SAP MODULE 1 – DETAILED STATISTICAL METHODOLOGY

Protocol No. 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

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The sponsor of the application 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.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
BUN	Blood urea nitrogen
CCH	Collagenase clostridium histolyticum
CI	Confidence Interval
CR-PCSS	Clinician-reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
eCRF	Electronic case report form.
EOS	End of Study
ET	Early Termination
FAS	Full Analysis Set
GGT	Gamma-glutamyl transferase
IABSS	Investigator Assessment of Bruising Severity Scale
I-GAIS	Investigator Global Aesthetic Improvement Scale
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
PCI	Potentially Clinically Important
PT	Preferred Term
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SoA	Schedule of Assessments
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses to assess different interventions designed to reduce bruising following QWO (CCH-aaes) treatment of moderate to severe cellulite of the buttocks in adult females.

General information about the study is described in the EN3835-226 CEL Clinical Study Protocol, protocol amendment 2 dated August 12, 2022.[1]

2. STUDY OBJECTIVES AND ENDPOINTS

The primary and secondary objectives and corresponding endpoints are outlined in Table 1 below.

Table 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.

Table 1: Objectives and Endpoints (Continued)

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) 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].

3. STUDY DESIGN AND MEASURES

3.1. Study 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, in order to have at least 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 2). Participants will receive QWO (CCH-aaes) in different doses, strength (concentrations), diluent additives, depth of injection, and methods of injection in a split buttock arrangement, with the right buttock serving as the control, and the left buttock serving as the investigational side.

Table 2: 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 2: 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 (0.23 mg/mL) of QWO (CCH-aaes) vs a 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 a 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 on both the investigational and the control sides in all cohorts. In Cohort 7, along with QWO (CCH-aaes) during each treatment visit, oral tranexamic acid will be given before and after the first treatment with QWO (CCH-aaes) for the investigational buttock. There will be three treatment sessions at Day 1, 22 and 43 for Cohorts 1-5 and two treatment sessions at Day 1 and 43 for Cohort 6. 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. 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 site 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).

There will be 4 follow-up visits (1 to 2 days, 3 to 5 days, 6 to 9 days and 10 to14 days) after each treatment (Cohort 6 will have a fifth follow-up visit at 18-24 days after initial treatment visit). 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. 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 the completion of the treatment period, there will be 3 follow-up visits at Day 90, 135 and 180/End of Study (EOS)/Early Termination (ET).

For more details, refer to protocol section 5.1.

3.1.1. End-of-Study Definition

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

3.1.2. Schedule of Assessments

Table 3, Table 4, Table 5, and Table 6 below describes the schedule of activities and assessments performed during Screening visit, Treatment period, and Follow-up visit for Cohorts 1-5, Cohort 6, Cohort 7a, and Cohort 7b, respectively.

Table 3: Schedule of Assessments (Cohort 1-5)

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

Table 4: 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] 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 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

Table 5: 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

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)**
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]							
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 →																						

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)**
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
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

Table 6: 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

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)**
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]							
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															

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)**
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

3.2. Participant 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 CSS Total Score of ≤ 12.
5. Has a Fitzpatrick Skin Type of I-IV.

Type of Participant

6. Cohort 1-6: 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/ET 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.

3.3. 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 wellbeing, 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 Wart, green tea, ginseng, feverfew, saw palmetto, turmeric, bromelain]) or foods (eg, pineapple) that have, or have been reported to have anticoagulant effects within 14 days of treatment.
    e. 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: have 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 cannabanoids.

3.4. Treatment Area

A treatment area is the buttock of the participants. The left buttock acts as investigational side and right buttock acts as control side. The dose, volume of injection, number of injections and other study interventions are detailed in Table 7.

3.5. Study Intervention Administration

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 7. The dose of tranexamic acid is provided in Table 8.

Table 7: 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

Table 7: 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 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 7: 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)[b]	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)[a]	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)[d]	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)[c]	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 8: 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 by the site
Packaging and Labeling	Product will be provided in bottles of 30 tablets each.

For more details regarding the study intervention administration in the 7 cohorts refer to protocol section 7.2.

3.6. Determination of Sample Size

The sample size for this Phase 2 study is expected to be approximately 210 participants, with up to 30 participants in each of the 7 cohorts, in order to have at least 168 participants complete the study.

3.7. Blinding and Randomization

This is an open label study, blinding and randomization is not applicable.

3.8. Efficacy Assessments

Efficacy assessments will be evaluated at times specified in the SoA (Table 3, Table 4, Table 5, and Table 6). Below is a general description of each of these assessments.

3.8.1. Digital Photography

At the time points indicated on the SoA (Table 3, Table 4, Table 5, and Table 6), 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. Each buttock will be photographed separately regardless of whether an individual buttock is treated.
- During the treatment and follow-up visits designated in the SoA (Table 3, Table 4, Table 5, and Table 6).
- 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.

3.8.2. Investigator Assessment of Bruising Severity Scale

At the time points indicated on the SoA (Table 3, Table 4, Table 5, and Table 6), 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.

3.8.3. Investigator-Global Aesthetic Improvement Scale

At the time points indicated in the SoA (Table 3, Table 4, Table 5, and Table 6), 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 9). I-GAIS will not be completed at Tx Visit 2 (Day 22) for the non-treated buttock for Cohorts 7a and 7b. Therefore, at Tx Visit 2 (Day 22) the I-GAIS will only be assessed for the investigational buttock (ie, left buttock) for Cohort 7a and only assessed for the control buttock (ie, right buttock) for Cohort 7b. For each buttock, the investigator will provide the rating from those below that best represents his/her answer.

Table 9: 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

3.9. 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.

3.10. 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 Day 1 and Day 180/EOS/ET visits.

3.11. Fitzpatrick Skin Scale

The Fitzpatrick Skin Scale is a 6-level scale (levels I-VI) for assessment of skin color and propensity for tanning.

- Level I: Pale white skin, blue/hazel eyes, blond/red hair; Always burns, does not tan
- Level II: Fair skin, blue eyes; Burns easily, tans poorly
- Level III: Darker white skin; Tans after initial burn
- Level IV: Light brown skin; Burns minimally, tans easily
- Level V: Brown skin; Rarely burns, tans darkly easily
- 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 Screening. Only participants with a Fitzpatrick Skin level of I-IV will be included in the study.

3.12. Hexsel Cellulite Scale Severity

The Hexsel CSS is a photonumeric scale used to assess 5 key morphologic features of cellulite.[2],[3]

(A) number of evident depressions,

(B) depth of depressions,

(C) morphological appearance of skin surface alterations,

(D) laxity, flaccidity or sagging of skin,

(E) current classification scale

Each of these features is evaluated on a 4-point scale from a low of 0 to a high of 3 (Table 10). 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 SoA (Table 3, Table 4, Table 5, and Table 6).

Table 10: 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.

3.13. 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 with ratings given in Table 11. 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.

Table 11: CR-PCSS Ratings

Rating	Level of Severity	Description
0	None	No dimples or evident cellulite.
1	Almost None	Few dimples that are mostly superficial in depth.
2	Mild	Several dimples of which most are shallow in depth.
3	Moderate	Many dimples of which most are moderate in depth.
4	Severe	A lot of dimples with some of more severe depth.

3.14. Prior/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.

3.14.1. 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 Wart, green tea, ginseng, feverfew, saw palmetto, turmeric, bromelain]) or foods (eg, pineapple) that have, or have been reported to have anticoagulant effects within 14 days of treatment.
- 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.

3.14.2. Permitted Concomitant Medications

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.

3.15. Adverse Events and Serious Adverse Events

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

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, 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.

3.15.1. Adverse Events (AE)

An AE is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, 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.

3.15.2. Serious Adverse Events (SAE)

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.

For more details on the time period, frequency, methods of collection of adverse events, etc. please refer to protocol section 9.4.

3.16. Safety Assessments

All safety assessments will be performed at the time points outlined in the SoA (Table 3, Table 4, Table 5, and Table 6). Additional (unscheduled) safety assessments may be performed as needed.

3.16.1. Vital Signs

Vital signs (temperature, pulse, systolic and diastolic blood pressures) will be collected for Cohort 1-5 on Screening, Day 1, Day 22, Day 43 and Day 180/EOS/ET, for Cohort 6 on Screening, Day 1, Day 43 and Day 180/EOS/ET and for Cohort 7 on Screening, Day 1, Day 22, Day 43, Day 64 and Day 180/EOS/ET. For treatment visits, ie, on Day 1, Day 22 and Day 43 for Cohort 1-5; Day 1 and Day 43 for Cohort 6 and Day1, Day 22, Day 43 and Day 64 for Cohort 7, the vital signs will be collected up to 2 hours prior to, and at 15 and 30 minutes after, QWO (CCH-aaes) administration. Pulse and blood pressure will be collected after the participant has

been sitting for 5 minutes. Any vital sign value meeting the investigator's criteria for clinical significance will be recorded as an AE (or SAE, if appropriate).

3.16.2. Pregnancy Testing

All female participants of childbearing potential will have serum and/or urine pregnancy tests at the time points outlined in the SoA (Table 3, Table 4, Table 5, and Table 6). 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 withdrawn from the study.

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

3.16.3. Clinical Laboratory Determinations

At the time points listed in the SoA (Table 3, Table 4, Table 5, and Table 6), clinical laboratory tests will be conducted. Required clinical laboratory tests are outlined in Table 12.

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).

Table 12: Clinically Important Laboratory Parameters

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

4. STUDY PARAMETERS

4.1. Participant Disposition

A participant will be considered to have completed the study if they complete the Day 180/EOS Visit. Any participant terminating early from the study before the end of the study is said to be ET.

If a participant withdraws from the study, all EOS/ET procedures should be conducted as detailed in the SoA (Table 3, Table 4, Table 5, and Table 6). The reason and date for discontinuation will be recorded in the eCRF for participants who do not complete the study. 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.

4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics will include following parameters:

Table 13: Demographic and Baseline Characteristics

Continuous Variables	Categorical Variables
Age (years) Height (cm) Weight (kg) BMI (kg/m^2) Time since last menstrual period (days)	Gender Race Ethnicity Skin category based on Fitzpatrick scale assessment Substance Use • Alcohol use (Never, Current and Former) • Tobacco use (Never, Current and Former) Hexsel CSS scores CR-PCSS Score IABSS Ratings at Visit 1 (Day 1) Cellulite History

4.3. COVID-19 Related Protocol Deviations

All study assessments conducted outside of the allowed windows outlined in the SoA (Table 3, Table 4, Table 5, and Table 6) 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.

4.4. Prior/Concomitant Medications and Procedures

All medications will be coded using World Health Organization (WHO) Drug Dictionary Version Global B3 March, 2022, by active ingredient and WHO anatomical therapeutic chemical (ATC) classification of ingredients.

- A prior medication/procedure is defined as any medication/procedure taken/done prior to first injection (Day 1).

- A concomitant medication (or non-drug therapy) is any medication (or therapy) taken on or after the Baseline Visit through the Day 180/EOS/ET Visit or the medication is reported as ongoing.

Please note that if a medication star.ted prior to Screening and end date is after screening/ongoing, it will be counted as both prior and concomitant medication.

4.5. Efficacy Parameters

4.5.1. IABSS Ratings

The IABSS rating is directly obtained from the investigator's assessments at treatment visits and their corresponding follow-up visits, ie, Visit 1 (Day 1) through Visit 15 (Day 57) for Cohorts 1-5, Visit 1 (Day 1) through Visit 11 (Day 57) for Cohort 6, and Visit 1 (Day 1) throughVisit 20 (Day 78) for Cohort 7.

For the primary and secondary analysis, the following definition will be used for Cohorts 1 to 7 for the primary endpoint: A one-level IABSS responder at Visit A versus Visit B is defined as the participant whose left buttock (investigational side) at Visit A demonstrates at least a 1-level lower IABSS score versus the right buttock (control side) at Visit B, where Visit A and B can either be same or different.

[redacted]

4.5.2. I-GAIS Ratings

The I-GAIS ratings are directly obtained from the investigator's assessment at Visit 6 (Day 22), Visit 11 (Day 43), Visit 16 (Day 90), Visit 17 (Day 135) and Visit 18 (Day 180) for Cohort 1-5. For Cohort 6, the I-GAIS ratings will be obtained at Visit 7 (Day 43), Visit 12 (Day 90), Visit 13 (Day 135) and Visit 14 (Day 180) and for Cohort 7, at Visit 6 (Day 22), Visit 11 (Day 43), Visit 16 (Day 64), Visit 21 (Day 90), Visit 22 (Day 135) and Visit 23 (Day 180).

A one-level I-GAIS responder for a treatment area (left buttock or right buttock) is defined as any participant with an improved (+1, +2 or +3) score on the I-GAIS at an analysis visit for that treatment area.

4.6. Safety Parameters

4.6.1. Adverse Events

AEs will be coded using MedDRA version 25.0 by preferred term (PT) within each system organ class (SOC).

4.6.1.1. Treatment-Emergent Adverse Events

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).

4.6.1.2. Intensity of Adverse Events

Intensity (or severity) of AEs will be graded as follows:

- Mild
- Moderate
- Severe

For AEs with missing severity, the most severe assessment will be imputed for analyses, following worst case principle. If the intensity of an AE changes, then the most severe intensity during the continuous episode will be recorded.

4.6.1.3. Relationship to Study Intervention

The causal relationship with study intervention will be classified by the investigator and will be reported as follows:

- Not related
- Unlikely related
- Possibly related
- Probably related

Consider “probably related” and “possibly related” causality assessments as positive causality. “Not related” and “unlikely related” causality assessments are considered as negative causality.

Any missing relationship of an AE to study intervention will be considered as related to study intervention for the analyses, following worst-case principle.

4.6.2. Vital Signs and Clinical Laboratories

4.6.2.1. Laboratory Values

Clinical laboratory data (hematology, biochemistry and urinalysis) will be analyzed for observed value and change from baseline to180/EOS/ET. Refer to Table 17 for the definition of baseline and Last.

In addition, participants reporting any sponsor-defined potentially clinically important (PCI) laboratory values during the study will be summarized.

PCI laboratory values are presented in Table14.

Table 14: Potentially Clinically Important Laboratory values

Parameter	PCI Low ≤	PCI High ≥
Hemoglobin (g/L)	≤100	≥ 190
Hematocrit (%)	≤ 30	≥ 60
Platelets (10^9/L)	≤ 100	≥ 650
ALT (U/L)		≥ 3 × ULN
AST (U/L)		≥ 3 × ULN
Creatinine (µmol/L)		≥ 300
BUN (mmol/L)		≥ 12

ALT=Alanine transaminase; AST=Aspartate transaminase; BUN=Blood urea nitrogen; ULN=Upper limit of normal.

4.6.2.2. Vital Signs

Vital signs will be analyzed for observed value and change from baseline separately for vital signs on injection days and vital signs at each visit (excluding post injection time points on injection days). Refer to Table 17 for the definition of baseline.

In addition, participants reporting any sponsor-defined PCI vital sign values during the study will be summarized.

Vital sign values are PCI if they meet both the observed value criteria and the change from baseline criteria. The PCI vital sign values are presented in Table 15 below.

Table 15: Potentially Clinically Important Vital Sign Criteria

Parameter	PCI Low	PCI High
Systolic blood pressure	≤90 mmHg and decrease ≥20 mmHg from baseline	≥180 mmHg and increase ≥20 mmHg from baseline
Diastolic blood pressure	≤50 mmHg and decrease ≥15 mmHg from baseline	≥105 mmHg and increase ≥15 mmHg from baseline
Pulse rate	≤50 bpm and decrease ≥15 bpm from baseline	≥120 bpm and increase ≥15 bpm from baseline
Temperature		≥38.3°C and increase ≥1.1°C from baseline

bpm=Beats per minute

5. ANALYSIS POPULATIONS

The study will use the following analysis populations for data summaries.

Table 16: Analysis Populations

Population	Definition	Analysis
Safety Population	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
Full Analysis Set (FAS)	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.

6. STATISTICAL METHODS

6.1. General Methodology

All statistical tests, summary tables and data listings will be prepared using SAS version 9.4 or higher.

All statistical tests will be performed with a significance level of α=0.05, unless specified otherwise and will be supported by presenting estimates and 95% confidence intervals (CI).

Continuous data will be summarized using descriptive statistics. Discrete data will be summarized using frequency and percentages. The denominator will be based on the number of evaluable participants in the appropriate population.

For the purpose of display, the summary results will be rounded as follows:

- Minimum and maximum: same number of decimal places as the raw data
- Mean and Median: one decimal place more than the raw data
- Standard deviation (SD): Two decimal places more than the raw data
- Percentages will be displayed with one decimal place precision

For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables.

Summary tables, participant listings and any supportive SAS output will include footnotes that will indicate:

- Date of data extraction
- Date and time of output generation
- SAS program name, including the path, which generated the output

When calculating percentages, the denominator will be based on the number of participants with non-missing values. If the denominator is expected to change over time, then the denominator used to calculate the percentage will be based on the number of participants with non-missing

values at each visit. Any participant removed from an analysis will be noted at the bottom of the table along with the reason the participant was removed.

Empty summary tables will be presented with a note stating that "No Participants Met Criteria".

Participant listings of all data from the eCRFs as well as any derived variables will be presented.

6.2. Derived Variables

Table 17 defines the derived variables for study parameters.

Table 17: Derived Variables and Definition

Variable	Definition
Age Group (years)	18 – <30 30 – <45 45 – 60
Height (cm)	If height is recorded in inches, then height is equal to the recorded value multiplied by 2.54 and then rounded to 1 decimal place.
Weight (kg)	If weight is recorded in pounds, then weight is equal to the recorded value multiplied by 0.454 and then rounded to 1 decimal place.
Body Mass Index (BMI)	BMI will be computed using height measured at screening and body weight measured at respective visits as, BMI (kg/m^2) = Weight (kg) / Height $(m)^2$
Relative Day	The day of first injection of study intervention will be considered as relative Day 1.
Study Day (for assessment on or after Day 1)	Study Day will be computed as: Date of Assessment – Date of Day 1 + 1
Study Day (for assessment before Day 1)	Study Day will be computed as: Date of Assessment – Date of Day 1
Baseline	Baseline is defined as the last non-missing measurement/assessment prior to the first dose of study intervention. The assessments made in unscheduled visits will be considered in calculation of the baseline.
Baseline for Vital Signs on Injection Days	For vital signs on injection days, the baseline value will be the vital sign measure immediately prior to the first dose of study intervention.
Change from baseline	Change from baseline will be derived as: post baseline visit/time point value – the baseline value.
Last (analysis)	Last is defined as the last non-missing measurement/assessment post the first dose of study drug intervention
Duration (Minutes) of Exposure at each visit	Date/Time of Last Injection – Date/Time of First Injection
Duration (Days) of AE	AE end date – AE start date + 1
AE Start Day	AE start date – Date of Day 1 + 1
AE Stop Day	AE end date – Date of Day 1 + 1
Cellulite History (years) (≥ 5 or < 5)	Day of Screening – Start Date of Cellulite History

6.3. Handling of Missing Data

Participants who withdraw from the study after the initiation of the study intervention will not be replaced and available data for these participants until the point of withdrawal will be summarized. However, the participants lost to follow-up at any time after the first dose of QWO (CCH-aaes) may be replaced.

Missing baseline assessments will not be imputed.

For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables.

There will be no imputation of missing values for safety data, however a missing relationship between AE and study intervention will be considered as related to study intervention following worst case principle. Missing severity of an AE will be summarized as a severe AE. Duration of the AE is classified in the '>21 Days" category if an AE is ongoing for more than 21 days by the last visit of the participant in the study.

6.3.1. Imputation of Partial Dates

6.3.1.1. TEAE Status for Completely Unknown Start Date

The following rules will apply in cases where start date of an AE is completely unknown:

- If the AE onset date is unknown and the end date is on or after first injection on Day 1 or ongoing, then the AE will be considered a TEAE.
- If the AE onset date is unknown and the end date is before first injection on Day 1, then the AE will not be considered a TEAE.
- If both the start and end dates are unknown (or end date is ongoing), then the AE will be considered a TEAE, following the worst-case principle.
- If the AE onset date is partly present and month/year is prior to the first injection date, then the AE will not be considered a TEAE.

6.3.1.2. Concomitant Status of Medication for Completely Unknown Start Date

The following rules will apply in cases where start date of concomitant medication is completely unknown:

- If the medication onset date is unknown and the end date is after the screening date but before the Day 180/EOS/ET visit date or the medication is ongoing, then the medication will be considered as concomitant.
- If the medication onset date is unknown and the end date is before the screening date, then the medication will not be considered as concomitant.
- If both the start and end dates are unknown, then the medication will be considered as concomitant. This approach is considered to be the most conservative following the worst-case principle.
- If the medication onset date is partly present and month/year is prior to the first injection date, then the medication will not be considered as concomitant.

6.3.1.3. Missing Last Menstrual Date

Missing date of last menstrual period will be imputed with the last day of the month and missing onset month will be imputed with December.

6.4. Interim Analysis

No interim analysis is planned for this study.

6.5. Stopping Rules for Study

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

7. STATISTICAL ANALYSES

7.1. Participant Disposition

The number of participants included in each study population will be summarized by each cohort and overall. Participants excluded from the Safety Population and FAS will be listed.

The frequency and percentages of participants screened, enrolled, completed, and/or withdrawn from the study, as well as the reason for withdrawal from study will be summarized by each cohort and overall.

A listing of disposition data will be provided. Screen failure reasons will also be listed. In addition, listing for inclusion/exclusion criteria will also be presented.

7.2. Protocol Deviations

Protocol deviations will be summarized by deviation classification (important/not important), for each of the 7 cohorts and overall. A listing of all protocol deviations will be presented.

7.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by overall and each cohort for both the Safety Population and FAS. Refer to Table 14 for the list of parameters.

All the continuous variables will be summarized using descriptive statistics. Rest of the categorical variables will be summarized by frequency and percentages.

The following baseline characteristics will be summarized using frequency and percentages:

- CR-PCSS cellulite severity ratings for buttock by visit (mean and SD will also be provided).
- Hexsel CSS scores by visit (mean and SD will also be provided).
- IABSS by visit (mean and SD will also be provided).

All demographic and baseline characteristics will be presented in participant listings.

7.4. Medical and Surgical History

Medical history will be coded using MedDRA version 25.0. Medical and surgical history data will not be summarized; however, a participant listing will be provided.

7.5. Prior/Concomitant Medications and Procedures

Prior and concomitant medications will be summarized by each cohort and overall using frequency and percentages by active ingredient within each ATC, with ATC and active ingredients ordered alphabetically. Prior and concomitant procedures (nondrug therapies) will be summarized by each cohort and overall using frequency and percentages with name of the procedures ordered alphabetically. Multiple uses of the same medication/procedure by a participant will be counted only once.

A participant listing of medications indicating prior and concomitant medications and procedures will be provided. Similarly, only listing for cellulite history will also be presented.

7.6. Efficacy Analyses

Efficacy parameters will be summarized for each treatment areas for each cohort using the FAS.

7.6.1. Primary Analysis

7.6.1.1. Cohort 1-6: The proportion of one-level IABSS responders, at Visit 3, three to five days after initial QWO (CCH-aaes) injection.

The primary estimand for cohort 1 to 6 is defined by the following:

- **The *primary* clinical question of interest is:** In adult female participants with moderate to severe cellulite, what is the proportion of participants in Cohort 1-6, whose left buttock (investigational side) demonstrates at least 1-level lower IABSS score versus the right buttock (control side) on the IABSS, at Visit 3, 3 to 5 days after initial QWO (CCH-aaes) injection?
- **Treatment condition:** Participants will be assigned to 1 of 6 cohorts.
- **Target Population:** Adult females with a CR-PCSS score of 3 or 4 on both buttocks, Hexsel CSS $\leq$ 12, with a BMI of 18 to < 32 kg/m^2 (normal or overweight) and Fitzpatrick skin type of I-IV who are included in the FAS.
- **Variable (Endpoint) of interest:** Proportion of one-level IABSS responders at Visit 3, 3 to 5 days after initial QWO (CCH-aaes) injection for Cohort 1-6. Refer to Section 4.5.1 for one-level IABSS responder definition.
- **Treatments being compared:** The labelled dose and concentration will be compared to administering the labelled dose or lower doses in different diluent additives, concentrations, depths of injection, and methods of injection (refer to Table 2).
- **Intercurrent Event:** Not applicable.
- **Population Level-Summary measure:** Not applicable.

- **Method of Analyses:** The one-level IABSS responders will be summarized for each cohort using frequency, proportion and corresponding 95% CI based on the Clopper-Pearson method for one-level IABSS responders at Visit 3, 3 to 5 days after the initial QWO (CCH-aaes) injection for Cohort 1-6.
- **Supportive analysis to primary endpoint:** Not applicable.

IABSS ratings will be summarized by treatment area at each visit for all 7 cohorts and overall. A listing of IABSS ratings by participant will be provided.

7.6.1.2. Cohort 7a: The proportion of one-level IABSS responders, at Visit 3 versus Visit 8, three to five days after initial QWO (CCH-aaes) injection at respective visit.

The primary estimand for cohort 7a is defined by the following:

- **The *primary* clinical question of interest is:** In adult female participants with moderate to severe cellulite, what is the proportion of participants in Cohort 7a whose left buttock (investigational side), at Visit 3, demonstrates at least 1-level lower IABSS score versus the right buttock (control side), at Visit 8?
- **Treatment condition:** Participants will be assigned to Cohort 7a.
- **Target Population:** Adult females with a CR-PCSS score of 3 or 4 on both buttocks, Hexsel CSS $\leq$ 12, with a BMI of 18 to < 32 kg/m^2 (normal or overweight) and Fitzpatrick skin type of I-IV who are included in the FAS.
- **Variable (Endpoint) of interest:** Proportion of one-level IABSS responders at Visit 3 versus Visit 8, 3 to 5 days after initial QWO (CCH-aaes) injection for each respective visit for Cohort 7a. Refer to Section 4.5.1 for one-Level IABSS responder definition.
- **Treatments being compared:** The labelled dose and concentration will be compared to administering the labelled dose or lower doses in different diluent additives, concentrations, depths of injection, and methods of injection (refer to Table 2).
- **Intercurrent Event:** Not applicable.
- **Population Level-Summary measure:** Not applicable.
- **Method of Analyses:** The one-level IABSS responders will be summarized for each cohort using frequency, proportion and corresponding 95% CI based on the Clopper-Pearson method for one-level IABSS responders at Visit 3 versus Visit 8, 3 to 5 days after initial QWO (CCH-aaes) injection for each respective visit for Cohort 7a.
- **Supportive analysis to primary endpoint:** Not applicable.

7.6.1.3. Cohort 7b: The proportion of one-level IABSS responders, at Visit 8 versus Visit 3, three to five days after initial QWO (CCH-aaes) injection at respective visit.

The primary estimand for Cohort 7b is defined by the following:

- **The *primary* clinical question of interest is:** In adult female participants with moderate to severe cellulite, what is the proportion of participants in Cohort 7b whose left buttock (investigational side), at Visit 8, demonstrates at least 1-level lower IABSS score versus the right buttock (control side), at Visit 3?
- **Treatment condition:** Participants will be assigned to Cohort 7b.
- **Target Population:** Adult females with a CR-PCSS score of 3 or 4 on both buttocks, Hexsel CSS ≤ 12, with a BMI of 18 to < 32 kg/m^2 (normal or overweight) and Fitzpatrick skin type of I-IV who are included in the FAS.
- **Variable (Endpoint) of interest:** Proportion of one-level IABSS responders at Visit 8 versus Visit 3, 3 to 5 days after initial QWO (CCH-aaes) injection for each respective visit for Cohort 7b. Refer to Section 4.5.1 for one-Level IABSS responder definition.
- **Treatments being compared:** The labelled dose and concentration will be compared to administering the labelled dose or lower doses in different diluent additives, concentrations, depths of injection, and methods of injection (refer to Table 2).
- **Intercurrent Event:** Not applicable.
- **Population Level-Summary measure:** Not applicable.
- **Method of Analyses:** The one-level IABSS responders will be summarized for each cohort using frequency, proportion and corresponding 95% CI based on the Clopper-Pearson method for one-level IABSS responders at Visit 8 versus Visit 3, 3 to 5 days after initial QWO (CCH-aaes) injection for each respective visit for Cohort 7b.
- **Supportive analysis to primary endpoint:** Not applicable.

7.6.2. Secondary Efficacy Endpoints

7.6.2.1. Secondary Endpoint 1: 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 1st secondary estimand is defined by following:

- **The *secondary* clinical question of interest is:** In the adult female participants with moderate to severe cellulite, what is the proportion of participants in Cohort 1-6 whose left buttock (investigational side) demonstrates at least 1-level lower score versus the right buttock (control side) on the IABSS, at each visit?
- **Treatment condition:** Participants will be assigned to 1 of 6 cohorts.
- **Target Population:** Adult females with a CR-PCSS score of 3 or 4 on both buttocks, Hexsel CSS ≤ 12, with a BMI of 18 to < 32 kg/m^2 (normal or overweight) and Fitzpatrick skin type of I-IV who are included in the FAS.
- **Variable (Endpoint) of interest:** In Cohort 1-6, proportion of one-level IABSS responders at each visit. Refer to Section 4.5.1 for one-level IABSS responder definition.

- **Treatments being compared:** The labelled dose and concentration will be compared to administering the labelled dose or lower doses in different diluent additives, concentrations, depths of injection, and methods of injection (refer to Table 2).
- **Intercurrent Event:** Not applicable.
- **Population Level-Summary measure:** Not applicable.
- **Method of Analyses:** The one-level IABSS responders will be summarized for each cohort using frequency, proportion and corresponding 95% CI based on the Clopper-Pearson method for one-level IABSS responders. For Cohort 1-5, the summary tables will be given for Visit 2-Visit 15 and for Cohort 6 it will be for Visit 2-Visit 11.
- **Supportive analysis to secondary endpoint:** Not applicable.

7.6.2.2. Secondary Endpoint 1: 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 and at each follow up visit thereafter.

The 2nd secondary estimand is defined by following:

- **The *secondary* clinical question of interest is:** In the adult female participants with moderate to severe cellulite, what is the proportion of participants within Cohort 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?
- **Treatment condition:** Participants will be assigned to Cohort 7a and 7b.
- **Target Population:** Adult females with a CR-PCSS score of 3 or 4 on both buttocks, Hexsel CSS ≤ 12, with a BMI of 18 to < 32 kg/m^2 (normal or overweight) and Fitzpatrick skin type of I-IV who are included in the FAS.
- **Variable (Endpoint) of interest:** In Cohort 7, proportion of one-level IABSS responders, 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. Refer to Section 4.5.1 for one-level IABSS responder definition.
- **Treatments being compared:** The labelled dose and concentration will be compared to administering the labelled dose or lower doses in different diluent additives, concentrations, depths of injection, and methods of injection (refer to Table 2).

- **Intercurrent Event:** Not applicable.
- **Population Level-Summary measure:** Not applicable.
- **Method of Analyses:** The one-level IABSS responders will be summarized for each cohort using frequency, proportion and corresponding 95% CI based on the Clopper-Pearson method for one-level IABSS responders at Visit 2-Visit 20 for Cohort 7a and 7b.
- **Supportive analysis to secondary endpoint:** Not applicable.

7.6.2.3. Secondary Endpoint 2: The proportion of participants with an improved (+1 or better) score on the Investigator-Global Aesthetic Improvement Scale (I-GAIS) by treatment area for Cohort 1-5 at Visit 6 (Day 22), Visit 11 (Day 43), Visit 16 (Day 90), Visit 17 (Day 135) and Visit 18 (Day 180). For Cohort 6 at Visit 7 (Day 43), Visit 12 (Day 90), Visit 13 (Day 135) and Visit 14 (Day 180) and for Cohort 7 at Visit 6 (Day 22), Visit 11 (Day 43), Visit 16 (Day 64), Visit 21 (Day 90), Visit 22 (Day 135) and Visit 23 (Day 180).

The 3rd secondary estimand is defined by following:

- **The *secondary* clinical question of interest is:** In the adult female participants with moderate to severe cellulite, what is the proportion of participants with an improved (+1 or better) score on I-GAIS for each treatment area for Cohort 1-5 at Visit 6 (Day 22), Visit 11 (Day 43), Visit 16 (Day 90), Visit 17 (Day 135) and Visit 18 (Day 180); for Cohort 6 at Visit 7 (Day 43), Visit 12 (Day 90), Visit 13 (Day 135) and Visit 14 (Day 180) and for Cohort 7 at Visit 6 (Day 22), Visit 11 (Day 43), Visit 16 (Day 64), Visit 21 (Day 90), Visit 22 (Day 135) and Visit 23 (Day 180)?
- **Treatment condition:** Participants will be assigned to 1 of 7 cohorts.
- **Target Population:** Adult females with a CR-PCSS score of 3 or 4 on both buttocks, Hexsel CSS $\leq$ 12, with a BMI of 18 to < 32 kg/m^2 (normal or overweight) and Fitzpatrick skin type of I-IV who are included in the FAS.
- **Variable (Endpoint) of interest:** Proportion of one-level I-GAIS responders for Cohort 1-5 at Visit 6 (Day 22), Visit 11 (Day 43), Visit 16 (Day 90), Visit 17 (Day 135) and Visit 18 (Day 180). For Cohort 6 at Visit 7 (Day 43), Visit 12 (Day 90), Visit 13 (Day 135) and Visit 14 (Day 180) and for Cohort 7 at Visit 6 (Day 22), Visit 11 (Day 43), Visit 16 (Day 64), Visit 21 (Day 90), Visit 22 (Day 135) and Visit 23 (Day 180). Refer to Section 4.5.2 for one-level I-GAIS responder definition.
- **Treatments being compared:** The labelled dose and concentration will be compared to administering the labelled dose or lower doses in different diluent additives, concentrations, depths of injection, and methods of injection (refer to Table 2).
- **Intercurrent Event:** Not applicable.
- **Population Level-Summary measure:** Not applicable.

- **Method of Analyses:** The one-level I-GAIS responders will also be summarized by treatment area for each cohort using frequency, proportion and corresponding 95% CI based on the Clopper-Pearson method for one-level I-GAIS responders. The summary tables will be provided for Cohort 1-5 at Visit 6 (Day 22), Visit 11 (Day 43), Visit 16 (Day 90), Visit 17 (Day 135) and Visit 18 (Day 180). For Cohort 6 at Visit 7 (Day 43), Visit 12 (Day 90), Visit 13 (Day 135) and Visit 14 (Day 180) and for Cohort 7 at Visit 6 (Day 22), Visit 11 (Day 43), Visit 16 (Day 64), Visit 21 (Day 90), Visit 22 (Day 135) and Visit 23 (Day 180).
- **Supportive analysis to secondary endpoint:** Not applicable.

I-GAIS ratings will be summarized for Cohort 1-5 at Visit 6 (Day 22), Visit 11 (Day 43), Visit 16 (Day 90), Visit 17 (Day 135), and Visit 18 (Day 180). For Cohort 6 at Visit 7 (Day 43), Visit 12 (Day 90), Visit 13 (Day 135), and Visit 14 (Day 180) and for Cohort 7 at Visit 6 (Day 22), Visit 11 (Day 43), Visit 16 (Day 64), Visit 21 (Day 90), Visit 22 (Day 135) and Visit 23 (Day 180) by treatment area for each of the cohorts. The I-GAIS ratings by participant at each visit will be listed.

7.6.3. Exploratory Efficacy Analysis

7.6.3.1. [redacted]

The exploratory estimand is defined by the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- **Intercurrent Event:** Not applicable.
- **Population Level-Summary measure:** Not applicable.

- [redacted]
- **Supportive analysis to primary endpoint:** Not applicable.

7.7. Safety Analyses

Safety data will be summarized by treatment area (left and right buttock) and overall, for each of the 7 cohorts using the Safety Population.

7.7.1. Study Intervention Exposure

The following will be summarized at each treatment visit by each of the 7 cohorts for each treatment area (left or right) using descriptive statistics:

- Total number of injections given
- Dose (mg) of each treatment visit
- Duration of exposure (refer to Table 17 for computation of exposure duration)

The number of participants treated at each treatment visit will be summarized using frequency and percentages by treatment area for each cohort.

A participant listing of intervention exposure information will be provided by cohort.

7.7.2. Adverse Events

All AE summary tables will include only TEAEs, unless otherwise specified. TEAEs will be summarized by SOC and PT. A participant will only be counted once per SOC and PT.

For TEAEs by severity grade (mild, moderate, severe), if a participant has multiple events occurring in the same SOC or same PT, then the event with the maximum intensity (ie, severe) will be counted.

For TEAEs by relationship to study intervention, if a participant has multiple events occurring in the same SOC or same PT, the event with the highest association (ie, related) to study intervention will be summarized.

An overall summary of TEAEs and TEAEs related to study intervention will be presented and will include:

- Total number of TEAEs reported
- Total Number of TEAEs of Injection site reaction
- Total number of TEAEs reported by severity
- Participants with any TEAE
- Participants with TEAEs of Injection site reaction
- Participants with any serious TEAE

- Participants with any severe TEAE
- Participants with no severe TEAEs, but at least one moderate TEAE
- Participants with no severe TEAEs, but at least one mild TEAE
- Participants with any TEAEs leading to intervention interruption/discontinuation
- Participants with any TEAEs leading to withdrawal from study
- Participants with any TEAEs resulting in death

The following summary tables will be presented by SOC and PT:

- All TEAEs
- Study intervention related TEAEs
- TEAEs by severity
- Study intervention related TEAEs by severity
- Duration of study intervention related TEAEs
- Serious TEAEs

Refer to Table 17 for computation of duration of AEs. All TEAEs will be presented for Left Buttock, Right Buttock, Others (Not Applicable) and overall. For AEs where treatment location is neither Left Buttock nor Right Buttock will be collected as "Not Applicable" and is displayed under Others (Not Applicable) category.

The proportion of participants reporting TEAEs of injection site reaction in the left vs the right buttock will be summarized using frequency, proportion and corresponding 95% CI based on the Clopper-Pearson method.

The most common non-serious TEAEs by order of frequency (most frequent, 2nd most frequent, and 3rd most frequent) will be summarized by PT. The most common non-serious AEs are those with any PT that at least 5% of the participants reported at least once.

The following listings will be presented by participant:

- All AEs
- Fatal AEs
- Non-fatal serious AEs
- Non-fatal non-serious AEs leading to study discontinuation
- Non-fatal non-serious AEs resulting in intervention interruption/withdrawn

7.7.3. Clinical Laboratory

Hematology and biochemistry results will be summarized by treatment area and overall using descriptive statistics for observed and change from baseline to Last.

The PCI laboratory values will be summarized by treatment area and overall using frequency and percentages. Refer to Table 14 for PCI criteria.

A participant listing (including urinalysis results) will be presented for all laboratory parameters. Serum and urine pregnancy test results will also be listed.

7.7.4. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, body weight, BMI and body temperature) will be summarized by each cohort and overall using descriptive statistics for the observed and change from baseline values for all assessments visits. Baseline (study baseline) will be the vital sign value taken at Day 1, 2 hours prior to injection for the by-visit analyses.

The PCI vital signs values will be summarized by each cohort and overall using frequency and percentages. Refer to Table 15 for PCI criteria.

A participant listing will be presented for vital sign results.

7.7.5. Physical Examination

Physical examination results (by body system) at baseline will be presented by cohort and overall using frequency and percentages.

A participant listing will be presented for the physical examination result (by body system).

8. CHANGE FROM PROTOCOL

This SAP is prepared based on Protocol Amendment 2: August 12, 2022. Table 18 lists any significant changes in the SAP from what is proposed in the protocol.

Table 18: Changes from Protocol

Text in Protocol	Change in SAP	Justification
Section 9.1.3 - The investigator (or qualified designated physician) will determine the Fitzpatrick skin type for all participants on Day 1.	Section 3.9.3 - The investigator (or qualified designated physician) will determine the Fitzpatrick skin type for all participants on Screening.	As per SoA (Table 3, Table 4, Table 5, and Table 6) Fitzpatrick skin type for all participants should be on Screening.
Section 7.5: 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.	Any medication/procedure taken/done prior to first injection (Day 1) will be reported as prior medication/procedure.	As per discussion with Endo, this has been updated.
Section 7.1: In Table 2, the footnotes are incorrectly aligned with the table text. For example, in the text: Cohort 7a Right Buttock (control side)[a] where, [a] The investigational side will be treated with QWO (CCH-aaes) on Days 1, 22, and 43.	SAP Section 3.5: In Table 7, footnotes are now correctly aligned with table text. For example, in the text: Cohort 7a Right Buttock (control side)[b] where, [b] The control side will be treated with QWO (CCH-aaes) on Days 22, 43, and 64.	

9. REFERENCES

1. Protocol Amendment 2: 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 [Clinical Study Protocol EN3835-226 CEL]. Dated: August 12, 2022
2. 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
3. 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
4. Protocol Administrative Change Letter No. 01: 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 [Clinical Study Protocol EN3835-226 CEL]. Dated: September 15, 2022

10. APPENDIX

All the SAS codes will be provided in SAP Module 2.

11. TABLES, LISTINGS, AND GRAPH SHELLS

The layouts of the summary tables, participant listings, and graphs are presented in SAP Module 2. These layouts incorporate all the appropriate table titles, table numbers, and footnotes.