications[n]	X	X																						
Concomitant medications/ procedures	Collect throughout the study																							
Adverse events[o]	Collect throughout the study																							

[a] Performed prior to any study-required assessments.
[b] Reassessed and verified prior to dosing.
[c] CR-PCSS rating must be a '3' (moderate) or '4' (severe) on each buttock and the Hexsel CSS total score must be ≤ 12.
[d] To be performed by a qualified designated physician.
[e] Participants will be assigned to 1 of 7 cohorts using an interactive response technology (IRT) system.
[f] Medical and surgical history will include a review of all medical history and surgical procedures completed in the prior 10 years and any surgery completed at any time in the treatment area. Tobacco and ethanol (EtOH) use will also be collected.
[g] Vital signs (temperature, pulse, systolic blood pressure, and diastolic blood pressures) will be collected up to 2 hours prior to, and at 15 and 30 minutes after, QWO (CCH-aaes) administration on the days of treatment. Pulse and blood pressure will be collected after the participant has been sitting for 5 minutes.
[h] Prior to treatment with QWO (CCH-aaes).
[i] No manipulation of the treatment area should be done prior to any "before" images.
[j] On the days of treatment, the buttocks will be photographed before and after injection site and dimple marking.
[k] Participants will take tranexamic acid 1300 mg orally TID for 5 days (prior to the day of the first injection of QWO (CCH-aaes) to the investigational buttock (Day -1) , the day of the first injection (Day 1) and for the 3 days following the first injection (Days 2 to 4). Tranexamic acid use should be documented on the Tranexamic Acid Administration page of the eCRF.
[l] Based on live assessments while the participant is in front of the investigator. Assessments will be performed for each buttock separately.
[m] 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 during the live assessment.
[n] Prior medications (other than QWO [CCH-aaes]) include medications taken 90 days before Screening. All prior QWO (CCH-aaes) use should be captured.

[o] Serious adverse events (SAEs) and adverse events (AEs) will be collected by the investigator from the time of signing the informed consent through the Day 180 EOS/ET Visit. All ongoing AEs must be followed until they have resolved or for 28 days after the participant's last treatment visit, whichever comes first. For participants who withdraw from the study early, SAEs and AEs will be collected for 28 days after the last dose of QWO (CCH-aaes).

[p] Participants are encouraged to remain in the study for follow-up until the Day 180 Visit. Participants who discontinue from the study or study intervention and do not agree to remain in the study for follow-up until Day 180, will be asked to complete an early termination (ET) visit and a 28-day post-treatment Safety Follow-up Visit (or phone call if a visit is not possible) if applicable. The status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs will be assessed.

EOS = end of study; FU = follow-up; TID = three times daily; Tx = Treatment; V = visit

2.9. Schedule of Assessments for Cohort 7b

Activities	Screening 28 days	Treatment Period 90 days																			Follow-Up Period 90 days		
Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
Visit	**Screening**	**Tx Visit 1**	**Tx V1 FU1**	**Tx V1 FU2**	**Tx V1 FU3**	**Tx V1 FU4**	**Tx Visit 2**	**Tx V2 FU1**	**Tx V2 FU2**	**Tx V2 FU3**	**Tx V2 FU4**	**Tx Visit 3**	**Tx V3 FU1**	**Tx V3 FU2**	**Tx V3 FU3**	**Tx V3 FU4**	**Tx Visit 4**	**Tx V4 FU1**	**Tx V4 FU2**	**Tx V4 FU3**	**Tx V4 FU4**	**90 Day Follow-up Visit**	**135 Day Follow-up Visit**	**EOS / ET Visit[p]**
Visit Windows (Days)	**(Day -28 to Day -1)**	**Day 1**	**1 to 2 Days After TV1**	**3 to 5 Days After TV1**	**6 to 9 Days After TV1**	**10 to 14 Days After TV1**	**Day 22 (±3 Days)**	**1 to 2 Days After TV2**	**3 to 5 Days After TV2**	**6 to 9 Days After TV2**	**10 to 14 Days After TV2**	**Day 43 (±3 Days)**	**1 to 2 Days After TV3**	**3 to 5 Days After TV3**	**6 to 9 Days After TV3**	**10 to 14 Days After TV3**	**Day 64 (±3 Days)**	**1 to 2 Days After TV4**	**3 to 5 Days After TV4**	**6 to 9 Days After TV4**	**10 to 14 Days After TV4**	**Day 90 (±7 Days)**	**Day 135 (±7 Days)**	**Day 180 (±7 Days)**
Informed consent[a]	X																							
Inclusion/Exclusion criteria review	X	X[b]																						
Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)[c,d]	X	X[b]																						
Hexsel Cellulite Severity Scale (CSS)[c,d]	X	X[b]																						
Cohort assignment[e]		X																						
Medical and surgical history[f]	X																							
Cellulite history	X																							
Physical examination (including height)	X																							
Weight	X	X																						X
Fitzpatrick Skin Type [d]	X																							
Vital signs	X	X[g]					X[g]					X[g]					X[g]							X
Clinical laboratory tests (chemistry, hematology, urinalysis)	X																							X
Serum pregnancy test	X																							X
Urine pregnancy test		X[h]					X[h]					X[h]					X[h]							
Selection and marking of dimples to be treated within both buttocks		X[h]					X[h]					X[h]					X[h]							

Activities	Screening 28 days	Treatment Period 90 days																			Follow-Up Period 90 days		
Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
Visit	**Screening**	**Tx Visit 1**	**Tx V1 FU1**	**Tx V1 FU2**	**Tx V1 FU3**	**Tx V1 FU4**	**Tx Visit 2**	**Tx V2 FU1**	**Tx V2 FU2**	**Tx V2 FU3**	**Tx V2 FU4**	**Tx Visit 3**	**Tx V3 FU1**	**Tx V3 FU2**	**Tx V3 FU3**	**Tx V3 FU4**	**Tx Visit 4**	**Tx V4 FU1**	**Tx V4 FU2**	**Tx V4 FU3**	**Tx V4 FU4**	**90 Day Follow-up Visit**	**135 Day Follow-up Visit**	**EOS / ET Visit[p]**
Visit Windows (Days)	**(Day -28 to Day -1)**	**Day 1**	**1 to 2 Days After TV1**	**3 to 5 Days After TV1**	**6 to 9 Days After TV1**	**10 to 14 Days After TV1**	**Day 22 (±3 Days)**	**1 to 2 Days After TV2**	**3 to 5 Days After TV2**	**6 to 9 Days After TV2**	**10 to 14 Days After TV2**	**Day 43 (±3 Days)**	**1 to 2 Days After TV3**	**3 to 5 Days After TV3**	**6 to 9 Days After TV3**	**10 to 14 Days After TV3**	**Day 64 (±3 Days)**	**1 to 2 Days After TV4**	**3 to 5 Days After TV4**	**6 to 9 Days After TV4**	**10 to 14 Days After TV4**	**Day 90 (±7 Days)**	**Day 135 (±7 Days)**	**Day 180 (±7 Days)**
Digital photography[i]	X	X[j]	X	X	X	X	X[j]	X	X	X	X	X[j]	X	X	X	X	X[j]	X	X	X	X	X	X	X
QWO (CCH-aaes) administration[d] (Investigational Buttock)							X[k]					X					X							
QWO (CCH-aaes) administration[d] (Control Buttock)		X					X[k]					X												
Dispensing of tranexamic acid						X	X																	
Tranexamic acid use							← D21, D22, D23, D24, D25 →																	
Compliance check for tranexamic acid								X	X															
Collection of tranexamic acid										X														
Investigator Assessment of Bruising Severity Scale (IABSS) [d,l]		X[h]	X	X	X	X	X[h]	X	X	X	X	X[h]	X	X	X	X	X[h]	X	X	X	X			
Investigator-Global Aesthetic Improvement Scale (I-GAIS) [d,l,m]							X[h]					X[h]					X[h]					X	X	X
Prior medications[n]	X	X																						
Concomitant medications/procedures	Collect throughout the study																							
Adverse events[o]	Collect throughout the study																							

[a] Performed prior to any study-required assessments.
[b] Reassessed and verified prior to dosing.
[c] CR-PCSS rating must be a '3' (moderate) or '4' (severe) on each buttock and the Hexsel CSS total score must be ≤ 12.
[d] To be performed by a qualified designated physician.
[e] Participants will be assigned to 1 of 7 cohorts using an interactive response technology (IRT) system.
[f] Medical and surgical history will include a review of all medical history and surgical procedures completed in the prior 10 years and any surgery completed at any time in the treatment area. Tobacco and ethanol (EtOH) use will also be collected.
[g] Vital signs (temperature, pulse, systolic blood pressure, and diastolic blood pressures) will be collected up to 2 hours prior to, and at 15 and 30 minutes after, QWO (CCH-aaes) administration on the days of treatment. Pulse and blood pressure will be collected after the participant has been sitting for 5 minutes.
[h] Prior to treatment with QWO (CCH-aaes).
[i] No manipulation of the treatment area should be done prior to any "before" images.
[j] On the days of treatment, the buttocks will be photographed before and after injection site and dimple marking.
[k] Participants will take tranexamic acid orally TID for 5 days (prior to the day of the second injection on Day 21, the day of the second injection (Day 22) and for the 3 days following the second injection (Day 23 to Day 25). Tranexamic acid use should be documented on the Tranexamic Acid Administration page of the eCRF.
[l] Based on live assessments while the participant is in front of the investigator. Assessments will be performed for each buttock separately.
[m] 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 during the live assessment.
[n] Prior medications (other than QWO [CCH-aaes]) include medications taken 90 days before Screening. All prior QWO (CCH-aaes) use should be captured.
[o] Serious adverse events (SAEs) and adverse events (AEs) will be collected by the investigator from the time of signing the informed consent through the Day 180 EOS/ET Visit. All ongoing AEs must be followed until they have resolved or for 28 days after the participant's last treatment visit, whichever comes first. For participants who withdraw from the study early, SAEs and AEs will be collected for 28 days after the last dose of QWO (CCH-aaes).
[p] Participants are encouraged to remain in the study for follow-up until the Day 180 Visit. Participants who discontinue from the study or study intervention and do not agree to remain in the study for follow-up until Day 180, will be asked to complete an early termination (ET) visit and a 28-day post-treatment Safety Follow-up Visit (or phone call if a visit is not possible) if applicable. The status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs will be assessed.

EOS = end of study; FU = follow-up; TID = three times daily; Tx = Treatment; V = visit

3. INTRODUCTION

Collagenase clostridium histolyticum (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.

3.1. Background

Collagenases are proteinases that hydrolyze collagen in its native triple helical conformation under physiological conditions. To investigate the use of collagenases in the treatment of cellulite, Endo Pharmaceuticals Inc. (Endo) has developed a novel formulation of AUX-I and AUX-II referred to as CCH-aaes. CCH effectively lyses the subdermal located fibrous septae, the underlying cause of the skin dimpling in women with cellulite, at the site of injection.

QWO (CCH-aaes) is approved for the treatment of moderate to severe cellulite in the buttocks of adult women. Approval was based on studies demonstrating an improvement in the severity of cellulite, as determined by both the investigator and the participant, in participants treated with QWO (CCH-aaes) administered at a dose of 0.84 mg per treatment area every 21 days for 3 sessions. Across all previous studies, CCH has demonstrated an acceptable safety and immunogenicity profile.

3.2. Rationale

Although QWO (CCH-aaes) related post-injection bruising generally resolves within 21 days (CSR EN3835-302; CSR EN3835-303), and before the next treatment session, bruising is bothersome to participants due to the risk of potential skin discoloration and associated swelling and pain. Study EN3835-401 (MOBI) was a Phase 4, open-label study designed to assess the effects of mitigation treatments on bruising due to QWO (CCH-aaes) treatments on buttock cellulite after the first treatment with QWO. Mitigation treatments included a compression garment, instant cold packs, arnica (OcuMend®) Patches, laser treatment, and INhance Post-Injection Serum with TriHex Technology®. Improvement in the severity of bruising when QWO (CCH-aaes) was administered with and without different mitigation treatments was assessed by the Investigator using the Investigator-Bruising Improvement Scale and the IABSS. Furthermore, participants also assessed the intensity of the temporal pattern of post-injection pain using an Injection Pain Assessment Scale. The safety of QWO (CCH-aaes) with mitigation treatment was also assessed.

Consistent with the known effects of QWO (CCH-aaes), bruising was transient, mild to moderate in severity, and in most participants resolved before the next treatment session on Day 22. Injection site pain, 48-hours after QWO (CCH-aaes) injection, was also mild in severity. There were no differences among the mitigation treatment cohorts in the severity of bruising. In cohorts where only 1 buttock was treated with a mitigation strategy (ie, cold packs, OcuMend [arnica], INhance Post-Injection Serum, and pulse dye laser), there was no difference between the mitigation-treated buttock, and the buttock that did not receive mitigation treatment. Mitigation treatment also did not impact pain related to injection site bruising (CSR EN3835-401). It is

important to note that the labeled dose and concentration of QWO (0.84 mg administered at a concentration of 0.23 mg/mL) was administered consistently in the MOBI study. Alternate doses, concentrations, depth of injection or diluent additives were not used

APHRODITE-1 will use different single and combination mitigation strategies to decrease the severity of bruising after QWO (CCH-aaes) injection. A description of the chemistry, pharmacology, efficacy, and safety of QWO (CCH-aaes) is provided in the QWO Prescribing Information.

3.3. Benefit-Risk Assessment

During this study, QWO (CCH-aaes) will be administered by a qualified designated physician using different doses, strengths (concentrations), diluent additives, depths of injection, and methods of injection to determine if these methods will decrease the extent, severity, and duration of bruising. The benefit and risk of each study intervention is described in this section.

3.3.1. QWO (CCH-aaes)

QWO is approved for the treatment of moderate to severe cellulite in the buttocks of adult women. The results of all Phase 2 and 3 studies conducted demonstrated a consistent effect of QWO (CCH-aaes) in reducing the severity of cellulite. The results of two Phase 3 pivotal efficacy studies (Studies EN3835-302 and EN3835-303) established the efficacy of CCH administration in the treatment of moderate to severe cellulite in the buttocks of adult women when injected subcutaneously at a dose of 0.84 mg per treatment area every 21 days for 3 treatment visits. A treatment area was defined as a single buttock receiving up to 12 injections, 0.3 mL each (up to a total of 3.6 mL), of QWO (CCH-aaes). Two treatment areas (2 buttocks) were treated at each visit.

A reduction in the severity of cellulite was observed as assessed by validated assessment scales as early as 21 days after administration of the first treatment session of QWO (CCH-aaes) and was sustained throughout the 71-day double-blind study period. Furthermore, overall patient-reported satisfaction, emotional impact, and visual appearance measures showed a greater and statistically significant improvement in the QWO (CCH-aaes) group over the placebo group. The TEAEs observed were predominantly localized injection site reactions that were nonserious, primarily mild to moderate in severity, transient, and decreased in frequency with each subsequent treatment session. Bruising was quite common, reported in 84% of subjects (QWO Prescribing Information).

Further details about the known and expected risks and reasonably expected adverse events (AEs) can be found in the QWO prescribing information (QWO Prescribing Information).

3.3.2. Lidocaine and Epinephrine

Lidocaine is a local anesthetic that helps reduce pain or discomfort caused by invasive medical procedures such as needle punctures. Epinephrine has vasoconstriction properties that when combined with local anesthetics (ie, lidocaine) prolongs the localized action of lidocaine and results in local vasoconstriction. A total dose of 1260 to 2880 mg lidocaine corresponding to 10.5 to 34.4 mg/kg was administered to patients undergoing lipectomy and was found to be safe (Samdal et al, 1994). Doses intended for use in this study are considerably lower (maximum of 36 mg of lidocaine and 9 mcg epinephrine per dose). Epinephrine has been used in cosmetic

surgery extensively, such as a tumescent anesthetic in the majority of current-day liposuction procedures, and has been used to reduce intra-procedural bleeding and post-procedural bruising. Epinephrine causes vasoconstriction of surrounding vessels which can limit both bleeding and bruising and also inhibits activation of eosinophils that play a role in bruising (Funt and Pavicic, 2013).

While very rare, an allergic reaction to lidocaine may occur.

3.3.3. Half-dose QWO (CCH-aaes)

In Cohorts 1 and 5, half the labeled dose (0.42 mg) of QWO (CCH-aaes) will be administered to the investigational side to determine the extent to which dose may be associated with the severity of bruising. In Cohort 6, half the labeled dose (0.42 mg) of QWO (CCH-aaes) will be administered to the control side. A similar dose (0.48 mg) was implemented in Study AUX-CC-831, a small dose ranging study, where improvements were also observed in cellulite appearance at a dose of CCH 0.48 mg per region. Bruising and discoloration were reported at slightly numerically less than the labeled 0.84 mg also tested in that study. The AUX-CC-831 study did not compare severity of bruising between doses tested.

In Cohorts 1 and 5, the total dose administered to the participant in both the investigational side and the control side through the course of the study will be QWO (CCH-aaes) 3.78 mg (after 3 treatment sessions each 21 days apart). Details regarding the total dose for Cohort 6 can be found in Section 3.3.4. The risk of half-dose of QWO (CCH-aaes) therefore is expected to remain consistent with the risks of the labeled dose of QWO (CCH-aaes).

3.3.4. Quarter-dose QWO (CCH-aaes)

In Cohort 6, one-quarter of the labeled dose (0.21 mg) at one-half of the labeled concentration (0.12 mg/mL) of QWO (CCH-aaes) will be administered to the investigational side. Half of the labeled dose (0.42 mg) at the labeled concentration (0.23 mg/mL) of QWO (CCH-aaes) will be administered to the control side. Cohort 6 will consist of 2 treatment sessions, 6 weeks apart. The total dose administered for Cohort 6 to the participant in both the investigational and control sides during the study will be QWO (CCH-aaes) 1.26 mg. The purpose of decreasing the dose/concentration and lengthening the interval between Treatment Session 1 (Day 1) and Treatment Session 2 (Day 43+ 3 days) is to determine whether there will be an improvement in both bruising and subsequent discoloration.

3.3.5. 2.5-Fold and 5-Fold Diluted Concentrations of QWO (CCH-aaes)

A 5-fold dilution of QWO (CCH-aaes) was administered in Studies EN3835-209, EN3835-224, and EN3835-305. Administering QWO (CCH-aaes) using this dilution has been shown to be safe. In Study EN3835-224, a lower frequency of discoloration was observed using this 5-fold dilution. An approximate 2.5-fold dilution of QWO (CCH-aaes) representing approximately 40% of the labeled concentration will also be evaluated during this study (Cohort 4). Given that the same dose (0.84 mg) of QWO (CCH-aaes) will be administered using these concentrations, the benefit-risk profile is expected to remain consistent with the benefit-risk of the labeled dose of QWO (CCH-aaes).

3.3.6. Tranexamic Acid

To date, this is the first company-conducted study of oral tranexamic acid to potentially reduce bruising associated with QWO (CCH-aaes) injections and as such its benefit is unknown. Tranexamic acid is a synthetic lysine amino acid derivative which competitively inhibits the activation of plasminogen to plasmin, resulting in inhibition of fibrinolysis. By inhibiting the formation of plasmin, a proinflammatory cell activator (Rorich and Cho, 2018), it acts as an anti-inflammatory agent. Bruising is often caused by localized bleed that extravasates into the surrounding interstitial tissues. Based on its mechanism of action, it is thought that tranexamic acid may mitigate bruising associated with QWO (CCH-aaes).

Tranexamic acid is indicated for menorrhagia (Tranexamic Acid Prescribing Information) at a dose of 1300 mg TID orally for 5 days during multiple cycles. It is widely used to prevent and treat blood loss in a range of situations such as heavy menstrual bleeding, dental procedures, and various surgeries including plastic surgery (Ockerman et al, 2021; Rorich and Cho, 2018). Tranexamic acid is also routinely used as an adjunct in aesthetic procedures to minimize swelling, ecchymosis and bruising (Mehdizadeh et al, 2018; Wokes et al, 2021).

One of the more serious risks associated with tranexamic acid is an increased risk of vascular occlusive events. However, these appear to be rare. In a nationwide registry study from Denmark (Meaidi et al, 2021) 2 million women were followed for 13.8 million person-years. While the study found use of oral tranexamic acid to be positively associated with venous thromboembolism, the number needed to harm per 5 days of treatment was high, at 78,549 women, which is unlikely to be seen in a study of this size. The registry study concluded that in a population of healthy women, venous thromboembolism and arterial thrombosis are very rare adverse events during short-lasting use of oral tranexamic acid, comparable to that of combined oral contraception. A systemic review and metanalysis (Taeuber et al, 2021) reached a similar conclusion regarding the association between intravenous tranexamic acid with thromboembolic events. After analyzing a total of 216 eligible trials including 125,550 patients, their findings showed no increased risk of thromboembolic events with tranexamic acid.

While very rare, an allergic reaction to tranexamic acid may occur. To mitigate the risk of a hypersensitivity reaction, participants with a known hypersensitivity reaction to tranexamic acid will be excluded from study participation.

While relatively safe for use in most women, to mitigate the risk of thromboembolic events strict inclusion/exclusion criteria and addition of combination hormonal contraceptives and hormonal therapies as prohibited medications have been implemented within the study design to assist in mitigating the risk of thromboembolic events. Participants will be instructed to inform their physician should they have visual or ocular symptoms, or signs of an allergic reaction.

3.3.7. Summary of Benefit-Risk Assessment

Based on assessment of the benefit-risks for the study interventions administered in each cohort, the benefit-risk assessment for this study remains favorable.

4. OBJECTIVES AND ENDPOINTS

4.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effects of interventions on bruising of the buttocks of participants with cellulite after the first treatment with QWO (CCH-aaes).	• Cohorts 1 to 6: The proportion of participants whose left buttock (investigational side) demonstrates at least 1-level lower score versus the right buttock (control side) on the Investigator Assessment of Bruising Severity Scale (IABSS), at Visit 3, three to 5 days after initial QWO (CCH-aaes) injection. The IABSS is a 5-point scale ranging from 0-4, with 0 indicating no bruising or almost none, and 4 indicating very severe bruising. • Cohort 7a: The proportion of participants whose left buttock (investigational side), at Visit 3, demonstrates at least 1-level lower score versus the right buttock (control side), at Visit 8 on the Investigator Assessment of Bruising Severity Scale (IABSS). These visits are three to 5 days after initial QWO (CCH-aaes) injection for each respective buttock. • Cohort 7b: The proportion of participants whose left buttock (investigational side), at Visit 8, demonstrates at least 1-level lower score versus the right buttock (control side), at Visit 3, on the Investigator Assessment of Bruising Severity Scale (IABSS). These visits are three to 5 days after initial QWO (CCH-aaes) injection for each respective buttock.
Secondary	
• To assess the effects of interventions on bruising of the buttocks of participants with cellulite after each treatment with QWO (CCH-aaes).	• The proportion of participants whose left buttock (investigational side) demonstrates at least 1 level lower score versus the right buttock (control side) on the IABSS, by visit. The IABSS is a 5-point scale ranging from 0-4, with 0 indicating no bruising or almost none, and 4 indicating very severe bruising.

Objectives	Endpoints
	• Cohorts 7a and 7b: The proportion of participants within each cohort (ie, 7a and 7b) whose left buttock (investigational side) demonstrates at least 1-level lower score versus the right buttock (control side), on the IABSS, by corresponding treatment visit by buttock (first dose of QWO [CCH-aaes] on the investigational buttock with tranexamic acid vs the first dose of QWO [CCH-aaes] without tranexamic acid on the control side; second dose of QWO [CCH-aaes] on the investigational buttock vs second dose of QWO [CCH-aaes] on the control side; third dose of QWO [CCH-aaes] on the investigational side vs third dose of QWO [CCH-aaes] on the control side); and at each follow up visit thereafter.
• To assess the level of aesthetic improvement of cellulite after treatment with QWO (CCH-aaes).	• The proportion of participants with an improved (+1 or better) score on the Investigator-Global Aesthetic Improvement Scale (I-GAIS) by treatment area at Days 22, 43, 64, 90, 135 and 180 Visits. The I-GAIS is a 7-point scale ranging from +3 (very much improved) to -3 (very much worse).
• To assess the safety of QWO (CCH-aaes) for each study intervention in participants with cellulite.	• Proportion of participants reporting each treatment-emergent adverse events (TEAEs) throughout the study.
• To assess the safety of QWO (CCH-aaes) in participants for each study intervention in participants with cellulite.	• Proportion of participants reporting TEAEs of injection site reactions in the left buttock (investigational side) vs the right buttock (control side).
Exploratory	
• [redacted]	• [redacted]

Objectives	Endpoints
	• [redacted]

5. STUDY DESIGN

5.1. Overall Design

This is a Phase 2 open-label, self-controlled study to assess different interventions designed to reduce bruising following QWO (CCH-aaes) treatment of moderate to severe cellulite of the buttocks in adult females. The study is expected to enroll approximately 210 participants, with up to 30 participants allocated to each of 7 cohorts, such that up to 168 participants complete the study.

The study will comprise a Screening Period, a Treatment Period, and a Follow-up Period. After the Screening Period, on Day 1, participants who meet study criteria will be assigned to 1 of 7 study intervention cohorts using an interactive response technology (IRT) system (Table 1). Participants will receive QWO (CCH-aaes) in different doses, strengths (concentrations), diluent additives, depths of injection, and methods of injection in a split buttock arrangement, with the right buttock serving as the control, and the left buttock (investigational side) receiving a study intervention.

Table 1: Study Intervention Cohorts

Cohort	N	Study Interventions Tested	Left Buttock – Investigational Side	Right Buttock – Control Side
Cohort 1	30	Labeled dose (0.84 mg/ control side) of QWO (CCH-aaes) vs half the labeled dose (0.42 mg/investigational side)	Labeled injection technique (3 aliquots) using half the labeled dose (0.42 mg/ investigational side) but maintaining the labeled concentration (0.23 mg/mL).	Labeled injection technique (3 aliquots) using the labeled dose (0.84 mg/control side) and concentration (0.23 mg/mL).
Cohort 2	30	Labeled dose (0.84 mg/ buttock) and concentration of QWO (CCH-aaes) vs an ~5-fold dilution of the labeled concentration	Labeled injection technique (3 aliquots) using the labeled dose (0.84 mg/investigational side) but using a ~ 5-fold dilution (0.05 mg/mL) of the labeled concentration (0.23 mg/mL).	Labeled injection technique (3 aliquots) using the labeled dose (0.84 mg/control side) and concentration (0.23 mg/mL).
Cohort 3	30	Labeled dose (0.84 mg/ buttock) and concentration of QWO (CCH-aaes) at an injection depth of ½ inch vs ¼ inch	Labeled injection technique (3 aliquots) using the labeled dose (0.84 mg/investigational side) and concentration (0.23 mg/mL) but with an injection depth of ¼ inch.	Labeled injection technique (3 aliquots) using the labeled dose (0.84 mg/area) and concentration (0.23 mg/mL). Labeled injection at labeled depth of ½ inch.
Cohort 4	30	Labeled dose (0.84 mg/ buttock) and concentration of QWO (CCH-aaes) vs an ~2.5-fold dilution of the labeled concentration AND a single aliquot at ¼-inch depth of injection (both buttocks)	Labeled dose (0.84 mg/ investigational side) using an ~2.5-fold dilution of the labeled concentration (0.09 mg/mL) but administering only a single aliquot at ¼-inch depth per injection administered as up to 30 injections.	Labeled dose (0.84 mg/ control side) and concentration (0.23 mg/mL) but administering only a single aliquot at ¼-inch depth per injection administered as up to 12 injections.

Table 1: Study Intervention Cohorts (Continued)

Cohort	N	Study Interventions Tested	Left Buttock – Investigational Side	Right Buttock – Control Side
Cohort 5	30	Labeled dose (0.84 mg/ control side) and concentration of QWO (CCH-aaes) vs half the labeled dose (0.42 mg/investigational side) of QWO (CCH-aaes) with lidocaine 2% and epinephrine 1:200,000 utilized as diluent additive.	Labeled injection technique (3 aliquots) using half the labeled dose (0.42 mg/ investigational side) with lidocaine 2% and epinephrine 1:200,000 as diluent additive.	Labeled injection technique (3 aliquots) using the labeled dose (0.84 mg/control side) and concentration (0.23 mg/mL).
Cohort 6	30	Half of the labeled dose (0.42 mg/control side) while maintaining the labeled concentration (0.23mg/mL) of QWO (CCH-aaes) vs one-quarter of the labeled dose (0.21 mg/investigational side) at one-half the labeled concentration (0.12 mg/mL) with both the control and investigational sides receiving only 2 treatment sessions administered 6 weeks apart.	Labeled injection technique (3 aliquots) using one-quarter of the labeled dose (0.21 mg/investigational side) at one-half the labeled concentration (0.12 mg/mL). Treatment sessions will be administered 6 weeks apart.	Labeled injection technique (3 aliquots) using one-half the labeled dose (0.42 mg/control side) but maintaining the labeled concentration (0.23 mg/mL). Treatment sessions will be administered 6 weeks apart.
Cohort 7a	15	Labeled dose (0.84 mg/side) and concentration (0.23 mg/mL) of QWO (CCH-aaes) with oral tranexamic acid.	Labeled dose (0.84 mg/side), injection technique, and concentration (0.23 mg/mL) of QWO (CCH-aaes) to both the investigational and control buttocks. Participants will take tranexamic acid 1300 mg orally acid three times a day (TID) for 5 days (on Day -1 [the day prior to the day of the first injection to the investigational side], on Day 1 [the day of the first injection] and for the 3 days after the first injection of QWO (CCH-aaes) to the investigational side on Days 2-4) during the first treatment session.	
Cohort 7b	15	Labeled dose (0.84 mg/side) and concentration (0.23 mg/mL) of QWO (CCH-aaes) with oral tranexamic acid.	Labeled dose (0.84 mg/side), injection technique, and concentration (0.23 mg/mL) of QWO (CCH-aaes) to both the investigational and control buttocks. Participants will take tranexamic acid 1300 mg orally TID for 5 days (on Day 21 [the day prior to the day of the first injection to the investigational side], on Day 22 [the day of the first injection], and for the 3 days following the first injection on Days 23-25) during the second treatment session. Investigational side will not receive QWO (CCH-aaes) during the first treatment session.	

All participants will receive QWO (CCH-aaes) throughout the study to both the investigational and the control sides. Enrolled participants assigned to Cohorts 1 and 5 will receive a maximum dose of up to 0.84 mg of QWO (CCH-aaes) on the control side and a maximum dose of up to 0.42 mg of QWO (CCH-aaes) to the investigational side per treatment session (Days 1, 22, and 43) for a maximum total dose of 3.78 mg. Participants assigned to Cohorts 2, 3, and 4 will receive a maximum dose of up to 0.84 mg of QWO (CCH-aaes) per treatment area (to the control and investigational sides) per treatment session (total maximum dose of 1.68 mg per treatment

session × 3 treatment sessions [Days 1, 22, and 43] for a maximum total dose of 5.04 mg). Participants in Cohort 6 will receive a maximum dose of up to 0.42 mg of QWO (CCH-aaes) on the control side and a maximum dose of up to 0.21 mg of QWO (CCH-aaes) on the investigational side per treatment session for 2 treatment sessions (Days 1 and 43) for a maximum total dose of 1.26 mg. All participants in Cohort 7 will receive a maximum dose of up to 0.84 mg of QWO (CCH-aaes) on the control side and a maximum dose of up to 0.84 mg of QWO (CCH-aaes) to the investigational side per treatment session × 3 treatment sessions for a maximum total dose of 5.04 mg. Participants in Cohort 7a will have the investigational side treated with QWO (CCH-aaes) on Days 1, 22, and 43 with the control side treated with QWO (CCH-aaes) on Days 22, 43 and 64. Treatment will be staggered for participants in Cohort 7b vs Cohort 7a. Participants in Cohort 7b will have the investigational side treated on Days 22, 43, and 64 and the control side treated on Days 1, 22, and 43. Tranexamic acid will be provided by the sponsor and self-administered by all participants enrolled in Cohort 7. Participants in Cohort 7a will take tranexamic acid 1300 mg orally TID for 5 days (prior to the day of the first injection of QWO (CCH-aaes) of the investigational buttock (Day -1), the day of the first injection (Day 1). and for the 3 days following the first injection (Days 2 to 4). Participants in Cohort 7b will take tranexamic acid orally TID for 5 days (prior to the day of the second injection on Day 21, the day of the second injection (Day 22) and for the 3 days following the second injection (Day 23 to Day 25).

Bruising will be observed throughout the study. In an effort to standardize the risk and scope of bruising, the investigational and control sides in Cohorts 1 and 5 should be treated with the same concentration, same number of injections, and same number of aliquots per injection, but at different doses per injection or addition of diluent additive. In Cohort 2, the investigational and control sides will be treated with the same dose and number of injections, but the concentrations will vary. In Cohort 3, the investigational and control sides will be treated with the same dose, aliquots per injection, and number of injections, but at different injection depths. In Cohort 4, the dose will remain consistent between buttocks, but the number of injections and concentration will vary between the investigational and control sides. In Cohort 6, the investigational and control sides will be treated with the same number of injections, the same number of aliquots per injection, and an extended treatment interval, but at different doses and concentrations. In Cohort 7, the investigational and control sides should be treated with the labeled dose, injection technique and concentration of QWO (CCH-aaes) during each treatment visit, but oral tranexamic acid will be given before and after the first treatment with QWO (CCH-aaes) for the investigational buttock.

Participants will return to the site for 4 follow-up visits (1 to 2 days, 3 to 5 days, 6 to 9 days, and 10 to 14 days) after each treatment of QWO (CCH-aaes), for additional evaluations and digital photography to monitor the severity of bruising. Digital photographs will be obtained using a standardized method at each visit throughout the study. The effect of the different QWO (CCH-aaes) doses, strengths (concentrations), diluent additives, depths of injection, and methods of injection on the severity of bruising will be assessed by the investigator using the IABSS. The investigators will be evaluating the left (investigational) and right (control) buttocks separately with the IABSS. To assess the effect of QWO (CCH-aaes) on the severity of cellulite (efficacy), the investigator will complete the I-GAIS. Each buttock will be evaluated independently.

After completing the Treatment Period, participants will return for 3 follow-up visits at Days 90, 135, and 180 (EOS Visit).

At the EOS visit, the investigator will complete the I-GAIS and safety assessments will be evaluated. The total duration of study participation, including the Screening (28 days), Treatment (90 days) and Follow-up Periods (90 days) is approximately 208 days.

5.2. Scientific Rationale for 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) and diminishes after the second or third treatment sessions (CSR EN3835-205; CSR EN3835-302, CSR EN3835-303). In most participants, bruising typically resolves within 21 days.

Given the prevalence of bruising after administration of QWO (CCH-aaes) there is an expressed interest in evaluating if modifications of dose, strength (concentration), diluent additives, and methods of administration associated with administration of QWO (CCH-aaes) can reduce or potentially diminish bruising post injection.

To examine the effect of these interventions, the buttocks of participants will be treated in a split-buttock manner. Each buttock will receive QWO (CCH-aaes); the right buttock will serve as a control and the left buttock will be treated with a study intervention designed to potentially decrease bruising. Among the study interventions (designed to decrease bruising) to be evaluated include using half the labeled dose (0.42 mg) of QWO (CCH-aaes) (Cohort 1); the labeled concentration (2.3 mg/mL) vs an approximate 5-fold diluted concentration (Cohort 2); the labeled dose and concentration at the labeled ½-inch depth of injection vs a shallower injection depth (¼ inch; Cohort 3); the labeled concentration vs a 2.5-fold diluted concentration while maintaining a shallower injection depth (¼ inch) as a common factor (Cohort 4); and the labeled dose and concentration vs half-dose QWO (CCH-aaes) (0.42 mg) with lidocaine and epinephrine as a diluent additive (Cohort 5); half the labeled dose (0.42 mg) of QWO (CCH-aaes) and one-quarter of the labeled dose (0.21 mg) at one-half the labeled concentration (0.12 mg/mL) of QWO (CCH-aaes) (Cohort 6). For Cohort 6, there will be 2 treatment sessions given 6 weeks apart.

Support for the use of more dilute concentrations of QWO (CCH-aaes) is derived from Studies EN3835-209 and EN3835-224 (see Section 3.3.3). Support for half-dose and quarter-dose of QWO (CCH-aaes) is derived from Study AUX-CC-831 (see Section 3.3.5). Study AUX-CC-831 tested QWO (CCH-aaes) at 0.06 mg, 0.48 mg, and 0.84 mg. The study demonstrated improvement in a variety of parameters with the 0.06 mg dose, and investigators determined that approximately 45% of participants had improvement in their cellulite, although it was not statistically significant. The 0.48 mg dose was associated with statistically significant improvements. Therefore, in this study, Cohort 6 will evaluate a QWO (CCH-aaes) dose between the lowest and the middle dose given in Study AUX-CC-831, to determine whether there will be a decrease in bruising while experiencing an improvement in cellulite.

Administering QWO (CCH-aaes) using a shallower depth of injection (¼ inch) rather than the labeled depth (½ inch) injection is supported by the results of a study conducted by Whipple et al (2021). Using ultrasound, the investigators identified the depth of the fibrous septa causing cellulite and delineated their anatomical orientation. The average skin thickness in 92 buttock dimples was 0.28 cm and the depth of superficial fascia was 0.84 cm. A depth of a ¼-inch

(0.64-cm) injection would place the tip of the needle within the superficial subcutaneous tissue. The majority of fascial bands originate from the superficial fascia and therefore using a shallower depth of injection could facilitate the lysis of the causative bands while potentially avoiding more expanded vasculature when using a deeper injection. This approach is further supported by the method used in a subcision technique for cellulite, which uses a depth of 0.06 cm to 0.10 cm (Green and Cohen, 2015).

In Study EN3835-224, a more dilute concentration of QWO (CCH-aaes) was used to treat cellulite. In this study's 2-aliquot cohort, a concentration of QWO (CCH-aaes) 0.05 mg/mL, combined with injecting QWO (CCH-aaes) at ¼-inch and ½-inch depths, was demonstrated to be safe and well-tolerated with a low incidence of discoloration. In this study (APHRODITE-1), Cohorts 2 (~5-fold dilution) and 4 (~2.5-fold dilution) will evaluate using lower concentrations of QWO (CCH-aaes). Cohort 3 will evaluate using a shallower depth of injection. Taken together, this study will attempt to isolate the impact of each of these variables on bruising.

For Cohort 7 the labeled dose, concentration and depth will be used throughout the study, however, there will be 2 sub-cohorts (7a and 7b) each with asynchronous treatment sessions of QWO (CCH-aaes) and different timing of treatment with oral tranexamic acid.

- For Cohort 7a, oral tranexamic acid will be provided by the sponsor and self-administered by participants, before and after the investigational buttock receives the first dose of QWO (CCH-aaes) on Day 1. The control buttock will receive the first treatment of QWO (CCH-aaes) on Day 22 to allow for the systemic effects of oral tranexamic acid to dissipate.
- For Cohort 7b, tranexamic acid will be provided by the sponsor and self-administered, orally, by participants, before and after the investigational buttock receives the first dose of QWO (CCH-aaes), on Day 22. This corresponds to the second dose of QWO (CCH-aaes) for the control buttock. This allows for a treatment session of the control buttock (initial treatment) without the presence of oral tranexamic acid.

Staggering administration of tranexamic acid with QWO (CCH-aaes) will allow for a comparison between the investigational and control buttocks within a cohort and between cohorts.

- See Section 3.3.6 for the rationale for administration of tranexamic acid.

The endpoints will evaluate the proportion of participants with a reduction (improvement) in bruising severity on the variable buttock receiving study intervention vs the control side, as reported by the investigator.

5.2.1. 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, ensuring the safety of clinical study participants is our primary concern. In addition, the integrity of data obtained from clinical studies must be ensured.

To ensure participant safety and protect data integrity with Endo's approval, Endo may allow remote visits for certain safety assessments. This is aligned with the FDA Guidance on *Conduct*

of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency (March 2020, updated 30 August 2021).

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

- A participant who had received any dose of QWO (CCH-aaes) in the study prior to an interruption will be allowed to continue in the study.

5.3. Justification for Endpoints

The primary endpoint, for Cohorts 1 to 6, will be the investigator's assessment of bruising in each buttock based on observed, in-person assessments on the IABSS, at Visit 3, three to five days after the initial QWO (CCH-aaes) injection. This endpoint will be assessed after the first treatment visit since this is historically when bruising has been the most severe. For Cohorts 1-6 this will occur at Visit 3.

The primary endpoint for Cohort 7a is the proportion of participants whose left buttock (investigational side), at Visit 3, demonstrates at least 1-level lower score versus the right buttock (control side), at Visit 8 on the IABSS. The primary endpoint for Cohort 7b is the proportion of participants whose left buttock (investigational side), at Visit 8, demonstrates at least 1-level lower score versus the right buttock (control side), at Visit 3, on the IABSS. These visits are three to 5 days after initial QWO (CCH-aaes) injection for each respective buttock.

For Cohorts 7a and 7b, similar to Cohorts 1 to 6, this endpoint will be assessed after the first treatment visit since this is historically when bruising is most severe. In Cohorts 1 to 6, for all endpoints and in Cohorts 7a and 7b, for all endpoints other than the primary endpoint, all participants enrolled in the study will serve as their own control, since the study is designed to evaluate the effect of using different doses, different concentrations, and different methods of injection for QWO (CCH-aaes) applied unilaterally to the investigational side. The bruising on the left-buttock (investigational side) will be compared to the right buttock (control side).

The comparison of buttocks for the primary endpoint by visit for Cohorts 7a and 7b is shown in Figure 1.

Figure 1: Primary Endpoints for Cohorts 7a and 7b

Cohort 7a		
	Control Side	**Investigational Side**
Day -1	TXA (Study Days -1,1,2,3,4)	
Day 1	-	QWO Dose 1
Day 21		
Day 22	QWO Dose 1	QWO Dose 2
Day 43	QWO Dose 2	QWO Dose 3
Day 64	QWO Dose 3	-

Cohort 7b		
	Control Side	**Investigational Side**
Day -1		
Day 1	QWO Dose 1	-
Day 21	TXA (Study Days 21,22,23,24,25)	
Day 22	QWO Dose 2	QWO Dose 1
Day 43	QWO Dose 3	QWO Dose 2
Day 64	-	QWO Dose 3

Given the staggered treatment with QWO (CCH-aaes) within cohorts to the investigational and control sides, additional within cohort comparisons can be made. A secondary endpoint is the proportion of participants within each cohort (ie, 7a and 7b) whose left buttock (investigational side) demonstrates at least 1-level lower score versus the right buttock (control side), on the IABSS, by corresponding treatment visit. Given the staggered timing of the first dose of QWO (CCH-aaes), an asynchronous comparison for each respective buttock within cohorts will be made. The comparison of buttocks is shown in Figure 2.

Figure 2: Secondary Endpoints (Within Cohort Comparison) for Cohorts 7a and 7b

Cohort 7a		
	Control Side	**Investigational Side**
Day -1	TXA (Study Days -1,1,2,3,4)	
Day 1	-	QWO Dose 1
Day 21		
Day 22	QWO Dose 1	QWO Dose 2
Day 43	QWO Dose 2	QWO Dose 3
Day 64	QWO Dose 3	-

Cohort 7b		
	Control Side	**Investigational Side**
Day -1		
Day 1	QWO Dose 1	-
Day 21	TXA (Study Days 21,22,23,24,25)	
Day 22	QWO Dose 2	QWO Dose 1
Day 43	QWO Dose 3	QWO Dose 2
Day 64	-	QWO Dose 3

[redacted]

[redacted]

Figure 3: [redacted]

5.4. Justification for Dose

The dosage of QWO (CCH-aaes) selected for this study for the control side is the labeled dose or lower. The labeled dose of 1.68 mg (0.84 mg per region) for a single treatment session and cumulative dose of 5.04 mg (after 3 treatment sessions each 21 days apart) when used at a concentration of 0.23 mg/mL have been shown to be safe and well-tolerated.

For Cohorts 1 and 5, half the labeled dose (0.42 mg per investigational side) will be administered to determine if the dose is associated with the severity of bruising. A similar dose was implemented in Study AUX-CC-831, a dose ranging study, where improvements were also observed in cellulite appearance at a dose of 0.48 mg per treatment region. The total cumulative dose in the investigational side and the control side for the participants allocated to these cohorts will be QWO (CCH-aaes) 3.78 mg (after 3 treatment sessions each 21 days apart).

For Cohort 6, half the labeled dose (0.42 mg for the control side) and one-quarter of the labeled dose at one-half the labeled concentration (0.21 mg at a concentration of 0.12 mg/mL for the investigational side) will be administered as 2 treatment sessions, 6 weeks apart. This is to determine whether a decrease in the dose and concentration combined with lengthening the time between treatment administration will decrease bruising and subsequent discoloration (refer to Section 5.2 for additional information).

For Cohort 7a and 7b, the labeled dose of QWO (CCH-aaes) will be administered. This is the first company sponsored study of tranexamic acid use to reduce bleeding due to QWO (CCH-aaes) which is 1300 mg TID for 5 days. Tranexamic acid will be taken during a single treatment session to help evaluate the potential effect in reducing bruising during QWO administration. Tranexamic acid will only be given during the first treatment session for the investigational buttock. The systemic effects are not expected to persist into the subsequent treatment visit.

5.5. End of Study Definition

A participant is considered to have completed the study if the participant has completed the Day 180 visit.

The end of the study is defined as the completion of the final assessment (Day 180) for the last participant enrolled in the study.

6. SELECTION AND WITHDRAWAL OF PARTICIPANTS

6.1. Participant Inclusion Criteria

Diagnosis and Inclusion Criteria

To be eligible to participate in the study, at the Screening Visit and on Day 1, participants must:

Age and Sex

1. Be female ≥ 18 and ≤ 60 years of age at the time of consent.

Disease Characteristics

2. Have a body mass index (BMI) of 18 to < 32 kg/m^2 and intends to maintain stable body weight during the study (a variation of ≤10% from baseline body weight is permitted).
3. Have both buttocks with a score of 3 or 4 (moderate or severe cellulite) as reported by the investigator using the CR-PCSS.
4. Have a Hexsel Cellulite Severity Scale (CSS) Total Score of ≤ 12.
5. Has a Fitzpatrick Skin Type of I-IV.

Type of Participant

6. Cohort 1 to 6: Be of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or postmenopausal with no history of menstrual flow in the 12 months prior to the Screening Visit); or, if of childbearing potential, be

nonpregnant, nonlactating and agree to use effective contraception when with a male partner for the duration of the study and for 28 days after any active treatment period. Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, and injections), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), surgical sterilization of the male partner, and abstinence. Cohort 7: Combination hormonal contraceptives cannot be used.

7. Be willing and able to comply with all protocol required visits and assessments, including photography.
8. Be willing to apply sunscreen to the treatment areas before each exposure to the sun for the duration of the study (from the Screening Visit through the Day 180/Early Termination [ET] Visit).
9. Be willing to avoid the use of tanning beds, tanning booths or tanning lamps as well as outdoor tanning for the duration of the study (from the Screening Visit through the Day 180/Early Termination Visit).
10. Be a non-employee or non-family member of the sponsor or research staff conducting the study.

Informed Consent

11. Be adequately informed and understand the nature and risks of the study and be able to provide consent.

6.2. Participant Exclusion Criteria

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

Medical Conditions

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 keloid 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 participant'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. Is pregnant and/or is breast-feeding or plans to become pregnant and/or to breast-feed during the course of the study.

3. Has any of the following local conditions in the areas to be treated:
    a. History of lower extremity thrombosis or post-thrombosis syndrome.
    b. A current vascular disorder (eg, vasculitis, varicose veins, telangiectasia).
    c. Inflammation or active infection (including lesions that indicate an active infection).
    d. Active cutaneous alteration including, but not limited to, rash, eczema or psoriasis.
    e. A tattoo or other artificially inflicted body marker in the treatment area.
    f. A mole located within 2 cm of any injection site.

Prior/Concomitant Therapy

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, such as (clopidogrel [Plavix®], including aspirin) at any dose within 14 days of treatment.
    b. Anticoagulants, such as warfarin (Coumadin®); heparin analogues, or Factor Xa inhibitors, 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, gingko biloba, ginger, St John's Wort, 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. Has received treatment with tranexamic acid within 30 days before treatment.
5. Has used any of the following for the treatment of cellulite on either buttock within the specified timelines, or intends to use any of the following at any time during the study:
    a. Liposuction during the 12-month period before dosing with study intervention.
    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) during the 12-month period before injection of study intervention.
    c. Any investigational treatment for cellulite during the 12-month period before the injection of study intervention.
    d. Endermologie or similar treatments during the 6-month period before injection of study intervention.
    e. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate cellulite during the 2-week period before injection of study intervention.
6. Intends to initiate an intensive sport or exercise program during the study.
7. Intends to initiate an intensive weight reduction program during the study.
8. Intends to engage in strenuous activity within 48 hours of study intervention administration.

9. Has recently tanned or intends to tan (outdoors or indoors). This includes, but is not limited to, the use of any tanning products or tanning booths/beds/lamps during the study.
10. Has a history of hypersensitivity or allergy to collagenase or any other excipient of CCH.
11. For Cohort 5: has a known history of hypersensitivity to local anesthetics of the amide type or a history of hypersensitivity to epinephrine.
12. For Cohort 5: are concurrently receiving to certain drugs like nitrites, antibiotics, or anticonvulsants, or any other drug which increases the risk of methemoglobinemia.
13. Has any condition(s) that, in the investigator's opinion, might indicate the participant to be unsuitable for the study.

Prior/Concurrent Clinical Study Experience

14. Has participated in a previous investigational study of CCH (EN3835, QWO [CCH-aaes]) or received any collagenase treatments at any time prior to treatment in this study for the treatment of cellulite of the buttocks.
15. Has received treatment with any investigational product within 30 days (or 5 half-lives, whichever is longer) of the start of the Screening Visit or throughout the study.

Additional Exclusion Criteria for Cohort 7

In addition to the applicable aforementioned exclusion criteria, participants enrolling in Cohort 7 will be excluded from study participation if the participant:

Medical Conditions

16. Has any of the following medical conditions:
    a. history of venous or arterial thromboembolism or current thromboembolic disease.
    b. history of or current renal impairment.
    c. serum creatinine concentration > 1.4 mg/dL at Screening.

Prior/Concomitant Therapy

17. Requires the following concomitant medications during the study and cannot discontinue these medications within the time specified before QWO (CCH-aaes) treatment:
    a. concurrently taking combination hormonal contraceptives.
    b. concurrently undergoing hormone replacement therapy.
    c. has a known history of hypersensitivity to tranexamic acid.
    d. is a current smoker of nicotine or cannabinoids.

6.3. Lifestyle Considerations

Participants will be instructed to refrain from strenuous exercise for 48 hours after each treatment with QWO (CCH-aaes) and will be instructed to not initiate intensive sports, exercise, or weight reduction programs during the study.

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

Participants should not use any tanning booth/beds/lamps, or tanning products during the study.

Participants in Cohort 7 should avoid smoking (including vaping, nicotine, or marijuana cigarettes) during the study.

6.4. Screen Failures

Screening procedures will be conducted during the Screening Period (Day -28 to Day -1).

Participants who do not meet all of the eligibility criteria will be deemed a screen failure and the following information must be recorded for all participants who are screen failures:

- Demography (age, gender, race/ethnicity).
- Reason for screen failure.
- Which eligibility criterion was not met.
- Any AEs (including SAEs) experienced by the participant.

No participant can be rescreened during this study.

7. STUDY INTERVENTION

Study intervention comprises QWO (CCH-aaes) and different doses, different concentrations, and different methods of administration of QWO (CCH-aaes) including diluent additives designed to decrease bruising.

7.1. Selection and Marking of Dimples

To ensure that the non-interventional buttock can serve as a control, and that a similar level of injection site bruising may be expected, participants should have a similar number of dimples requiring treatment on each buttock. Participants in Cohorts 1, 2, 3, 5, and 6 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 following the first treatment session, 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.

Participants in Cohort 7 can be treated with up to 12 injections of QWO (CCH-aaes) on each buttock. Dimples will only need to be marked on the days of treatment. In Cohort 7a, on Day 1 only, the investigational buttock will be treated with QWO (CCH-aaes) and on Day 64 only the control buttock will be treated with QWO (CCH-aaes). On Days 22 and 43, both buttocks will be treated with QWO (CCH-aaes). In Cohort 7b, on Day 1, only the control buttock will be treated with QWO and on Day 64, only the investigational buttock will be treated with QWO (CCH-aaes). On Days 22 and 43, both buttocks will be treated with QWO (CCH-aaes).

For treatment, a qualified designated physician will select up to 12 dimples within each treatment area (each buttock) that are well-defined, evident when the participant is standing, and suitable for treatment.

For each dimple selected for treatment, a qualified designated physician 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 qualified designated physician will then use a surgical marker to circle each of the dimples selected for treatment.

In Cohort 4, the investigational side will receive QWO (CCH-aaes) at a labeled dose (0.84 mg) using a 2.5-fold diluted concentration (0.09 mg/mL) for up to 30 injections. The investigator will adapt an injection site stencil, which will be transferred to the location of injection. The number of injections will be adjusted by the clinician to best address the clinical presentation and need for treatment. QWO (CCH-aaes) will be administered as a single aliquot at a ¼-inch depth per injection. The control side will receive QWO (CCH-aaes) at the labeled dose (0.84 mg/treatment area) and concentration (0.23 mg/mL) but administering only a single aliquot at ¼-inch depth per injection administered as 12 injections.

7.2. Treatment Administration

7.2.1. QWO (CCH-aaes)

QWO (CCH-aaes) and the other study interventions to potentially decrease bruising will be provided by Endo. The dose and volume of QWO (CCH-aaes) and other study interventions are detailed in Table 2. The dose of tranexamic acid is provided in Table 3.

Table 2: Study Intervention (CCH-aaes) by Buttock

Cohort and Treatment Area	Dose per Each Injection	Injection Volume per Each Injection	Number of Injections at Each Treatment Visit	Dose (mg) at Each Treatment Visit	Injection Volume (mL) per Each Treatment Visit	Concentration (mg/mL)
Cohort 1 Right Buttock (control side)	CCH-aaes 0.07 mg	0.3 mL (given as three 0.1 mL aliquots)	Up to 12	Up to 0.84 mg	Up to 3.6 mL	0.23 mg/mL
Cohort 1 Left Buttock (investigational side)	CCH-aaes 0.035 mg	0.15 mL (given as three 0.05 mL aliquots)	Up to 12	Up to 0.42 mg	Up to 1.8 mL	0.23 mg/mL
Cohort 2 Right Buttock (control side)	CCH-aaes 0.07 mg	0.3 mL (given as three 0.1 mL aliquots)	Up to 12	Up to 0.84 mg	Up to 3.6 mL	0.23 mg/mL
Cohort 2 Left Buttock (investigational side)	CCH-aaes 0.07 mg	1.5 mL (given as three 0.5 mL aliquots)	Up to 12	Up to 0.84 mg	Up to 18 mL	0.05 mg/mL
Cohort 3 Right Buttock (control side)	CCH-aaes 0.07 mg	0.3 mL (given as three 0.1 mL aliquots)	Up to 12	Up to 0.84 mg	Up to 3.6 mL	0.23 mg/mL
Cohort 3 Left Buttock (investigational side)	CCH-aaes 0.07 mg	0.3 mL (given as three 0.1 mL aliquots)	Up to 12	Up to 0.84 mg	Up to 3.6 mL	0.23 mg/mL
Cohort 4 Right Buttock (control side)	CCH-aaes 0.07 mg	0.3 mL (given as one 0.3 mL aliquot)	Up to 12	Up to 0.84 mg	Up to 3.6 mL	0.23 mg/mL
Cohort 4 Left Buttock (investigational side)	CCH-aaes 0.028 mg	0.3 mL (given as one 0.3 mL aliquot)	Up to 30	Up to 0.84 mg	Up to 9 ml	0.09 mg/mL
Cohort 5 Right Buttock (control side)	CCH-aaes 0.07 mg	0.3 mL (given as three 0.1 mL aliquots)	Up to 12	Up to 0.84 mg	Up to 3.6 mL	0.23 mg/mL
Cohort 5 Left Buttock (investigational side)	CCH-aaes 0.035 mg	0.15 mL (given as three 0.05 mL aliquots)	Up to 12	Up to 0.42 mg	Up to 1.8 mL	0.23 mg/mL
	Lidocaine 2% and Epinephrine 1:200,000			36 mg Lidocaine 9 mcg Epinephrine		Lidocaine 20 mg/mL Epinephrine 5 mcg/mL
Cohort 6 Right Buttock (control side)	CCH-aaes 0.035 mg	0.15 mL (given as three 0.05 mL aliquots)	Up to 12	Up to 0.42 mg	Up to 1.8 mL	0.23 mg/mL
Cohort 6 Left Buttock (investigational side)	CCH-aaes 0.018 mg	0.15 mL (given as three 0.05 mL aliquots)	Up to 12	Up to 0.21 mg	Up to 1.8 mL	0.12 mg/mL

Table 2: Study Intervention (CCH-aaes) by Buttock (Continued)

Cohort and Treatment Area	Dose per Each Injection	Injection Volume per Each Injection	Number of Injections at Each Treatment Visit	Dose (mg) at Each Treatment Visit	Injection Volume (mL) per Each Treatment Visit	Concentration (mg/mL)
Cohort 7a Right Buttock (control side)[a]	CCH-aaes 0.07 mg	0.3 mL (given as three 0.1 mL) aliquots)	Up to 12	Up to 84 mg	Up to 3.6 mL	0.23 mg/mL
Cohort 7a Left Buttock (investigational side)[b]	CCH-aaes 0.07 mg	0.3 mL (given as three 0.1 mL	Up to 12	Up to 84 mg	Up to 3.6 mL	0.23 mg/mL
Cohort 7b Right Buttock (control side)[c]	CCH-aaes 0.07 mg	0.3 mL (given as three 0.1 mL) aliquots)	Up to 12	Up to 84 mg	Up to 3.6 mL	0.23 mg/mL
Cohort 7b Left Buttock (investigational side)[d]	CCH-aaes 0.07 mg	0.3 mL (given as three 0.1 mL	Up to 12	Up to 84 mg	Up to 3.6 mL	0.23 mg/mL

[a] The investigational side will be treated with QWO (CCH-aaes) on Days 1, 22, and 43.
[b] The control side will be treated with QWO (CCH-aaes) on Days 22, 43, and 64.
[c] The investigational side will be treated with QWO (CCH-aaes) on Days 22, 43, and 64.
[d] The control side will be treated with QWO (CCH-aaes) on Days 1, 22, and 43.

Table 3: Study Intervention (Tranexamic Acid) in Cohort 7

Product Name	Tranexamic acid
Type	Drug
Dose Formulation	Tablet
Unit Dose Strengths	650 mg
Dose amount and Frequency	2 × 650 mg tablets (1300 mg) orally TID × 5 days
Route of Administration	Oral
Sourcing	Provided centrally by sponsor
Packaging and Labeling	Product will be provided in bottles of 30 tablets each.

7.2.2. Cohorts 1-5, Control Sides, QWO (CCH-aaes) – Labeled Dose and Concentration

Dosage and Mode of Administration: For the control side, a dose of up to 0.84 mg of QWO (CCH-aaes) up to 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 with the exception of Cohort 4 in which a single 0.3 mL injection will be utilized) for a total dose of 1.68 mg. There will be 3 treatment visits at intervals of approximately 21 days as described in schedule of assessments. All injections will be given at the labeled depth of ½ inch, except in Cohort 3 and 4, where injections will be given at a depth of ¼ inch.

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 must be recorded. The volume and dose of injection at each treatment visit for each buttock will be prepared per the Pharmacy Manual and injected per the Injection Guide in the Study Operations Manual.

7.2.3. Cohort 1, Investigational Side Only, QWO (CCH-aaes) – Half-dose of Labeled Concentration

Dosage and Mode of Administration: For the investigational side, a dose of up to 0.42 mg of QWO (CCH-aaes) up to 1.8 mL will be administered as up to 12 subcutaneous injections (0.15-mL injection administered as three 0.05-mL aliquots per injection). There will be 3 treatment visits at intervals of approximately 21 days as described in schedule of assessments. The volume and dose of injection at each treatment visit for each buttock will be prepared per the Pharmacy Manual and injected per the Injection Guide in the Study Operations Manual.

7.2.4. Cohort 2, Investigational Side Only, QWO (CCH-aaes) – Labeled Dose ~5-fold Diluted Concentration

Dosage and Mode of Administration: For the investigational side, a dose of up to 0.84 mg of QWO (CCH-aaes) in up to 18 mL will be administered as up to 12 subcutaneous injections (1.5-mL injection administered as three 0.5-mL aliquots per injection). There will be 3 treatment visits at intervals of approximately 21 days as described in schedule of assessments. The volume and dose of injection at each treatment visit for each buttock will be prepared per the Pharmacy Manual and injected per the Injection Guide in the Study Operations Manual.

7.2.5. Cohort 3, Investigational Side Only, QWO (CCH-aaes) – Labeled Dose and Concentration at ¼-inch Depth

Dosage and Mode of Administration: For the investigational side, a dose of up to 0.84 mg of QWO (CCH-aaes) up to 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 at a depth of ¼ inch) for a total dose of 1.68 mg. There will be 3 treatment visits at intervals of approximately 21 days as described in schedule of assessments. The volume and dose of injection at each treatment visit for each buttock will be prepared per the Pharmacy Manual and injected per the Injection Guide in the Study Operations Manual.

7.2.6. Cohort 4, Investigational Side Only, QWO (CCH-aaes) – Labeled Dose ~2.5-fold Diluted Concentration at ¼-inch Injection Depth

Dosage and Mode of Administration: For the investigational side, a dose of up to 0.84 mg of QWO (CCH-aaes) up to 9 mL will be administered as up to 30 subcutaneous injections (0.3-mL injection administered as one 0.3-mL aliquot per injection at a depth of ¼ inch) for a total dose of 1.68 mg. There will be 3 treatment visits at intervals of approximately 21 days as described in schedule of assessments. The volume and dose of injection at each treatment visit for each buttock will be prepared per the Pharmacy Manual and injected per the Study Operations Manual.

7.2.7. Cohort 5, Investigational Side Only, QWO (CCH-aaes) – Half-dose at a Labeled Concentration with Lidocaine 2% and Epinephrine 1:200, 000 as a Diluent Additive

Dosage and Mode of Administration: For the investigational side, a dose of up to 0.42 mg of QWO (CCH-aaes) up to 1.8 mL will be administered as up to 12 subcutaneous injections (0.15-mL injection administered as three 0.05-mL aliquots per injection). There will be 3 treatment visits at intervals of approximately 21 days as described in the Schedule of Assessments. The volume and dose of injection at each treatment visit for each buttock will be prepared per the Pharmacy Manual and injected per the Injection Guide in the Study Operations Manual. QWO (CCH-aaes).

7.2.8. Cohort 6, Investigational Side Only, QWO (CCH-aaes) – Quarter-dose with One-Half Concentration and Two Treatment Sessions at Approximately 42 Days Between Visits

Dosage and Mode of Administration: For the investigational side, a dose of up to 0.21 mg of QWO (CCH-aaes) up to 1.8 mL will be administered as up to 12 subcutaneous injections (0.15-mL injection administered as three 0.05-mL aliquots per injection). Half the standard concentration (0.12 mg/mL) will be used.

There will be 2 treatment visits at an interval of approximately 42 days as described in Schedule of Assessments for Cohort 6. The volume and dose of injection at each treatment visit for each buttock will be prepared per the Pharmacy Manual and injected per the Injection Guide in the Study Operations Manual.

7.2.9. Cohort 6, Control Side Only, QWO (CCH-aaes) – Half of the Labeled Dose (0.42 mg/control side) Using the Labeled Concentration (0.23 mg/mL) at Approximately 42 Days between Visits

For the control side, a dose of up to 0.42 mg of QWO (CCH-aaes) up to 1.8 mL will be administered as up to 12 subcutaneous injections (0.15 mL injection administered as three 0.05-mL aliquots per injection). The standard concentration (0.23 mg) will be used.

There will be 2 treatment visits at an interval of approximately 42 days as described in the Schedule of Assessments for Cohort 6. The volume and dose of injection at each treatment visit for each buttock will be prepared per the Pharmacy Manual and injected per the Injection Guide in the Study Operations Manual.

7.2.10. Cohort 7, Labeled Dose and Concentration of QWO (CCH-aaes) with Tranexamic Acid

Dose and Mode of Administration: Cohorts 7a and 7b: For the control and investigational sides, a dose of up to 0.84 mg of QWO (CCH-aaes) up to 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).

Cohort 7a:

- The investigational side will be treated with QWO (CCH-aaes), on Days 1, 22, and 43.

- The control side will be treated with QWO (CCH-aaes) on Days 22, 43, and 64.
- Tranexamic acid 1300 mg orally TID×5 days, prior to the day of the first injection, on the day of the first injection (Day 1), and for 3 days after the first injection (Days 2, 3, and 4). Tranexamic acid will be provided by the sponsor and self-administered by the participant.

Cohort 7b:

- The investigational side will be treated with QWO (CCH-aaes), on Days 22, 43, and 64.
- The control side will be treated with QWO (CCH-aaes) on Days 1, 22, and 43.
- Tranexamic acid 1300 mg orally TID×5 days, prior to the day of the first injection of QWO (CCH-aaes) (Day 21), on the day of the first injection (Day 22), and for 3 days after the first injection (Days 23, 24, and 25). Tranexamic acid will be provided by the sponsor and self-administered by the participant.

7.2.11. Care Procedures After Injection

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

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

7.2.12. Preparation/Handling/Storage/Accountability

QWO (CCH-aaes) 0.92 mg, its diluent (4 mL), and lidocaine (2%) and epinephrine (1:200,000) will be supplied by the sponsor. Each vial of study intervention and diluent will be minimally labeled with contents, sponsor identification, storage, administration/use, and appropriate caution statements. QWO (CCH-aaes) and the diluent must be kept in a temperature-monitored refrigerator (2°C to 8°C) with locked access until used or returned to the sponsor (or designee).

Tranexamic acid, oral tablets will be supplied by the sponsor. Tranexamic acid will also be labeled with contents, sponsor identification, storage, administration/use and appropriate caution statements. Each participant will receive 1 bottle containing 30 tablets of tranexamic acid 650 mg oral tablets. Oral tranexamic acid can be stored at room temperature.

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

Only participants enrolled in the study will receive study intervention and only authorized study staff will dispense study intervention.

In accordance with the International Council for Harmonisation (ICH) requirements, at all times the investigator will be able to account for all study intervention furnished to the study site. An accountability record will be maintained for this purpose. The investigator must maintain accurate records indicating dates and quantity of study intervention received, to whom it was administered (participant-by-participant accounting), and accounts of any study intervention accidentally or deliberately destroyed.

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

7.3. Measures to Minimize Bias

This is an open label study, however, the study intervention for each participant will be assigned in a 1:1:1:1:1:1:1 ratio using an IRT.

7.3.1. Interactive Response Technology

The investigator or designee will utilize the IRT system to register participants at screening. Each participant's unique identification (ID) number will be assigned by the IRT system and will be used to identify the participant for the duration of the study within all systems and documentation.

If a participant is not eligible to receive study intervention, or should discontinue from the study, the participant ID number will not be reassigned to another participant. Specific instructions for the use of the IRT system will be included in the IRT User Manual.

The investigator must maintain a participant master log linking the participant ID to the participant's name. The investigator must follow all applicable privacy laws in order to protect a participant's privacy and confidentiality. Information that could identify a participant will be masked on material received by the sponsor.

7.4. Study Intervention Compliance

Participants will only receive QWO (CCH-aaes) at the study site and all dosing information will be recorded for each participant at each visit. Drug inventory will be maintained in the IRT. Used drug and diluent vials and 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 9.5).

For participants enrolled in Cohort 7a, tranexamic acid will be dispensed prior to the Day 1 visit. Participants will be expected to bring the bottle of tranexamic acid to follow up Visits 2 and 3 to conduct a compliance check. Participants will return the bottle of tranexamic acid at follow-up Visit 4.

For participants enrolled in Cohort 7b, tranexamic acid will be dispensed prior to the Day 22 Visits. Participants will be expected to bring the bottle of tranexamic acid to follow up Visits 7 and 8 to conduct a compliance check. Participants will return the bottle of tranexamic acid at follow-up Visit 9.

7.5. Prior and Concomitant Medications and Procedures

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior medications (taken within the 90 days prior to the Screening Visit) will be recorded. All prior EN3835, CCH, XIAFLEX®, and QWO (CCH-aaes) use should be recorded.

The start and stop date, dose, unit, frequency, route of administration, and indication for all concomitant (taken from the Baseline Visit through the Day 180 Visit) medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) received will be recorded.

7.5.1. Prohibited Medications/ Procedures

During the study, the following treatments are prohibited:

- Antiplatelet medication, such as (clopidogrel [Plavix®], including aspirin) at any dose within 14 days of treatment.
- Anticoagulants, such as warfarin (Coumadin®); heparin analogues, or Factor Xa inhibitors, within 14 days of treatment.
- NSAIDs, such as ibuprofen (Motrin®, Advil®) and naproxen (Aleve®), 7 days before the study.
- Any medications (eg, corticosteroids, certain antidepressants [eg, citalopram, fluoxetine], nutritional/homeopathic supplements [eg, fish oil, Vitamin E, omega 3, gingko biloba, ginger, St John's Wort, 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.
- Tranexamic acid within 30 days before treatment.
- For participants allocated to Cohort 5, drugs associated with methemoglobinemia.
- For participants allocated to Cohort 7, combination hormonal contraceptives and hormonal therapy received during the study.

During the study, the following procedures are prohibited in the buttocks:

- Liposuction during the 12-month period before dosing with study intervention.
- Injections radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis or surgery during the 12-month period before injection of study intervention.
- Any investigational treatment for cellulite during the 12-month period before the injection of study intervention.
- Endermologie or similar treatments during the 6-month period before injection of study intervention.
- Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate cellulite during the 2-week period before injection of study intervention.

If a prohibited medication or procedure is used during the study, all pertinent information will be recorded. The Sponsor must be informed to determine whether the participant can continue in the study.

7.5.2. 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.

7.5.3. 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.

8. DISCONTINUATION FROM STUDY INTERVENTION AND STUDY WITHDRAWAL

8.1. Discontinuation of Study Intervention

In certain instances, it may be necessary for a participant to be permanently discontinued from study intervention (QWO [CCH-aaes]) by the investigator or the sponsor. Treatment may be discontinued at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

Participants who request to discontinue study intervention will be encouraged to complete the remaining study visits and evaluations and provide any additional follow-up information as required by the study. Participants who discontinue from the study intervention and do not agree to remain in the study for follow-up, will be requested, (if applicable) to complete an ET visit and a 28-day post-treatment Safety Follow-up Visit (or phone call if a visit is not possible), if applicable. During this visit, the status of any ongoing AEs/SAEs, or the occurrence of any new AEs/SAEs will be recorded.

The date of and reason for discontinuation of study intervention will be recorded.

Participants who discontinue from study intervention at any time after the first dose of study QWO (CCH-aaes) will not be replaced.

8.2. Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at her own request. A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons, which is expected to be uncommon. The date and reason for withdrawal will be recorded.
- At the time of withdrawing from the study, if possible, an ET visit should be conducted, as shown in the Schedule of Assessments. See the Schedule of Assessments for data to be collected at the time of study withdrawal and follow-up and for any further evaluations to be completed.

- The participant will be permanently discontinued from the study intervention, and the study, at the time of withdrawal of consent.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before the withdrawal of consent.

The date a participant withdraws and the reason for withdrawal will be recorded in the source documentation and the electronic case report form (eCRF). This information should be recorded in the source documentation and the eCRF.

If a participant discontinues from the study, all end-of-study procedures should be conducted as detailed in Schedule of Assessments. The date a participant discontinues and the reason for discontinuation will be recorded in the source documentation and eCRF. If, however, a participant withdraws consent, no additional procedures are required except the collection of AE information at the Safety Follow-up Visit, 28 days after the last treatment. This information should be recorded in the source documentation and the eCRF.

Participants who have been withdrawn from the study at any time after the first dose of QWO (CCH-aaes) will not be replaced. However, additional participants may be enrolled in a given cohort to ensure that the required number of evaluable participants in each cohort is achieved in the applicable analysis population.

8.3. Lost to Follow-up

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

Participants lost to follow-up at any time after the first dose QWO (CCH-aaes) may be replaced.

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the schedule of assessments (Section 2.4). 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 participant should continue study intervention and/or be withdrawn from the study.

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

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

9.1. Screening Assessments

9.1.1. Medical and Surgical 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 will be recorded.

History of tobacco and alcohol use (never, current, former) will also be collected.

Medical and surgical history will include a review of all medical history and surgical procedures completed in the prior 10 years and any surgery completed at any time in the treatment area.

9.1.2. Physical Examination

A limited physical examination will be conducted at the Screening visit and will include evaluation of height and weight and the following organ systems: lungs, heart, abdomen, and extremities. Weight will also be recorded at the Days 1 and 180/ET visits.

All examinations will be performed by a qualified designated 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.

9.1.3. 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 qualified designated physician) will determine the Fitzpatrick skin type for all participants on Day 1. Only participants with a Fitzpatrick Skin level of I-IV will be included in the study.

9.1.4. 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 (Table 4). Participants must have a Hexsel CSS total score ≤ 12 to be included in the study. The Hexsel CSS Score will be assessed according to the time points on the Schedule of Assessments.

Table 4: Hexsel Cellulite Severity Scale

A – Number of Evident Depressions	0 = none/no depressions 1 = a small amount: 1-4 depressions are visible 2 = a moderate amount: 5-9 depressions 3 = a large amount: 10 or more depressions
B – Depth of Depressions	0 = no depressions 1 = superficial depressions 2 = medium depth depressions 3 = deep depressions
C – Morphological Appearance of Skin Surface Alterations	0 = no raised areas 1 = 'orange peel' appearance 2 = 'cottage cheese' appearance 3 = 'mattress' appearance
D - Grade of laxity, flaccidity, or sagging skin	0 = absence of laxity, flaccidity, or sagging skin 1 = slight draped appearance 2 = moderate draped appearance 3 = severe draped appearance
E – Current classification scale based on the scale originally described by Nürnberger and Müller (1978)	0 = Grade or Stage 0 = There is no alteration of the skin surface. 1 = Grade or Stage I = The skin of the affected area is smooth while the participant is standing or lying, but the alterations to the skin surface can be seen by pinching the skin or with muscle contraction. 2 = Grade or Stage II = The orange skin or mattress appearance is evident when standing, without the use of any manipulation (skin pinching or muscle contraction). 3 = Grade or Stage III = The alterations described in Grade or Stage II are present together with raised areas and nodules.

9.1.5. 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 validated 5-level photonumeric scale developed specifically for investigators and used by the investigator to assess the severity of the participant'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 participant is in the standing position with relaxed gluteus muscles. Investigators who are physicians will be trained and qualified in the use of the CR-PCSS-prior to assessing any participants.

Participants must have a baseline CR-PCSS rating of '3' (moderate) or '4' (severe) on each buttock at the Screening Visit to be included in the study.

9.2. 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 participant safety and protect data integrity, Endo, in accordance with the FDA Guidance on *Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency* (March 2020, updated 30 August 2021), will allow remote visits for certain efficacy assessments. Additionally, participants impacted by the health emergency will be allowed to continue in the study and complete remaining assessments when the investigational sites re-open.

9.2.1. Digital Photography

At the time points indicated on the schedule of assessments, the investigator or qualified designee will photograph bilateral buttocks and each buttock individually while the participant is standing in a consistent, standard relaxed pose, with relaxed gluteus muscles using the supplied Canfield camera system.

Buttocks will be photographed at the following time points:

- Cohorts 1-6: Before and after marking the dimples and injection sites on Days 1, 22, and 43.
- Cohort 7: Before and after marking the dimples and injection sites on Days 1, 22, 43, and 64.
- During the treatment and follow-up visits designated in the Schedule of Assessments.
- For Cohort 4, photographs will be taken before and after marking the treatment areas. Photographs will include pre-marking images, and post-marking images delineating the perimeter of areas to be injected inclusive of injection site stencil.

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, corporate communication, marketing, regulatory purposes, and/or legal applications as required/desired by Endo.

Digital photographs captured by the investigator will be uploaded to a web-based repository using the Canfield camera system. Further information is provided in the Photography Manual in Study Operations Manual.

9.2.2. 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.

9.2.3. Investigator-Global Aesthetic Improvement Scale

At the time points indicated in the Schedule of Assessments, the investigator will determine the degree of improvement of each buttock by comparing treated cellulite dimples from the Day 1 pre-treatment (Baseline) digital image of each buttock to the treated dimples observed in a live assessment (Table 5). For each buttock, the investigator will provide the rating from those below that best represents his/her answer.

Table 5: Investigator-Global Aesthetic Improvement Scale (I-GAIS)

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

9.3. 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 participant safety and protect data integrity, Endo, in accordance with the FDA Guidance on *Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency* (March 2020, updated 30 August 2021), will allow remote visits for certain safety assessments. Additionally, participants impacted by the health emergency will be allowed to continue in the study and complete remaining assessments when the investigational sites re-open.

9.3.1. Vital Signs

For Cohorts 1-7, vital signs (temperature, pulse, systolic blood pressure, and diastolic blood pressures) will be collected up to 2 hours prior to, and at 15 and 30 minutes after, QWO (CCH-aaes) administration on Days 1, 22, and 43. For Cohort 7, vital signs will also be collected on Day 64. Pulse and blood pressure will be collected after the participant 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).

9.3.2. Pregnancy Testing

All female participants of childbearing potential will have serum and/or urine pregnancy tests at the time points outlined in the Schedule of Assessments. Results must be available prior to QWO (CCH-aaes) administration. Participants with positive results at the Screening Visit or on Day 1 will be ineligible for study entry. Any female participant that becomes pregnant during the study will be immediately withdrawn from treatment and will have the pregnancy reported as per Section 9.4.5.

For all female participant of childbearing potential, the participant's agreement to use contraception throughout their study participation (Screening Visit through the Day 180 Visit, or for a minimum of 28 days after the last dose of study intervention for participants who terminate early) will be documented.

9.3.3. Clinical Laboratory Determinations

At the time points listed in the Schedule of Assessments, clinical laboratory tests will be conducted. Required clinical laboratory tests are outlined in Section 11.2. Clinical laboratory tests will be performed by a designated central laboratory. Each site will be provided with instructions on specimen collection, preparation, packaging, and transport. The results of the tests will be returned to the investigational sites.

Samples for laboratory testing may be collected under fasted or nonfasted conditions. Fasting early morning samples are preferred, but a random daytime sample is acceptable. The date and time of the sample collection must be documented in the laboratory report. Investigators must review and sign laboratory reports and document the clinical significance of each laboratory abnormality. New clinically significant laboratory abnormalities or clinically significant changes in laboratory values will be reported as AEs (or SAEs, if appropriate).

Clinical laboratory test data will be reviewed by the investigator, or qualified designated physician, and additional clinical laboratory tests may be ordered at his/her discretion (eg, if the results of any clinical laboratory test falls outside the reference range or clinical symptoms necessitate additional testing to ensure safety). Any additional testing will be performed by the designated central laboratory if needed to ensure participant safety.

9.4. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 11.3.

All AEs, including both observed or volunteered problems, complaints, signs or symptoms must be recorded, regardless of whether associated with the use of study intervention. Study intervention includes QWO (CCH-aaes) at the labeled dose and at different strengths (concentrations), diluent additives, depths of injection, and method of injection. 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 intervention will be captured as an AE; the onset date will be the date the event worsened. The AE should be recorded in standard medical terminology when possible.

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

SAEs and AEs will be collected by the investigator from the time of signing the informed consent through the Day 180 EOS/ET Visit.

Participants are encouraged to remain in the study for follow-up until the Day 180 Visit. Participants who discontinue from the study or study intervention and do not agree to remain in the study for follow-up until Day 180, will be asked to complete the 28-day post-treatment Safety Follow-up Visit (or phone call if a visit is not possible), if applicable. The status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs will be determined.

Investigators are not obligated to actively seek AEs and SAEs after conclusion of study participation. However, if the investigator learns of any SAE, including death, at any time after the participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must notify the sponsor within 24 hours as described in Section 11.3.4.1.

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 11.3.

9.4.2. 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 participant is the preferred method to inquire about AE occurrences.

At each visit, participants will be queried regarding any AEs that have occurred since the last visit. Study site personnel will then record all pertinent information. The study intervention compliance record should also be reviewed to detect potential intentional or unintentional overdoses.

In addition, investigators will document observed and elicited AE.

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All ongoing AEs must be followed until they have resolved or for 28 days after the participant's last dose of study intervention, 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 11.3.

9.4.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of an SAE due to QWO (CCH-aaes) or other study interventions is essential so that legal obligations and ethical responsibilities regarding the safety of the study intervention 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 intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements regarding safety reporting to regulatory authorities, Institutional Review Boards (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. The Reference Safety Information for this study is the QWO Prescribing Information.

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.

9.4.5. Pregnancy

All pregnancies in participants 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 intervention in participants who terminate from the study early, must be reported, followed to conclusion, and the outcome reported, even if the participant 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 11.3). Spontaneous miscarriages should also be reported and handled as SAEs.

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

A participant who becomes pregnant must be withdrawn from the study. Should a participant 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 participant discontinues treatment because of pregnancy.

9.5. Treatment Overdose

Study intervention overdose is any accidental or intentional use of treatment in an amount higher than the dose indicated by the protocol for that participant. Study intervention 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 intervention 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 11.3, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Endo Serious Adverse Event (SAE)/Reportable Event Form and in an expedited manner but should be noted as nonserious on the form and the AE eCRF.

10. STATISTICAL CONSIDERATIONS AND METHODS

10.1. Sample Size Determination

The proposed sample size is approximately 210 participants. The sample size is based on evaluation of the different study interventions in 7 cohorts of up to 30 participants each, such that up to 168 participants complete the study.

10.2. Populations for Analysis

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

The **Safety Population** is defined as all participants who received at least 1 injection of QWO (CCH-aaes). All safety analyses will be based on this population.

The **Full Analysis Set** is defined as all participants in the Safety Population who have at least 1 valid IABSS assessment at a treatment area after an injection of QWO (CCH-aaes). All efficacy analyses will be based on this population.

10.3. Statistical Hypotheses and Analyses

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

10.3.1. Efficacy Analysis

The primary endpoint for Cohorts 1-6: the proportion of participants whose left buttock (investigational side) demonstrates at least a 1-level lower score versus the right buttock (control side) on the IABSS, at Visit 3 will be summarized by cohort using appropriate descriptive statistics. In addition, the counts and percentages for each severity scale will be summarized by cohort and treatment area.

The primary endpoint for Cohort 7a: The proportion of participants whose left buttock (investigational side), at Visit 3, demonstrates at least 1-level lower score versus the right buttock (control side), at Visit 8 on the IABSS will be summarized by cohort using appropriate descriptive statistics. In addition, the counts and percentages for each severity scale will be summarized by cohort and treatment area.

The primary endpoint for Cohort 7b: The proportion of participants whose left buttock (investigational side), at Visit 8, demonstrates at least 1-level lower score versus the right buttock (control side), at Visit 3, on the IABSS will be summarized by cohort using appropriate

descriptive statistics. In addition, the counts and percentages for each severity scale will be summarized by cohort and treatment area.

For Cohorts 1-6, at each visit the proportion of participants whose left buttock (investigational side) demonstrates at least a 1 level lower score versus the right buttock (control side) on the IABSS will be summarized by cohort using appropriate descriptive statistics. In addition, the counts and percentages for each severity scale at each visit will be summarized by cohort and treatment area.

For Cohorts 7a and 7b: The proportion of participants whose left buttock (investigational side) demonstrates at least 1-level lower score versus the right buttock (control side), on the IABSS will be summarized by cohort using appropriate descriptive statistics at the corresponding treatment visit (first dose of QWO [CCH-aaes] on the investigational buttock with tranexamic acid vs the first dose of QWO [CCH-aaes] without tranexamic acid on the control side; second dose of QWO [CCH-aaes] on the investigational buttock vs second dose of QWO [CCH-aaes] on the control side; third dose of QWO [CCH-aaes] on the investigational side vs third dose of QWO [CCH-aaes] on the control side); and at each follow up visit thereafter.

The proportion of participants with an improved (+1 or better) score as reported by investigators on the I-GAIS will be summarized by treatment area and by cohort at each visit. The I-GAIS is a 7-level scale ranging from +3 (very much improved) to -3 (very much worse).

10.3.2. Safety Analyses

The safety parameters will include AEs, laboratory evaluations, and vital signs.

10.3.2.1. Adverse Events

AEs will be coded using MedDRA by preferred term (PT) within each system organ class (SOC). All TEAEs will be summarized by cohort for each SOC and PT. A participant will only be counted once per SOC and PT. All summary tables will include number of occurrences of the TEAEs and the number and percent of participants that experienced the TEAEs.

In addition, for TEAEs of the injection site, the following variables will be summarized by cohort and treatment area for each SOC and PT: the number of occurrences of the TEAEs, the number and percent of participants that experienced the TEAEs, severity, and duration of the TEAEs.

Only TEAEs will be included in all summaries, and all AEs will be listed.

10.3.2.2. Clinical Laboratory Tests and Vital Signs

The actual values and their changes from baseline for laboratory evaluations and vital signs will be summarized by cohort and visit (if applicable) using appropriate descriptive statistics.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

11.1.1. Regulatory and Ethical Considerations

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

The study will be conducted in full compliance with ICH E6 (R2), 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 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 ICF, advertisements, materials being provided to participants, and amendments (if any) will be approved by 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 local IRB with a copy of the current QWO Prescribing Information and the current Tranexamic Acid 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.

Any amendment to this protocol will be provided to the investigator in writing by the Sponsor. 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 participant, 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 participant, and must be immediately reported to the Sponsor.

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

11.1.2. 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.

11.1.3. Informed Consent Process

The ICF must be approved by the sponsor and the IRB before any participant 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 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 participant the objectives of the exploratory research. Participants 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 participant's agreement to allow any remaining specimens to be used for exploratory research. Participants 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), participants 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), participants 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.

Participants 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. Participants will be made aware that they may withdraw from the study at any time for any reason.

All versions of each participant'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 participant.

The participants 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 participant withdraws consent and/or HIPAA authorization, the investigator can no longer disclose health information, unless it is needed to preserve the scientific integrity of the study.

11.1.4. Data Protection

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

The participant 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 participant.

The participant 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.

11.1.5. Dissemination of Clinical Study Data

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

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

11.1.6. 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 (R2) consolidated guidelines, and other applicable regulations. The extent, nature, and frequency of monitoring and/or audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. At the conclusion of a program, a compliance statement will be generated by the sponsor (or designee) listing all audit activities performed during the clinical study.

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

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

11.1.7. Source Documents

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

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

The investigator shall retain and preserve a copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by GCP as essential. Essential documents should be retained until at least 3 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Prior to destruction of any study essential documents, the investigator must first obtain written approval from the sponsor.

11.1.8. Study and Site Closure

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

11.1.9. Publication Policy

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

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

11.2. Appendix 2: Clinical Laboratory Tests

Hematology	Biochemistry	Urinalysis
Hemoglobin	Glucose	Glucose
Hematocrit	Sodium	Protein
Red blood cell (RBC) count	Potassium	Specific gravity
Platelets	Calcium	pH
White blood cell (WBC) count	Chloride	Ketones
WBC Differential	Carbon dioxide (CO_2)	Bilirubin
Prothrombin time (PT)/ International Normalized Ratio (INR)	Blood urea nitrogen (BUN)	Urobilinogen
	Creatinine	Nitrite
	Aspartate aminotransferase (AST)	Blood[a]
	Alanine aminotransferase (ALT)	Leukocytes[a]
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Total protein	

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

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

11.3.1. Definitions

An AE is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, ECG, X-ray, etc), or worsening of a preexisting condition associated temporally with the use of the study intervention whether or not considered related to the study intervention. Note: Any medical condition or laboratory abnormality already present at screening or baseline should be reported as medical history. If the medical condition present at baseline changes in severity or seriousness at any time during the study, it should be reported as an AE. AEs will be captured once a participant has signed the informed consent. AEs include:

- Changes in the general condition of the participant.
- Subjective symptoms offered by or elicited from the participant.
- Objective signs observed by the investigator or other study personnel.
- All concurrent diseases and/or medical occurrences 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 intervention 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 participant using the study intervention 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 participant 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.

11.3.2. Relationship to Study Intervention

In this study, study intervention will comprise QWO (CCH-aaes), and administration of QWO (CCH-aaes) at different doses, strengths (concentrations), diluent additives, depths of injection, and method of injection.

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

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

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.

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.

11.3.3. 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 participant's daily activities.
- **Moderate** AEs introduce a low level of inconvenience or concern to the participant and may interfere with daily activities but are usually ameliorated by simple therapeutic measures.
- **Severe** AEs interrupt a participant's usual daily activity and typically require systemic drug therapy or other treatment.

11.3.4. Reporting Adverse Events and Serious Adverse Events

11.3.4.1. Reporting Adverse Events

Throughout the study, AEs will be documented on the source document and on the appropriate page of the eCRF whether or not considered treatment-related.

11.3.4.2. Reporting Serious Adverse Events

Any SAE, including death, resulting from any cause, which occurs to any participant 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 SAEs should be reported via email [redacted] or fax [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/IEC per their IRB/IEC policy.

11.3.4.3. 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 nonserious AE, or whether it should be considered as part of the participant's history. In addition, all events or other findings determined to be SAEs should be identified on the Endo Serious Adverse Event (SAE)/Reportable Event Form and the investigator should consider whether the event is related or not related to study intervention. All events determined to be nonserious should be reported on the eCRF.

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

See Section 6 and Section 9.4.5.

11.5. Appendix 5: Amendment 01

The primary reasons for Amendment 01 were to add Cohort 6, include the requirement of having a qualified designated physician administer CCH-aaes, include precautions regarding the potential of an allergic reaction, and add certain inclusion/exclusion criteria. The major changes to the protocol are outlined below. Revisions in style, minor corrections (such as spelling errors, etc), and other minor changes that do not impact content may also have been made.

Section	Reason for Change/Original Text	Revision
Section 2.1 Synopsis Section 3.3 Benefit-Risk Assessment Section 5.1 Overall Design Section 9.4 Adverse Events and Serious Adverse Events Section 11.3.2 Relationship to Study Intervention	Modifying the depth of injection will also be assessed in Cohorts 3 and 4: …different doses, strengths (concentrations), diluent additives, and methods of injection…	… different doses, strengths (concentrations), diluent additives, depths of injection, and methods of injection ….
Section 2.1 Synopsis	Added an additional cohort (Cohort 6).	Added a description of Cohort 6 to the Study Intervention Cohort in the Synopsis table.
Section 2.1 Synopsis Section 5.1 Overall Design	Added an additional cohort (Cohort 6).	Added a description of Cohort 6 in the overall study design. Participants in Cohort 6 will receive a maximum dose of up to 0.42 mg of QWO (CCH-aaes) on the control side and a maximum dose of up to 0.21 mg of QWO (CCH-aaes) on the investigational side per treatment session for 2 treatment sessions (Days 1 and 43) for a maximum total dose of 1.26 mg. In Cohort 6, the investigational and control sides will be treated with the same number of injections, the same number of aliquots per injection, and extended treatment interval, but at different doses and concentrations.

Section	Reason for Change/Original Text	Revision
Section 2.1 Synopsis Section 5.1 Overall Design	Clarified description of Cohorts 1 and 5.	In an effort to standardize the risk and scope of bruising, the investigational and control sides in Cohorts 1 and 5 should be treated with the same concentration, same number of injections, and same number of aliquots per injection, but at different doses per injection or addition of diluent additive.
Section 2.1 Synopsis Section 5.1 Overall Design Section 10 Sample Size Determination	Number of participants updated because of addition of Cohort 6.	… to enroll approximately 180 participants into 6 treatment cohorts of up to 30 participants each, such that up to 144 participants complete the study.
Section 2.3 Study Schema for Cohort 6		New study schema added for Cohort 6.
Section 2.4 Schedule of Assessments for Cohorts 1 to 5	In order to establish a baseline for bruising there should be an IABSS performed prior to study drug injection.	Added in the SoA that there should be an Investigator Assessment of Bruising Severity Scale (IABSS) performed at Day 1.
Section 2.4 Schedule of Assessments for Cohort 1 to 5 Section 3.3 Benefit-Risk Assessment Section 7.1 Selection and Marking of Dimples Section 9.1.2 Physical Examination Section 9.1.3 Fitzpatrick Skin Scale Section 9.3.3 Clinical Laboratory Determinations	Certain study assessments and administration of QWO (CCH-aaes) should always be performed by the investigator who will be a qualified physician.	Added "qualified designated physician" to various sections of the protocol.
Section 2.7 Schedule of Assessments for Cohort 6		New SoA added for Cohort 6.
Section 3.3.3 Half-dose QWO (CCH-aaes)	Added an additional cohort.	In Cohort 6, half the labeled dose (0.42 mg) of QWO (CCH-aaes) will be administered to the control side.

Section	Reason for Change/Original Text	Revision
Section 3.3.4 Quarter-dose QWO (CCH-aaes)	Added an additional cohort.	In Cohort 6, one-quarter of the labeled dose (0.21 mg) at one-half of the labeled concentration (0.12 mg/mL) of QWO (CCH-aaes) will be administered to the investigational side. Half of the labeled dose (0.42 mg) of QWO (CCH-aaes) at the labeled concentration (0.23 mg/mL) will be administered to the control side. Cohort 6 will consist of 2 treatment sessions, 6 weeks apart. The total dose administered for Cohort 6 to the participant in both the investigational and control sides during the study will be QWO (CCH-aaes) 1.26 mg. The purpose of decreasing the dose/concentration and lengthening the interval between Treatment Session 1 (Day 1) and Treatment Session 2 (Day 43 ± 3 days) is to determine whether there will be an improvement in both bruising and subsequent discoloration.
Section 5.2 Scientific Rationale for Study Design	Added an additional cohort.	…half the labeled dose (0.42 mg) of QWO (CCH-aaes) and one-quarter of the labeled dose (0.21 mg) of QWO (CCH-aaes) at one-half the labeled concentration (0.12 mg/mL) (Cohort 6). For Cohort 6, there will be 2 treatment sessions administered 6 weeks apart.
Section 5.4 Justification for Dose	Added an additional cohort.	For Cohort 6, half the labeled dose (0.42 mg for the control side) and one-quarter of the labeled dose at one-half the labeled concentration (0.21 mg at a concentration of 0.12 mg/mL for the investigational side) will be administered as 2 treatment sessions, 6 weeks apart. This is to determine whether a decrease in the dose and concentration combined with lengthening the time between treatment administration will decrease bruising and subsequent discoloration (refer to Section 5.2 for additional information).
Table 1 Study Intervention Cohorts Section 2.1 Synopsis	Added an additional cohort.	Cohort 6 information added to Table 1

Section	Reason for Change/Original Text	Revision
Table 2 Study Intervention by Buttock	Added an additional cohort.	Cohort 6 information added to Table 2
Section 5.2 Scientific Rationale for Study Design	Added an additional cohort.	Study AUX-CC-831 tested QWO (CCH-aaes) at 0.06 mg, 0.48 mg, and 0.84 mg. The study demonstrated improvement in a variety of parameters with the 0.06 mg dose, and investigators determined that approximately 45% of participants had improvement in their cellulite, although it was not statistically significant. The 0.48 mg dose was associated with statistically significant improvements. Therefore, in this study, Cohort 6 will evaluate a QWO (CCH-aaes) dose between the lowest and the middle dose given in Study AUX-CC-831, to determine whether there will be a decrease in bruising while experiencing an improvement in cellulite.
Section 7.2.8 Cohort 6, Investigational Side Only, QWO (CCH-aaes) – Quarter-dose with Two Treatment Sessions at approximately 43 Study Days in between Visits	Added an additional cohort.	**Dosage and Mode of Administration**: For the investigational side, a dose of up to 0.21 mg of QWO (CCH-aaes) up to 1.8 mL will be administered as up to 12 subcutaneous injections (0.15-mL injection administered as three 0.05-mL aliquots per injection). There will be 2 treatment visits at an interval of approximately 42 days as described in schedule of assessments for Cohort 6. The volume and dose of injection at each treatment visit for each buttock will be prepared per the Pharmacy Manual and injected per the Injection Guide in the Study Operations Manual.
Section 6.1 Participant Inclusion Criteria	Added text not allowing site staff to participate in the study.	Be a non-employee or non-family member of the sponsor or research staff conducting the study.
Section 6.2 Participant Exclusion Criteria	Added exclusion criterion to disallow other investigational product.	15. Has received treatment with any investigational product within 30 days (or 5 half-lives, whichever is longer) of the start of the Screening Visit or throughout the study.

Section	Reason for Change/Original Text	Revision
Section 6.3 Lifestyle Considerations	Clarified who could give advice.	Participants should avoid medications, homeopathic supplements, or foods as advised by the qualified designated physician or designee prior to QWO (CCH-aaes) treatment.
Section 7.2.11 Care Procedures After Injection	Added text regarding potential for an allergic reaction due to the foreign protein CCH.	New section added: Care After Injection. NOTE: CCH is a foreign protein and investigators must be prepared to address and manage an allergic reaction should it occur. At the time of each injection, a 1:1,000 solution of epinephrine for injection, 50 mg diphenhydramine injection or a suitable equivalent, and oxygen must be available, and the investigator and site staff must be familiar with their use. To evaluate the participant for possible immediate immunological AEs, the participant will remain in direct observation of medical personnel who are skilled in the management of an allergic reaction for 30 minutes after receiving the injections of the study intervention and until the participant exhibits no sign of an immunological or other clinically significant systemic or local AE. The participant's vital signs must be stable before the participant can leave direct observation.
Section 6.2.9 Continued Access to Study Intervention after the End of the Study	Section deleted. Additional treatment with QWO (CCH-aaes) will not be provided after the End of Study.	
Section 9.1.4 Hexsel Cellulite Scale Severity	Correct Hexsel CSS Total Score inconsistency found in Section 9.1.4 of protocol	Participants must have a Hexsel CSS total score ≤ 12 to be included in the study

11.6. Abbreviations

Abbreviation	Explanation
AE	Adverse event
CCH	Collagenase clostridium histolyticum
CR-PCSS	Clinician Reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
eCRF	Electronic case report form
ET	Early termination
HIPAA	Health Insurance Portability and Accountability Act
IABSS	Investigator Assessment of Bruising Severity Scale
ICF	Informed consent form
ICH	International Council for Harmonisation
I-GAIS	Investigator-Global Aesthetic Improvement Scale
IRB	Institutional Review Board
PT	Preferred term
SAE	Serious adverse event
SOC	System organ class
SUSAR	Suspected, unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
TID	Three times daily

12. 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

13. REFERENCES

Endo Pharmaceuticals Inc. A phase 2 open-label study of EN3835 in the treatment of edematous fibrosclerotic panniculopathy [Clinical Study Report EN3835-205]. Malvern, PA; 02 July 2019.

Endo Pharmaceuticals Inc. A phase 3, randomized, double-blind, placebo-controlled study of EN3835 in the treatment of edematous fibrosclerotic panniculopathy [Clinical Study Report EN3835-302]. Malvern, PA; 28 June 2019.

Endo Pharmaceuticals Inc. A phase 3, randomized, double-blind, placebo-controlled study of EN385 in the treatment of edematous fibrosclerotic panniculopathy [Clinical Study Report EN3835-303]. Malvern, PA; 15 July 2019.

Endo Pharmaceuticals Inc. A phase 4, open-label study to assess effects of mitigation treatments on bruising of CCH-aaes treatment of buttock cellulite in adult females [Clinical Study Report EN3835-401]. Malvern, PA; 21 March 2022.

Funt D, Pavicic T. Dermal fillers in aesthetics: an overview of adverse events and treatment approaches. *Clin Cosmet Investig Dermatol*. 2013;6:295-316. Published 2013 Dec 12. doi:10.2147/CCID.S50546

Green JB, Cohen JL. Cellfina observations: pearls and pitfalls. *Semin Cutan Med Surg*. 2015;34(3):144-146. doi:10.12788/j.sder.2015.0176

Hexsel DM, Dal'forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol*. 2009;23(5):523-528. doi:10.1111/j.1468-3083.2009.03101.x

Meaidi A, Mørch L, Torp-Pedersen C, Lidegaard O. Oral tranexamic acid and thrombosis risk in women. *EClinicalMedicine*. 2021;35:100882. Published 2021 May 6. doi:10.1016/j.eclinm.2021.100882

Mehdizadeh M, Ghassemi A, Khakzad M, et al. Comparison of the Effect of Dexamethasone and Tranexamic Acid, Separately or in Combination on Post-Rhinoplasty Edema and Ecchymosis. *Aesthetic Plast Surg*. 2018;42(1):246-252. doi:10.1007/s00266-017-0969-x

Nürnberger F, Müller G. So-called cellulite: an invented disease. *J Dermatol Surg Oncol.* 1978;4(3):221-229. doi:10.1111/j.1524-4725.1978.tb00416.x

Ockerman A, Vanassche T, Garip M, et al. Tranexamic acid for the prevention and treatment of bleeding in surgery, trauma and bleeding disorders: a narrative review. *Thromb J*. 2021;19(1):54. Published 2021 Aug 11. doi:10.1186/s12959-021-00303-9

QWO. Prescribing Information. Endo Global Aesthetics Limited; July 2020. Accessed 21 March 2022. www.qwo.com

Rohrich RJ, Cho MJ. The Role of Tranexamic Acid in Plastic Surgery: Review and Technical Considerations. *Plast Reconstr Surg*. 2018;141(2):507-515. doi:10.1097/PRS.0000000000003926

Samdal F, Amland PF, Bugge JF. Plasma lidocaine levels during suction-assisted lipectomy using large doses of dilute lidocaine with epinephrine. *Plast Reconstr Surg*. 1994;93(6):1217-1223. doi:10.1097/00006534-199405000-00017

Taeuber I, Weibel S, Herrmann E, et al. Association of Intravenous Tranexamic Acid With Thromboembolic Events and Mortality: A Systematic Review, Meta-analysis, and Meta-regression [published online ahead of print, 2021 Apr 14]. *JAMA Surg*. 2021;156(6):e210884. doi:10.1001/jamasurg.2021.0884

Tranexamic Acid. Prescribing Information. Amring Pharmaceuticals; December 2020. Accessed 02 August 2022. https://dailymed.nlm.nih.gov/dailymed

Verner I, Prag Naveh H, Bertossi D. Treatment of injection-induced ecchymoses with light/laser-assisted technology. *Dermatol Ther*. 2019;32(3):e12861. doi:10.1111/dth.12861

Whipple LA, Fournier CT, Heiman AJ, et al. The Anatomical Basis of Cellulite Dimple Formation: An Ultrasound-Based Examination. *Plast Reconstr Surg*. 2021;148(3):375e-381e. doi:10.1097/PRS.0000000000008218

Wokes JET, Erdmann MWH, McLean NR. The Role of Tranexamic Acid in Aesthetic Plastic Surgery: A Survey of the British Association of Aesthetic Plastic Surgeons. *Aesthet Surg J*. 2021;41(2):244-249. doi:10.1093/asj/sjaa149