CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761146Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multidisciplinary Review and Evaluation

Application Type	Original BLA, on specialized 10-month review (policy exception)
Application Number(s)	BLA 761146
Priority or Standard	Standard
Submit Date(s)	September 6, 2019
Received Date(s)	September 6, 2019
PDUFA Goal Date	July 6, 2020
Division/Office	Division of Dermatology and Dentistry /Office of Immunology and Inflammation
Review Completion Date	June 24, 2020
Established/Proper Name	Collagenase clostridium histolyticum-aaes
(Proposed) Trade Name	Qwo (collagenase clostridium histolyticum-aaes) for injection
Pharmacologic Class	Collagenase
Code Name	EN3835
Applicant	Endo Global Aesthetics Ltd.
Dosage Form	Sterile, lyophilized powder for reconstitution
Applicant Proposed Dosing Regimen	Inject 0.84 mg per treatment area as 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection)
Applicant Proposed Indication(s)/Population(s)	For the treatment of moderate to severe cellulite in the buttocks of adult women
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	301854006 /Skin dimple
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of moderate to severe cellulite in the buttocks of adult women
Recommended SNOMED CT Indication Disease Term for Each Indication (if applicable)	301854006 /Skin dimple
Recommended Dosing Regimen	Injected subcutaneously at a dose of 0.84 mg per treatment area [single buttock receiving up to 12 injections, 0.3 mL each (up to a total of 3.6 mL)]. A treatment visit may consist of up to 2 treatment areas. Treatment should be repeated every 21 days for 3 treatment visits.

Table of Contents

Table of Tables

Table of Figures

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OPQ = Office of Pharmaceutical Quality
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OPRO = Office of Program & Regulatory Operations
OPMA = Office of Pharmaceutical Manufacturing Assessment
PLT = Patient labeling
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
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Glossary

ADA	antidrug antibody
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
AUX-I	clostridial type I collagenase
AUX-II	clostridial type II collagenase
AR	adverse reaction
AUX-II	clostridial type II collagenase
AR	adverse reaction
AUX-II	clostridial type II collagenase
BLA	biologics license application
BMI	body mass index
CCH	collagenase clostridium histolyticum
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
COA	clinical outcome assessment
CR-PCSS	Clinician-Reported Photonumeric Cellulite Severity Scale
CQA	Critical Quality Attribute
DC	Dupuytren's contracture
DHOT	Division of Hematology Oncology Toxicology
DP	drug product
DS	drug substance
ECG	electrocardiogram
EFP	edematous fibrosclerotic panniculopathy
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
I-GAIS	Investigator Global Aesthetic Improvement Scale
IND	investigational new drug
ITT	intent-to-treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent-to-treat
NDA	new drug application
Nab	neutralizing antibody
OPDP	Office of Prescription Drug Promotion
PCI	potentially clinically important
PD	Peyronie's disease
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment

PMR	postmarketing requirement
PP	per protocol
PR-CIS	Patient-Reported Cellulite Impact Scale
PR-PCSS	Patient-Reported Photonumeric Cellulite Severity Scale
PRO	patient-reported outcome
REMS	Risk Evaluation and Mitigation Strategy
S-GAIS	Subject Global Aesthetic Improvement Scale
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOC	system organ class
SSRS	Subject Self-Rating Scale
SUR	safety update report
TEAE	treatment-emergent adverse event
TFF	tangential flow filtration

1. Executive Summary

1.1. Product Introduction

Endo Global Aesthetics Limited submitted original biologics license application (BLA) 761146 under section 351(a) of the Public Health Service Act for Qwo (collagenase clostridium histolyticum-aaes) for injection, for the treatment of moderate to severe edematous fibrosclerotic panniculopathy (EFP), otherwise known as cellulite, in the buttocks of adult women.

Collagenase clostridium histolyticum-aaes (CCH; previously identified as EN3835, AA4500) is a combination of bacterial collagenases, clostridial type I collagenase (AUX-I) and clostridial type II collagenase (AUX-II), in an approximate 1:1 mass ratio which are isolated and purified from the fermentation of the Clostridium histolyticum bacterium. Collagenase clostridium histolyticum (CCH) was approved as Xiaflex (collagenase clostridium histolyticum) for injection, for intralesional use in 2010 for the treatment of adult patients with Dupuytren's contracture with a palpable cord and in 2013 for the treatment of adult men with Peyronie's disease. The Applicant is seeking labeling for this product that is distinct from Xiaflex due to differences in the formulation and labeling for the target population.

After reconstitution with the supplied diluent, the proposed dosing regimen is injection of 0.84 mg of Qwo per treatment area as 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection). A treatment area is defined as a single buttock receiving up to 12 injections, 0.3 mL each (up to a total of 3.6 mL) of Qwo. A treatment visit may consist of up to 2 treatment areas. Treatment visits should be repeated every 21 days for 3 treatment visits. Qwo for injection is supplied as a sterile, preservative-free, lyophilized powder (appearing as a white cake) in single-dose vials for subcutaneous use after reconstitution with the Diluent for Qwo. For a single treatment area, one Qwo 0.92-mg single-dose vial is packaged with one diluent 4-mL single-dose vial; for two treatment areas, one Qwo 1.84-mg single-dose vial is packaged with one diluent 8-mL single-dose vial.

The Food and Drug Administration (FDA) concluded that the proposed proprietary name, Qwo, was acceptable from both a safety and misbranding perspective under BLA 761146 [Proprietary Name Review by Madhuri Patel, PharmD, MBA June 12, 2020].

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well-controlled trials [Trial EN3835-302 (302) and Trial EN3835-303 (303)] which provided evidence of the effectiveness of CCH for the treatment of moderate to severe cellulite in the buttocks of adult women. Both trials assessed the changes from baseline to Day 71 compared to placebo on a multicomponent endpoint

which required success (a 2-level improvement) on both the clinician and patient scales. The prespecified primary efficacy endpoint was the proportion of 2-level multicomponent responders at Day 71 of the target buttock defined as subjects with:

- an improvement in severity from baseline of at least 2 levels of severity in the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) as assessed live by the investigator of the target buttock, and
- an improvement in severity from baseline of at least 2 levels of severity in the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) as assessed by the subject while viewing the digital image of the target buttock.

CCH was statistically superior to placebo on the multicomponent endpoint in both trials. The Applicant has met the evidentiary standard for adequate and well controlled trials required by 21 CFR 314.126(a)(b) to support approval and has demonstrated that CCH is effective for its intended use in the target population.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Edematous fibrosclerotic panniculopathy (EFP), also known as cellulite, is a common, local metabolic condition of subcutaneous tissues which results in an irregular skin contour. The proposed indication for Qwo (collagenase clostridium histolyticum-aaes) for injection is the treatment of moderate to severe cellulite in the buttocks of adult women. Collagenase clostridium histolyticum (CCH), the active ingredient in Qwo, is a combination of bacterial collagenases, clostridial type I collagenase (AUX-I) and clostridial type II collagenase (AUX-II), which are isolated and purified from the fermentation of Clostridium histolyticum bacteria. Collagenases are proteinases that hydrolyze collagen in its native triple helical conformation under physiological conditions. The exact mechanism for the treatment of moderate to severe cellulite is unknown.

There are no Food and Drug Administration (FDA) approved pharmacologic therapies for the treatment of cellulite. For patients seeking treatment for cellulite, the primary therapeutic options include surgery with subcision of collagenous connective tissues, various laser or radiofrequency devices and fillers. All of the treatment options are associated with potential adverse reactions which include pain, infection, bleeding, hematoma and nodule formation. These approaches may require multiple treatment visits and provide variable and transient improvement. Because of these limitations, there is a recognized need for additional therapeutic options.

Substantial efficacy was demonstrated in two pivotal trials. In Trial 302 and 303, 843 adult female subjects with moderate to severe cellulite received CCH (N=424) or placebo (N=419). At baseline, subjects had two buttocks with a score of 3 (moderate) or 4 (severe) on both the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS). Subjects with a coagulation disorder, history of keloidal scarring/ abnormal wound healing, lower extremity thrombosis, vascular disorder, inflammation, active infection, severe skin laxity, flaccidity, and/or sagging were excluded from participation. Eligible subjects were randomized in a 1:1 ratio to receive either placebo or 0.84 mg of CCH per buttock as 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection). Subjects received injections of CCH or placebo in each buttock during a treatment visit which was repeated every 21 days for 3 treatment visits. The duration of each trial was 71 days.

The primary assessment of efficacy was the proportion of 2-level composite responders at Day 71 of the target buttock defined as subjects with:

- an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS as assessed live by the investigator of the target buttock, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock.

In Trials 302 /303, CCH was superior to placebo (Trial 302:7.6% vs. 1.9%; Trial 303: 5.6% vs. 0.5%, p-values 0.006 and 0.002 respectively). There were 8 key secondary endpoints for Trials 302 /303 which were grouped into 3 families according to the assessment scale (i.e., CR-PCSS/ PR-PCSS, Subject Self-rating Scale [SSRS]/ Patient-Reported Cellulite Impact Scale [PR-CIS] or Subject Global Aesthetic Improvement Scale [S-GAIS]). Secondary endpoints for both trials included the proportion of subjects at Day 71 who achieved i) 1-Level Improvement multicomponent success, ii) 1-Level Improvement PR-PCSS Success iii) 2-Level Improvement PR-PCSS success, and iv) 2-Level Improvement multicomponent success on the non-target buttock in addition to endpoints on other patient-reported outcome (PRO) scales (i.e., the SSRS, S-GAIS, and PR-CIS). The SSRS was assessed as fit-for-purpose[1] to evaluate cellulite emotional/visual impact including satisfaction with cellulite appearance. For the context of use in this drug development program, the S-GAIS and PR-CIS were not fit-for-purpose to measure global aesthetic improvement and cellulite appearance satisfaction. However, all secondary endpoints were statistically significant.

The primary safety database, which consisted of data from the pooled Phase 3 Trials 302 and 303, was adequate to characterize the safety profile of Qwo for the treatment of moderate to severe cellulite. The size of the overall safety database was considered adequate and consistent with ICH E1 and included 964 adult female subjects with EFP who received the proposed dose of CCH,

[1] Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use (FDA-NIH Biomarker Working Group 2016).

0.84 mg per treatment area (buttock or thigh). Among the 704 subjects who received the proposed dose for the proposed indication (EFP in the buttocks), 187 completed 6 months of follow-up and 110 completed 1 year of follow-up. A total of 18 subjects from Trial 202 with EFP in the buttocks received CCH and completed more than 1 year of follow-up.

Based on the analysis of the submitted data, treatment with CCH did not increase the risk of mortality or incidence of serious adverse events (SAEs). In the development program, there were no serious hypersensitivity reactions. After administration, systemic exposure to CCH was not quantifiable with the available assays. Therefore, the most common adverse reactions involved the injection site. Adverse reactions, occurring in ≥1% and observed more frequently in subjects who received CCH compared to placebo through Day 71 included: injection site bruising (84% vs. 21%), injection site pain (48% vs. 1%), injection site nodule (33% vs. 1%), injection site pruritus (15% vs. 1%), injection site erythema (9% vs. 5%), injection site discoloration (8% vs. 1%), injection site swelling (8% vs. 1%), and injection site warmth (3% vs. 0%).

As with all therapeutic proteins, there is potential for immunogenicity. By Day 71, most subjects (>96%) developed antibodies to AUX-I and AUX-II. In a subset of evaluable subjects, more than 50% of these subjects had neutralizing antibodies. The presence of anti-drug antibodies or their neutralizing status did not appear to impact the occurrence of injection site reactions or efficacy.

Prescription and patient labeling as well as routine pharmacovigilance measures are adequate to manage the risk of Qwo in the postmarketing setting; a Risk Evaluation and Mitigation Strategy (REMS) is not needed. As the benefits and risks are adequately characterized in the target population, postmarketing assessments under 505(o) are not required. Studies in the pediatric population are not required under the Pediatric Research Equity Act 21 U.S.C. 355c because studies are impossible or highly impracticable because the estimated number of pediatric patients with edematous fibrosclerotic panniculopathy (EFP or cellulite) is extremely small.

The available safety and efficacy data support the approval of Qwo for the treatment of adult females with moderate to severe cellulite. There are no FDA-approved pharmacologic therapies for this indication. None of the available treatment options including subcision and device-based approaches provide a permanent cure or universal response. All of these products are associated with one or more risks. Because treatment may be complicated by inadequate response, loss of response, and adverse reactions, there is a need for additional therapeutic options with acceptable benefit-risk profiles.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Edematous fibrosclerotic panniculopathy (EFP), also known as cellulite, is a local metabolic condition of subcutaneous tissues which results in irregular depressions in the skin. EFP manifests as dimpling localized to the gluteal-femoral region and, less commonly, the abdomen. EFP is a common disorder which affects an estimated 85 to 98% of post-pubertal females.	For some individuals, the dimpled skin surface creates an unacceptable cosmetic appearance which may impact self-esteem.
Current Treatment Options	• There are no FDA approved pharmacologic therapies for the treatment of EFP. Practitioners have used multiple modalities to attempt to restore the normal topography of the skin. Current approaches to treatment include surgical procedures (subcision), fillers and devices such as lasers, acoustic wave, light and radiofrequency devices. These modalities are used alone or in combination.	The effectiveness of the current treatment options is variable and may not be sustained. Other treatment options with an acceptable risk-benefit profile are needed for this common condition.
Benefit	• Qwo provides another treatment option with an acceptable risk-benefit profile for a common cosmetic concern. Some subjects maintain benefit for up to 1 year.	For patients seeking improvement in the appearance of EFP, a treatment option which may provide a sustained improvement with a limited number of treatment visits is a substantial benefit.
Risk and Risk Management	The most frequent identified risks are injection site reactions including bruising, pain and nodule formation. Systemic exposure was not quantifiable with the available assays. The presence of antidrug antibodies does not appear to impact efficacy or safety. This product is administered by a healthcare provider and product labeling is sufficient to manage the identified risks.	Risk management strategies beyond product labeling are not needed to assure safe use of this product. A REMS is not required.

1.4. Patient Experience Data

The Applicant evaluated the treatment effects of CCH in subjects with moderate to severe edematous fibrosclerotic panniculopathy (EFP) of the buttocks using a number of investigator and subject reported outcome measures. The multicomponent primary efficacy endpoint was based on assessments using two static 5-level photonumeric scales:

- Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS)
- Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS)

Other scales which assessed subject experience with the condition and treatment included:

- Subject Self-rating Scale (SSRS) is a measure that assesses subject satisfaction with appearance in association with cellulite on the buttocks using a 7-level scale that ranges from 0 (extremely dissatisfied) to 6 (extremely satisfied). (Day 1 and 71 with some differences in the questions for each timepoint.)
- Patient-Reported Cellulite Impact Scale (PR-CIS) assessed the visual and emotional impact of cellulite through 6 items (happy, bothered, self-conscious, embarrassed, looking older, or looking overweight or out of shape). Each item is rated on a numerical rating scale from 0 (not at all) to 10 (extremely).(Modified scoring so that all questions were directionally consistent.)
- Subject Global Aesthetic Improvement Scale (S-GAIS) is a 7-level scale designed for subjects to assess the global aesthetic improvement of the treated treatment area ranging from +3 (Very much improved) to -3 (Very much worse) using a single question.
- Subject Satisfaction with Cellulite Treatment Assessment is a 5-level rating scale ranging from +2 (very satisfied) to -2 (very dissatisfied) to assess satisfaction of the results of cellulite treatment on the buttocks. (Day 71)

These scales and results are discussed in greater detail in Section 9 of this review. There were no patient-reported outcome scales which measured safety parameters.

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	8
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	8
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Edematous fibrosclerotic panniculopathy (EFP) is also known as cellulite, gynoid lipodystrophy, nodular liposclerosis, edematofibrosclerotic panniculopathy, panniculosis, adiposis edematosa, dermopanniculosis deformans, and status protrusus cutis. EFP is a local metabolic condition of subcutaneous tissues which results in irregular depressions in the skin. EFP manifests as

dimpling localized to the gluteal-femoral region and, less commonly, the abdomen. For some individuals, the dimpled surface creates an unacceptable cosmetic appearance in the skin.

Some authors characterize EFP as an imbalance between the structural characteristics and biomechanical properties at the subdermal junction (Rudolph et al. 2019). The typical appearance of EFP results from the herniation of subcutaneous fat lobules through the dermo-hypodermal junction. Rigid strands of collagenous connective tissue separate subcutaneous fat lobes and connect the dermis to the underlying fascia. These septa provide stability to the subcutis. In EFP, shortening of the collagen septa due to fibrosis produces retraction at the insertion points which causes the dimpling.

An estimated 85% to 98% of post-pubertal females are affected with EFP (Khan et al. 2010) High estrogen states such as pregnancy and lactation may exacerbate the condition. Reports of EFP in males are rare. In general, EFP occurs in males with relative androgen deficiency due to castration, hypogonadism, Klinefelter's syndrome, or estrogen therapy for prostate cancer (Avram 2004). Some authors postulate that EFP affects females more frequently than males due to anatomic differences in the orientation of the fibrous septa as observed by magnetic resonance imaging. In females, the fibrous septa which cross the subcutaneous fatty layer to connect the reticular dermis to the deep fascia are perpendicular to the skin surface; in males, the fibrous septa are organized in a crisscross pattern. This orientation creates large rectangular fat lobules in females and smaller subcutaneous fat lobules in males. When the collagen septa undergo fibrosis and shortening, the retraction results in the characteristic dimpling in females but not in males (Casabona and Pereira 2017).

EFP may occur in individuals of normal weight as well as those who are obese. However, weight gain may cause EFP to become more evident. The changes that occur in adipocytes with obesity are different than those with cellulite. In generalized obesity, the increased adipose tissue mass is due to adipocyte hypertrophy and hyperplasia. By contrast, in EFP, large adipocytes which are localized to specific body regions (pelvis, thighs, abdomen and buttocks) remain metabolically stable (Quatresooz et al. 2006; Tokarska et al. 2018).

The etiopathogenesis of EFP is not completely understood. There is a complex interplay between environmental (lifestyle), hormonal and genetic factors. Current theories suggest a role for adipocyte dysfunction and abnormal structural changes including those related to the vascular endothelium and microcirculation(Tokarska et al. 2018). One theory suggests that estrogen with or without other hormones triggers an increase in the adipocyte size or number in the subcuticular lobules between the septa. The increased size of these adipocytes impacts the microcirculation and ischemia induces factors which cause thickening or shortening of the septae.

2.2. Analysis of Current Treatment Options

There are no FDA approved pharmacologic therapies for the treatment of EFP. Some of the first treatment options included: weight loss, exercise, topical therapy (e.g., methylxanthines, retinoids, and botanical extracts), mesotherapy, massage, and liposuction. More recently, practitioners have used surgical procedures (subcision), fillers and devices such as acoustic wave therapy, light therapy, laser treatment, radiofrequency devices to attempt to restore the normal topography of the skin. (Sadick et al. 2019). These modalities have been used alone or in combination. Some of the radiofrequency devices, lasers and vacuum or laser assisted subcision devices received 510 (K) clearance from the FDA for the improvement in the appearance of cellulite (Friedmann et al. 2017; Sadick et al. 2019).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Auxilium Pharmaceuticals, Inc. (Auxilium) markets collagenase clostridium histolyticum as Xiaflex (collagenase clostridium histolyticum) for injection, for intralesional use for the treatment of adult patients with Dupuytren's contracture (DC) with a palpable cord (BLA 125338 approved February 2, 2010) and for the treatment of adult men with Peyronie's disease (PD) with a palpable plaque and curvature deformity of at least 30 degrees (S-061 approved December 6, 2013). For a summary of the history of the Risk Evaluation and Mitigation Strategy (REMS) issued with the approval of Xiaflex refer to the Pharmacovigilance Review by Jessica Weintraub, PharmD (Dated February 11, 2020).

Endo Pharmaceuticals plc. acquired Auxilium on January 29, 2015 and transferred ownership of investigational new drug (IND) 110077 to Endo Global Aesthetics Limited on June 28, 2019.

3.2. Summary of Presubmission/Submission Regulatory Activity

Auxilium developed CCH under IND 110077. On May 12, 2011, the FDA issued pre-IND written responses regarding the development plan for CCH (referred to as EN3835 or AA4500) and the design of the proposed proof of concept trial, AUX-CC-830. The FDA recommended that the entry criteria include baseline disease severity, the primary endpoint be a multicomponent endpoint requiring a successful rating by both the investigator and subject to be considered a success and the efficacy evaluation be conducted as a "live" assessment using a scale with photographic representations of the severity categories.

The Applicant opened the IND on November 10, 2011, with Protocol AUX-CC-830. As the Applicant considered PIND recommendations in the design of the trial, the FDA provided limited comments in the Study May Proceed letter dated January 27, 2012.

During the development of CCH, the Applicant had additional interactions with the FDA at the following milestone meetings: Guidance meetings on December 17, 2014, December 14, 2015, June 28, 2017, October 24, 2017, March 26, 2018; End-of-Phase 2 meeting on February 8, 2017; Pre-BLA meeting on February 6, 2019. The primary topics of discussion during product development were: endpoints and appropriate measurement scales which were able to detect a clinically meaningful change, timepoint for the primary efficacy evaluation (Day 71), selection of the target population, evaluation of immunogenicity, approach to the assessment of short- and long-term safety, required number of Phase 3 trials, evaluation of durability of effect and responses after re-exposure. The Division recommended that the Applicant evaluate a prespecified region (buttocks or thigh) to allow interpretation of trial findings.

Discussion points from the key interactions included the following:

End of Phase 2 Meeting: Meeting Minutes Dated February 22, 2017

- The Applicant proposed to pursue the development of the high dose (0.84 mg) based on the results of the Phase 2a (AUX-CC-831) trial utilizing different scales than intended for Phase 3, the Cellulite Severity Scale (CSS) and the Cellulite Severity item (CSI) to evaluate the mean score change from baseline to Day 73.
- The Applicant proposed to power Phase 3 using the results from Phase 2b (EN3835-201) which demonstrated composite response [i.e., ≥2-point improvement on both the CR-PCSS and the PR-PCSS] rates of 10.6% for EN3835 and 1.6% for placebo; however, the response rate for buttock and thigh were substantially different at 13% and 4% respectively.
- The Agency agreed that the content validity for the CR-PCSS and PR-PCSS appeared to be reasonably established. However, there were concerns related to the reliability of the proposed instruments. The Agency indicated that if there was good agreement between the CR-PCSS and PRPCSS scales, that a composite endpoint of at least a 2-level improvement on both scales would be an appropriate primary efficacy endpoint.
- The Agency indicated that the preferred definition of durability of response was time from the primary efficacy evaluation (Day 71) until loss of success [not time from first improvement to return to baseline severity.]
- The Agency indicated that the scientific justification for the proposed method for handling missing data [last observation carried forward (LOCF)] was limited and the Applicant should propose a justification for this method or propose another method.
- The Agency indicated that they viewed global ratings (i.e., Investigator Global Aesthetic Improvement Scale [I-GAIS], S-GAIS) as exploratory measures that can be used as anchors for determining what constitutes a clinically meaningful change in another measure.
- Endo agreed with FDA proposal and will analyze plasma samples for ADA antibodies for each of the 4 time points (Days 1, 22, 43 and 71) at the end of the trial. In addition, a

subset of plasma samples from seropositive subjects will be assayed for neutralizing antibody activity.

- The Applicant acknowledged the need to provide safety data after re-exposure in an adequate number of subjects.

Special Protocol Assessment (SPA) Interaction [SPA – No Agreement Letter Issued January 11, 2018]

Agreements Included

- The proposal to conduct two identical, randomized, double-blind, vehicle-controlled, multicenter, parallel-group Phase 3 trials to evaluate EN3835 (CCH) for the treatment of EFP of the buttocks.
- The proposed patient population of females ≥18 years of age with each buttock having a disease severity score of 3 or 4 (moderate or severe) as reported by the subject on the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS), and a disease severity score of 3 or 4 (moderate or severe) as reported by the investigator on the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) at screening and Day 1.
- The proposed safety measures with the addition of an active local safety assessment using appropriate scales.
- The proposed primary analysis method of using the Cochran-Mantel-Haenszel test stratified by analysis center.
- The proposed primary method to handle missing data of imputing subjects with missing data as nonresponders and the sensitivity analyses of LOCF and multiple imputation (MI) were acceptable.

Non-Agreements Included

- The proposed primary endpoint of the proportion of 2-level "composite" responders at Day 71 defined as subjects with at least one of two treated buttocks with at least a 2-level improvement on both the CR-PCSS and PR-PCSS.
- The proposed secondary endpoints of the proportion of subjects with a ≥1-level improvement from baseline in PR-PCSS rating of the left and right buttock. We recommend evaluating endpoints using a ≥2-level improvement on the PR-PCSS.
- We do not concur that the Subject Global Aesthetic Improvement Scale (S-GAIS) can be used as a key secondary variable.
- We do not concur that a 1-point change in the PR-PCSS can be anchored with a 1-point change in the S-GAIS.

The Agency agreed that the other proposed primary endpoint [the proportion of 2-point "composite" responders at Day 71 of the target buttock (randomly selected prior to treatment)] was acceptable.

Agreed Initial Pediatric Study Plan Dated August 14, 2017

See Pediatrics and Assessment of Effects on Growth in Section 8.9.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

The overall quality of the clinical information contained in this submission was adequate. The Division requested that the Office of Scientific Investigations conduct clinical inspections of domestic 4 sites. The criteria used to select these sites were high enrollment, high efficacy (Sites 1348. 1299, and 1349), disparity of results on the clinician scale compared to the subject scale and prior inspection history.

Table 1. Clinical Inspection Summary

Name and Address	Site Number	# of Subjects	Classification	Inspection Dates
Trial EN3835-302 Bank, David 359 East Main Street Suite 4G Mount Kisco, NY 10549	1348	14	NAI	2-5 December 2019
Schlessinger, Joel 2802 Oak View Drive Omaha, NE 68144	1370	31	VAI	9-12 December 2019
Trial EN3835-303 Gold, Michael 2000 Richard Jones Road, Suite 223 Nashville, TN 37215	1299	37	NAI	6-9 January 2020
Coleman, III, William 4425 Conlin Street Metairie, LA 70006	1349	23	NAI	2-6 December 2019

Source: Reviewer's Table with data from CDER's Clinical Investigator Site Selection Tool Generated dated October 22, 2019 and OSI Review by Cheryl Grandinetti, PharmD dated May 13, 2020.
Key to Compliance Classifications
Abbreviations: NAI = No Action Indicated, VAI = Voluntary Action Indicated, OAI = Official Action Indicated

The Office of Scientific Investigation reviewer, Cheryl Grandinetti, PharmD, identified four subjects enrolled at Site #1370 who received CCH and one subject enrolled in Site #1348 who received placebo with unreported adverse events of special interest (AESI) (i.e., injection site bruising). Based upon the evidence of under-reporting of AESI in multiple subjects, Site #1370 received a Voluntary Action Indicated classification which indicated deviations from regulations. The other sites had no substantial deviations from regulations and were classified as No Action Indicated.

Dr. Grandinetti concluded that "the studies appear to have been conducted adequately, and the data, including the primary efficacy endpoint data for the two protocols (EN3835-302 and EN3835-303) otherwise appear acceptable in support of the respective indication" (Review by Cheryl Grandinetti, PharmD dated May 13, 2020).

4.2. Product Quality

4.2.1. Executive Summary

Product Overview

Collagenase clostridium histolyticum- aaes (CCH) is a parenteral lyophilized product comprised of two collagenase enzymes in an approximate 1:1 mass ratio: Collagenase I (AUX-I; clostridial type I collagenase) and Collagenase II (AUX-II; clostridial type II collagenase). These collagenases are isolated and purified from the fermentation of the bacteria *Clostridium histolyticum.* Collagenase I and Collagenase II have molecular weights of ~114 kDa and ~113 kDa respectively. CCH is licensed for the treatment of Peyronie's Disease and Dupuytren's Contracture in BLA 125338. For the proposed indication, the Applicant has generated a formulation containing (b) (4) (b) (4) mannitol (CCH Mannitol). CCH Mannitol is a sterile, white, lyophilized powder for reconstitution in a clear, colorless sterile diluent consisting of 0.03% calcium chloride dihydrate in 0.6% sodium chloride. Each 5 mL vial of CCH Mannitol drug product (DP) contains 0.92 mg of CCH Mannitol lyophilized powder for reconstitution in 4 mL of sterile diluent. Each 10 mL vial of CCH Mannitol DP contains 1.84 mg of CCH Mannitol lyophilized powder for reconstitution in 8 mL of sterile diluent.

Environmental Assessment

A categorical exclusion from submitting an Environmental Assessment of Qwo (collagenase clostridium histolyticum-aaes) is requested per 21 CFR 25, section 25.31(c). The protein molecule is a biodegradable product derived from a biological system. The expected concentration at the point of entry into the aquatic environment is well below 1 part per billion. No extraordinary conditions exist.

The request for categorical exclusion is granted.

Recommendations

Recommendation and Conclusion on Approvability
The Office of Pharmaceutical Quality, Center for Drug Evaluation and Research (CDER), recommends approval of BLA 761146 for Qwo (collagenase clostridium histolyticum-aaes) for injection, for subcutaneous use manufactured by Endo Pharmaceuticals, Incorporated. The data submitted in this application are adequate to support the conclusion that the manufacture of Qwo is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert.

Benefit/Risk Considerations

Review of manufacturing has identified that the methodologies used for drug substance (DS) and drug product (DP) manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. We also recommend approval of the commercial manufacture of CCH DS at Auxilium Pharmaceuticals, Horsham, Pennsylvania, USA and of CCH DP and DP sterile diluent (DPSD) at (b) (4) (b) (4). The OBP (Office of Biotechnology Products) product quality and immunogenicity assay assessments, OPMA (Office of Pharmaceutical Manufacturing Assessment) DS and DP microbiological and facility assessments, and OBP labeling technical assessments are located as separate documents in Panorama.

Recommendation on Phase 4 (Postmarketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if Approvable

PMC:

- Conduct a drug product (DP) transport qualification study shipping 5 mL and 10 mL vials of CCH Mannitol DP from (b) (4) to the (b) (4) packaging site (b) (4).
  - Target completion date: June 30, 2021
- The target filtration volume of (b) (4) mL was not achieved for one of the test filters (lot number: R6EA67189) in the bacterial retention study (b) (4) (b) (4). Conduct a bacterial retention study to simulate the target filtration volume and maximum flow rate throughout the study duration (b) (4).
  - Target completion date: June 30, 2021
- The validation runs (b) (4) (b) (4) (b) (4) in the "Manufacturing Equipment Validation Summary - Lyophilized Powder" ent in section P.3.5). In response to the Agency's Information Request dated May 6, 2020, (b) (4) (b) (4) (b) (4). Provide data summaries from recent validation runs (b) (4) (b) (4)
  - Target completion date: June 30, 2021

Summary of Quality Assessments

Critical Quality Attributes (CQAs) Identification, Risk and Lifecycle Knowledge Management

Risk and Lifecyle Knowledge Management are also informed by the BLA 125338 for CCH.

Table 2. Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Collagenase activity of AUX-I	Efficacy	Intrinsic activity to the enzyme	(b) (4)	CCH is an enzyme produced by *C. histolyticum* bacteria and therefore is not glycosylated.
Collagenase activity of AUX-II				
Synergistic collagenase activity of AUX-I and AUX-II				
Identity	Efficacy and Safety	Intrinsic to the enzyme		N/A
Metox/Desamido (fully characterized in BLA 125338)	Efficacy	Manufacturing process		Forced degradation studies assessing oxidation and deamidation revealed the presence of low molecular weight species impacting potency.
Thermal stability	Efficacy	Manufacturing process, exposure to high temperature		N/A
Zinc binding (fully characterized in BLA 125338 assessment)	Efficacy	Intrinsic to the enzyme	Zinc is not required exogenously.	N/A
Calcium (fully characterized in BLA 125338 assessment)	Efficacy	Intrinsic to the enzyme	Controlled in the formulation buffer of the DPSD.	N/A
Purity	Efficacy, Safety	Manufacturing process	(b) (4)	N/A

Table 3. DS CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Endotoxin (contaminant)	Safety and Purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process.	(b) (4)	N/A
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process.		N/A
Host cell protein (process related impurity)	Safety (Immunogenicity)	Production cell line		N/A
Host cell DNA (process related impurity)	Safety	Production cell line		N/A
(b) (4) (process related impurity)	Efficacy and Safety	Manufacturing process		N/A
(b) (4) (process related impurity)	Efficacy and Safety	Manufacturing process		N/A
Appearance	Stability	Formulation components and stability		N/A

CQA (Type)	Risk	Origin	Control Strategy (b) (4)	Other
Leachables (process-related impurity)	Safety and Stability	From manufacturing contact material and the DS container closure system (CCS)		Risk for leachables from CCS is low because the DS is stored frozen, and the same container is used with referenced BLA 125338.
Fermentation medium and buffer components	Safety	Cell bank cryopreservative medium, preculture medium, fermentation broth, process buffers		Levels are below toxicological concern based on the risk assessment.
Elemental impurities	Safety	Cell culture medium, product-contact surfaces, raw materials, excipients, and water		The assessment for this process is consistent with data provided in the referenced BLA 125338.

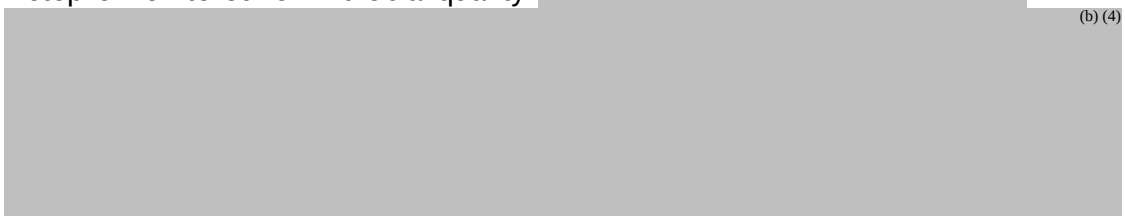
- Description:
  - CCH is comprised of two collagenase enzymes in an approximate 1:1 mass ratio: Collagenase I (AUX-I; Clostridial type I collagenase) and Collagenase II (AUX-II; Clostridial type II collagenase). These collagenases are isolated and purified from the fermentation of the bacteria *Clostridium histolyticum.* Collagenase I and Collagenase II have molecular weights of ~114 kDa and ~113 kDa respectively. CCH is licensed for the treatment of Peyronie's Disease and Dupuytren's Contracture in BLA 125338.
- Mechanism of Action:
  - The mechanism of action for CCH is the digestion of collagen. Collagenases are secreted as zymogens (inactive precursors), which are then activated extracellularly. As a mixture, AUX-I and AUX-II have approximately two-fold greater activity than individual enzymes on collagen. The cleavage of collagen can disrupt the thickening of the collagen septa that accompanies the development of EFP.
- Potency Assay:
  - The assays developed to assess the potency of CCH in BLA 125338 are utilized with this BLA. Validation of the assays using the formulation for CCH proposed for this BLA confirmed their acceptability. To determine individual collagenase activity, two enzymatic digestion assays with fluorescence readouts are used. AUX-I collagenase activity is measured by the digestion of soluble rat-tail collagen through the analysis of liberated peptides and fragments with fluorogenic fluorescamine. AUX-II

collagenase activity is assessed by the digestion of a targeted substrate (Carbobenzyoxy-glycyl-L-prolyl-glycyl-glycl-prolyl-L-alanine) into two derivatives. The amount of liberated glycyl-L-prolyl-L-alanine fragment is measured with fluorescamine. In both cases, the amount of fluorescence in proportional to the collagenase activity and is reported relative to reference standard.

- Reference Materials:
  - The reference material used for this BLA are identical to those used for CCH approved under BLA 125338. Reference materials are provided for the AUX-I intermediate, AUX-II intermediate and the DS based reference standard. The reference standards have been in place for the performance of the clinical trials under this IND and are representative of the clinical and manufacturing experience as well as BLA 125338 commercial experience. A protocol is provided for the qualification of future reference materials under BLA 125338. The protocols contain adequate testing and acceptance criteria. The procedures to monitor the stability of the reference standards are appropriate.
- Critical Starting Materials or Intermediates:
  - The master cell bank (MCB) is derived from a *C. histolyticum* culture (ATCC 21000) originally deposited in the American Type Culture Collection (ATCC). Characterization and qualification protocols for the MCB in 2004 is provided in the referenced BLA 125338. The current working cell bank (WCB) was also established in 2004 under the referenced BLA 125338. Both the MCB and WCB were adequately tested to ensure product safety from adventitious agents. The procedures for release, stability testing and generation of new cell banks are provided in the referenced BLA 125338 and are adequate for the maintenance of product quality.
  - The (b) (4) DS manufacturing process are controlled by in-process control testing for appearance, pH, identity, concentration potency, endotoxin, and bioburden as described in BLA 125338.
- Manufacturing Process Summary:
  - The manufacture of CCH Mannitol DS is identical to the process described in BLA 125338 (b) (4)

(b) (4)

  - The DS manufacturing process is under adequate microbial control and each critical step is monitored for microbial quality. (b) (4)



- Container Closure:
  - CCH Mannitol DS is stored in (b) (4) (b) (4) the same CCS as used in the referenced BLA 125338. The CCS is suitable for CCH Mannitol on the basis of stability data and the analysis of container closure integrity.
- Dating Period and Storage Conditions:
  - The dating period for the DS is (b) (4). The Applicant is monitoring stability of the CCH DS through 36 months as part of the process validation stability protocol and commits to testing through 36 months for their annual stability protocol.

Drug Product [CCH Mannitol] Quality Summary:
Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for DP CQAs that derive from the DP manufacturing process and general DP attributes.

Table 4. DP CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process or failure of container closure integrity	(b) (4)	N/A
Endotoxin (contaminant)	Safety, Purity, and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing process		
Container closure integrity (contaminant)	Safety (maintenance of sterility during shelf-life)	Container closure breaches during storage		N/A
Quantity	Efficacy	Manufacturing process		N/A
Appearance of lyophilized powder (general)	Stability	Formulation components and stability		N/A
Appearance of solution post reconstitution	Stability	Formulation components and stability		N/A
Reconstitution Time	Stability	Formulation components and stability		N/A
pH (general)	Efficacy and Stability	Formulation components and stability		N/A
Osmolality (general)	Stability	Composition of the DP		N/A
Volume in container (general)	Efficacy/Dosing	Fill process		N/A

CQA (Type)	Risk	Origin	Control Strategy	Other
Particulate matter for subvisible particles (b) (4)	Safety and Immunogenicity	Manufacturing process and CCS, (b) (4)	(b) (4)	N/A
Moisture content	Stability	Manufacturing process and CCS		N/A
Leachables (process-related impurities)	Safety	Manufacturing equipment and CCS	Leachables were assessed in the referenced BLA 125338 as well as by a risk assessment for this BLA. A real-time study is on-going and will be completed in Q2 of 2021.	The risk is deemed to be low, and the real-time study will be submitted as part of subsequent annual report.

- Potency and Strength:
  - CCH Mannitol is provided as 0.92 mg in a 5 mL vial for reconstitution with 4 mL of sterile diluent or 1.84 mg in a 10 mL vial for reconstitution with 8 mL of sterile diluent. The strength of CCH Mannitol is 0.23 mg/mL after reconstitution in the provided sterile diluent. Potency is defined as the ratio of activity relative to the current CCH reference. The potency assays are the same as described in the DS section of this memo.
- Summary of Product Design:
  - CCH Mannitol is supplied as 0.92 mg or 1.84 mg of lyophilized powder for reconstitution in sterile diluent to a final concentration of 0.23 mg/mL. CCH Mannitol is recommended for up to 12 injections of 0.3 mL (0.069 mg per injection) per treatment area. Reconstitution in 4 mL (0.92 mg) or 8 mL (1.84 mg) includes overfill to ensure sufficient volume for dose delivery.
- List of Excipients:
  - The CCH Mannitol DP excipients are (b) (4) tromethamine (Tris), (b) (4) sucrose and (b) (4) mM mannitol. The DPSD excipients are 0.03% calcium chloride dihydrate and 0.6% sodium chloride. After reconstitution, the pH is 8. (b) (4)
- Reference Materials:
  - The same reference standards are used for DS and DP.

- Manufacturing Process Summary:

  - The primary container closure systems for CCH Mannitol consist of the following presentations:
    - 0.92 mg Lyophilized Powder: A 5 mL Type I (b) (4) glass vial closed with a 13 mm (b) (4) stopper. The stopper is sealed (b) (4).
    - 1.84 mg Lyophilized Powder: A 10 mL Type I (b) (4) glass vial closed with a 20 mm (b) (4) stopper. The stopper is sealed (b) (4).
    - 4 mL Sterile Diluent: A 5 mL Type I (b) (4) vial closed with a 20 mm (b) (4), (b) (4) stopper. The stopper is sealed (b) (4) (b) (4).
    - 8 mL Sterile Diluent: A 10 mL Type I (b) (4) vial closed with a 20 mm (b) (4) (b) (4) stopper. The stopper is sealed (b) (4) (b) (4).
    - Appropriate compatibility studies were performed for identical materials used with the primary CCS in BLA 125338.
- Dating Period and Storage Conditions:
  - The dating period for the DP is 24 months when stored at 2 to 8°C and 24 months for the DPSD when stored at 2 to 30˚C. The data included in the BLA support storage for

up to 24 hours when stored at temperatures below 25°C once removed from refrigerator, as described in the labeling or up to (b) (4) hours in the refrigerator at 2 to 8˚C. The in-use stability testing was performed with the solution reconstituted in the vial, not in the injection syringe. The reconstituted solution is not meant to be stored in the syringe.

- Commercial Presentation:
  - The intended commercial presentation will be vials containing 0.92 mg or 1.84 mg of CCH Mannitol lyophilized powder along with vials containing 4 mL or 8 mL of sterile diluent for reconstitution.

Novel Approaches/Precedents:
None

Any Special Product Quality Labeling Recommendations:

- Store in a refrigerator at 2°C to 8°C
- Do not freeze
- The reconstituted solution can be kept in the vial at room temperature (20˚ to 25˚C) for up to 8 hours or refrigerated for up to 72 hours in the vial prior to administration
- Do not store in the syringe, administer immediately upon withdrawing from the vial

Facilities:

- Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided or referenced to BLA 761146 for Auxilium Pharmaceuticals (FEI 3006537159) and (b) (4) proposed for CCH DS and DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

Lifecycle Knowledge Management:

- Drug Substance:

Table 5.Drug Substance Protocols Approved

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.S.7.2	Annual stability protocol for DS with shelf-life extension	At -70˚C, at least one batch per year at 0, 3, 6, 9, 12, 18, 24, 30 and 36 months, as well as at -20˚C at least one batch per year at 0, 6, 12, 24 and 36 months according to the tests and acceptance criteria (AC) listed in 3.2.S.7.2.	Stability updates will be provided annually as part of the Annual Report.

Abbreviations: DS = drug substance, eCTD = electronic common technical document

  - Outstanding review issues/residual risk: None

- Future inspection points to consider: None

- Drug Product

Table 6. Drug Product Protocols Approved

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.P.2	Leachables study on stability samples of the CCH Mannitol DP packaged in the container closure system	A study of potential volatile leachables after 36 months of long term storage at 2-8˚C for CCH Mannitol DP lots 307984, 307985 and 313877 with a targeted completion of March 2021.	Study results will be submitted as part of the Annual Report.
3.2.P.8.2	Annual stability protocol for DP with shelf-life extension	At 5˚C, at least one lot per year at 0, 3, 6, 9, 12, 18, 24, 30 and 36 months, as well as at 25˚C at least one batch per year at 0, 6, 12, 24 and 36 months according to the tests and AC listed in 3.2.P.8.2 for lyophilized powder.	Stability updates will be provided annually as part of the Annual Report.
3.2.P.8.2	Annual stability protocol for DPSD with shelf-life extension	At 5˚C, at least one lot per year at 0, 3, 6, 9, 12, 18, 24, 30, 36 and 48 months, as well as at 30˚C at least one batch per year at 0, 6, 12, 24, 36 and 48 months according to the tests and AC listed in 3.2.P.8.2 for DPSD.	Stability updates will be provided annually as part of the Annual Report.

Abbreviations: CCH = Collagenase clostridium histolyticum, DP = drug product, DPSD = drug product sterile diluent, eCTD = electronic common technical document

- Outstanding review issues/residual risk: None
- Future inspection points to consider: None

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant has submitted an original BLA under section 351(a) of the Public Health Service Act for collagenase *Clostridium histolyticum-aaes* (CCH) for the treatment of moderate to severe EFP, otherwise known as cellulite, in the buttocks of adult women.

No pivotal nonclinical studies were included in this BLA. The Applicant is referencing the nonclinical studies conducted in support of their previously approved biologic product, Xiaflex (BLA 125338, approved February 2, 2010).

Collagenase *Clostridium histolyticum* for the treatment of moderate to severe EFP is approvable from a pharmacology/toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

BLA 125338, Xiaflex; approved February 2, 2010 for treatment of adult patients with Dupuytren's contracture with a palpable cord; approved December 6, 2013 for treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees.

5.3. Pharmacology

Collagenase *Clostridium histolyticum* is a mixture of two bacterial enzymes (AUX-I [clostridial type I collagenase] and AUX-II [clostridial type II collagenase]) derived from the fermentation of a non-spore forming phenotype of *Clostridium histolyticum* that selectively degrades collagen. Both collagenases are immunologically distinct and have different specificities. Together they work synergistically and hydrolyze collagen to numerous small peptides. CCH is being proposed as a nonsurgical means to treat EFP using locally injected CCH to disrupt the collagen of the dermal septae.

5.4. ADME/PK

Quantifiable levels of CCH (AUX-I and AUX-II) were measured in rats and dogs following single or repeat subcutaneous exposure. However, meaningful toxicokinetic parameters could not be calculated due to limited exposure.

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: AA4500 and BTC Collagenase: A 16-Day intravenous comparative toxicity and toxicokinetic study followed by a 14-day recovery period in Sprague-Dawley rats (Study Lab 1007-1671)

BTC refers to the original sponsor, Biospecifics Technologies Corporation.

Sprague-Dawley rats were administered CCH (15/sex/dose level; 0, 0.029, 0.13, or 0.29 mg/rat/dose) by intravenous bolus injection every other day for 16 days (total of 8 doses) to determine the target organ and the reversibility of any changes following a 14-day recovery period. The vehicle was sterile water containing sodium chloride (0.9%) and calcium chloride

(0.03%). Parameters monitored during the study were mortality, clinical observations, body weights, feed consumption, toxicokinetics, hematology, clinical chemistry, coagulation, urinalysis, antigenic response, macroscopic examination, organ weights, and microscopic examination.

The administration of CCH by intravenous injection every other day to rats at 0.29 mg/rat/dose, for 16 days resulted in a low number of mortalities that were associated with the presence of gelatinous red material in the abdominal cavity (consistent with blood clots) and friable livers and/or spleens and early terminations due to dose-limiting clinical signs at the injection site. Correlating macroscopic findings were generally seen at the injection site at all dose levels and consisted of perivascular edema, hemorrhage, inflammation, fibrosis, and/or necrosis; the latter two findings occasionally expanded into adjacent tissues (muscle and tendon sheath). Partial to complete reversal of all CCH-related injection site findings occurred following a 14-day recovery period.

Evidence of systemic toxicity consisted of changes in the liver and mild regenerative anemia which correlated with secondary changes in the spleen. The liver was affected in both male and female rats given ≥0.13 mg/rat/dose of CCH. Elevated aspartate aminotransferase and alanine aminotransferase levels and increased liver weights in male rats and macroscopic observations (masses, raised or dark foci) in both sexes corresponded with histologic changes of minimal to marked chronic active inflammation and/or bile duct hyperplasia. At 0.29 mg/rat/dose, additional liver findings (minimal to marked multifocal hemorrhage/hematoma, fibrosis, and/or hepatocellular necrosis) were noted. All liver findings reversed partially, with evidence of ongoing reversal, at 0.29 mg/rat/dose level.

In both sexes at 0.29 mg/rat/dose, mild, regenerative anemia (evidenced by alterations in erythrocyte parameters, and/or morphology) was noted at the end of the main study. These findings were more pronounced in female rats compared to male rats and correlated with increases in both absolute and relative group mean spleen weights in female rats and the presence of splenic extramedullary hematopoiesis in both sexes at this dose level. All of these changes reversed completely following the 14-day recovery period.

Based on liver changes at dose levels of ≥0.13 mg/rat/dose, 0.029 mg/rat/dose is considered the NOAEL for systemic toxicity. Despite the liver and injection site changes at 0.13 mg/rat/dose, their limited sequelae indicated that the dose level was reasonably well-tolerated.

Study title/ number: A 3-month (every other week) subcutaneous toxicity study with a 28-day recovery period in Sprague Dawley rats ((b) (4)-696003)

The Applicant conducted a 3-month repeat dose (every other week) subcutaneous toxicity study with a 28-day recovery period in rats (0, 0.015, 0.03, 0.045 mg/rat/dose; (b) (4)-696003). The vehicle was sterile water containing sodium chloride (0.9%) and calcium chloride (0.03%).

Injections were made in the metatarsal-phalangeal area of the right hindpaw. The concentration of the dosing solution was maintained at 3 mg/mL and different doses were achieved by varying the dosing volume. At the end of the dosing period, 10 rats/sex/dose level were necropsied; the remaining 5 rats/sex/dose level underwent an additional 28-day recovery period. Clinical signs were observed at all dose levels and included dose-dependent increases in the incidence of swelling, reddening, and/or purple discoloration of the limb and increased paw circumference. At ≥0.03 mg/rat/dose clinical observations also included transient impaired use and scabbing of the right hindlimb.

Effects related to CCH administration at gross necropsy were confined to the injection site and draining (popliteal) lymph node and consisted of swelling and dark red discoloration at the injection site and enlargement and/or red discoloration of the right popliteal lymph node. CCH-related histological findings at the injection site included acute/subacute inflammation, collagen lysis affecting the interstitium and/or superficial flexor tendons, hemorrhage, edema, fibrin exudation, skeletal muscle necrosis, fibroplasia/neovascularization, fibrinoid vascular necrosis, and intramural arterial hemorrhage without a definitive dose response. The normal tendon morphology of tightly packed, parallel, dense collagen fibers was replaced at the periphery by fibrous connective tissue composed of interwoven, wavy bundles of collagen and fibroblasts in a subset of CCH-treated male and female rats. Systemic toxicity was limited to an increased incidence of mononuclear infiltrates in the liver (rats of both sexes) and pancreas (male rats) at 0.045 mg/rat/dose.

At recovery necropsy microscopic observations were limited to the injection site and draining lymph node and were considered to be the residual effects of CCH administration. This included minimal to mild interstitial fibrosis at the injection site and pigmented macrophages in the right popliteal lymph node of most animals administered CCH. Toxicokinetic analysis measured quantifiable systemic exposure to both AUX-I and AUX-II on Day 0, but not Day 42. High and persistent titers of antibodies against both AUX-I and AUX-II were detected with minimal to no dose-, time- or sex-related differences. Based on these findings the NOAEL for local toxicity was <0.015 mg/rat/dose and for systemic toxicity it was 0.030 mg/rat/dose.

5.5.2. Genetic Toxicology

The Applicant has obtained the right of reference to the studies conducted to support Xiaflex (BLA 125338). The following information appears in the Mutagenesis Section of the labeling for Xiaflex.

Purified collagenase clostridium histolyticum was not mutagenic in *Salmonella typhimurium* (AMES test) and was not clastogenic in both an in vivo mouse micronucleus assay and an in vitro chromosomal aberration assay in human lymphocytes.

These studies were conducted prior to international agreement that genetic toxicology studies are not necessary for large proteins which do not cross the cell membrane and induce mutagenicity.

5.5.3. Carcinogenicity

The Applicant has obtained the right of reference to the studies conducted to support Xiaflex (BLA 125338). The following information appears in the Carcinogenicity Section of the labeling for Xiaflex.

Long-term animal studies to evaluate the carcinogenic potential of collagenase histolyticum have not been conducted.

5.5.4. Reproductive and Developmental Toxicology

The Applicant has obtained the right of reference to the studies conducted to support Xiaflex (BLA 125338). The following information appears in the corresponding fertility and embryofetal development sections of the labeling for Xiaflex.

Fertility and Early Embryonic Development

Collagenase clostridium histolyticum did not impair fertility and early embryonic development when administered intravenously in rats at exposures up to approximately 11 times the maximum recommended human dose (MRHD) on a mg/m^2 basis.

Embryo-Fetal Development

Reproduction studies have been performed in rats with intravenous exposures up to approximately 11 times the maximum recommended human dose (MRHD) of Xiaflex on a mg/m^2 basis, and have revealed no evidence of impaired fertility or harm to the fetus due to collagenase clostridium histolyticum.

Based on the lack of detectable systemic exposure in the clinical setting, a second species embryofetal development study and a prenatal and postnatal development study were not considered necessary. Since CCH is not measurable in human plasma following administration of the recommended human dosage for the current indication, measures of relative exposure will not be included in the label.

5.5.5. Other Toxicology Studies

The Applicant conducted a guinea pig sensitization test by intraperitoneal injections of the collagenase protein. Guinea pigs did not show signs of hypersensitivity reactions following repeated dosing.

6. Clinical Pharmacology

6.1. Executive Summary

Collagenase clostridium histolyticum-aaes ([CCH], Qwo, also known as EN3835, AA4500) comprises a mixture of 2 collagenases, Clostridial type I collagenase (AUX-I) and Clostridial type II collagenase (AUX-II) in an approximate 1:1 mass ratio. These collagenases are isolated and purified from the fermentation of the bacterium *Clostridium histolyticum*. Collagenase clostridium histolyticum was approved as Xiaflex in 2010 for the treatment of adult patients with Dupuytren's contracture with a palpable cord and in 2013 for the treatment of adult man with Peyronie's disease.

- Proposed indication: For the treatment of moderate to severe edematous fibrosclerotic panniculopathy (also known as cellulite) in the buttocks of adult women
- Proposed dosing regimen:
  - Inject 0.84 mg of Qwo per treatment area as 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection).
  - A treatment area is defined as a single buttock receiving up to 12 injections, 0.3 mL each (up to a total of 3.6 mL), of Qwo.
  - A treatment visit may consist of up to 2 treatment areas (a total of 1.68 mg of Qwo). The treatment visits should be repeated every 21 days for 3 treatment visits.
- Proposed dosage form and presentation: Qwo is supplied in the followings:
  - Single treatment area: 0.92-mg as a lyophilized powder with a 4-mL vial of sterile diluent
  - Two treatment areas: 1.84-mg as a lyophilized powder with an 8-mL vial of sterile diluent
    - Note that a lyophilized powder of Qwo will be reconstituted with the provided sterile diluent prior to use (subcutaneous injection).

The Applicant evaluated the safety and efficacy of Qwo in two pivotal Phase 3 trials in which Qwo was injected subcutaneously (SC) of a dose of 1.68 mg per treatment visit and repeated every 21 days for 3 treatment visits. The Applicant conducted three Phase 2 trials to support the dose selection for Phase 3 trials. The Applicant also submitted the results of four Phase 1 trials conducted in adult female with cellulite to support Clinical Pharmacology information of Qwo.

The key review findings with specific recommendations and comments are summarized in Table 7.

Table 7.Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Efficacy is established in two pivotal Phase 3 trials (EN3835-302 and EN3835-303). See Section 9.1 for efficacy trials and their results.
General dosing instructions	The efficacy and safety data from Phase 3 trials support the proposed dosing regimen, i.e., 1.68 mg of CCH administered as 24 SC injections to two buttocks per treatment visit for 3 treatment visits with at least 21-day interval between treatments.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Therapeutic individualization based on intrinsic or extrinsic factors is not necessary due to no detectable systemic exposure of AUX-I and AUX-II following SC administration in all subjects evaluated.
Immunogenicity	By Day 22, approximately 53% (203/383) and 26% (101/383) of subjects who completed the first treatment visit of Qwo at the recommended dose in the Phase 3 trials developed anti-AUX-I and anti-AUX-II antibodies, respectively. The majority (>96%) of subjects developed antibodies for AUX-I and AUX-II after second and third treatment visits. Antibody titers suggested that antibodies were retained for up to 360 days after receiving the first recommended dose. By Day 71, approximately 68% and 83% of subjects who developed antibodies to AUX-I and AUX-II were classified as neutralizing, respectively. Antibodies to AUX-I and AUX-II including those classified as neutralizing were not associated with changes in clinical response or adverse reactions at injection site in Phase 3 trials.
Drug interactions	Pharmacokinetic drug-drug interactions are unlikely as AUX-I/II are proteinases with the molecular weights of 113-114 kDa and systemic exposures to AUX-I and AUX-II were not detectable or below the lower limit of quantitation (LLOQ) after treatment visits at the recommended dose regimen.
Pediatric subjects	A full waiver for conducting trials in subject ≤18 years of age with cellulite has been agreed in the initial Pediatric Study Plan.
Bridge between the to-be-marketed and clinical trial formulations	Any kind of bridging is not needed because the to-be-marketed formulation was used in the Phase 3 trials and 2 of 4 Phase 1 trials (see Appendices 15.6 for details)

Abbreviations:AUX-I = Clostridial type I collagenase, AUX-II = Clostridial type I collagenase, CCH = Collagenase clostridium histolyticum, LLOQ = lower limit of quantitation, SC = subcutaneous

6.1.1. Recommendation

From a Clinical Pharmacology's standpoint, this BLA is acceptable to support the approval of Qwo (1.68 mg SC injections per treatment visit up to 3 treatment visits with at least 21-day interval between treatments) for the treatment of moderate to severe cellulite in the buttocks of adult women.

6.1.2. Postmarketing Requirements and Commitments (PMR/PMC)

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

6.2.1.1. Mechanism of Action and Pharmacodynamics

CCH is a combination of 2 purified collagenases (AUX-I and AUX-II) from *Clostridium histolyticum*. These collagenases are proteinases that can hydrolyze the triple-helical region of collagen under physiological conditions. However, the pharmacodynamic effect of CCH in humans has not been characterized.

6.2.1.2. Pharmacokinetics of CCH

Pharmacokinetics of CCH were evaluated in 140 adult women with cellulite in four Phase 1 trials. Plasma concentrations of AUX-I and AUX-II were not detectable or below the LLOQ of 5 ng/mL and 25 ng/mL, respectively, in all subjects evaluated (see Appendix 15.6 for details).

6.2.1.3. Immunogenicity

Among 383 evaluable subjects in the Phase 3 pivotal trials, 53% and 26% of subjects developed anti-AUX-I and anti-AUX-II antidrug antibodies (ADAs), respectively, on Day 22 after completed the first treatment of Qwo at the recommended dose. The majority (>96%) of subjects developed ADAs for AUX-I and AUX-II after the second and third treatment visits. ADA titers suggested that ADAs were retained for up to 360 days after receiving the first recommended dose. By Day 71, approximately 68% and 83% of subjects who developed ADAs to AUX-I and AUX-II were classified as neutralizing, respectively. The impact of the high incidence of immunogenicity on the efficacy and safety of this product was not observed in the Phase 3 trials. See Clinical review under Section 9 for further details.

6.2.1.4. Drug-Drug Interactions

Pharmacokinetic drug-drug interactions are unlikely as AUX-I/II are proteinases with the molecular weights of 113 to 114 kDa and systemic exposures to AUX-I and AUX-II were not detectable or below LLOQ at the recommended dose regimen.

Pharmacodynamic effects of co-administration of antiplatelet or anticoagulant therapy were observed in injection sites of subjects in the Phase3 trials. See Section 9 for details.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's proposed dosing regimen is to inject 1.68 mg of CCH per treatment visit as 24 SC injections to two buttocks (as 0.84 mg per buttock by 12 SC injections) of adult women with cellulite with a 21-day intervals between 3 treatment visits is supported by efficacy and safety

data from the two Phase 3 pivotal trials (EN3835-302 and EN3835-303). See Section 9 for efficacy and safety findings from Phase 3 trails.

6.2.2.2. Therapeutic Individualization

Therapeutic individualization was not evaluated in this BLA.

6.2.3. Outstanding Issues

There are no outstanding issues that would preclude the approval of Qwo in adult women with cellulite from a Clinical Pharmacology's perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General clinical pharmacology, pharmacokinetics and immunogenicity of Qwo are summarized in Table 8.

Table 8. Summary of Clinical Pharmacology and Immunogenicity of CCH

Characteristics	Description
Pharmacology Mechanism of Action	CCH is a combination of 2 purified collagenases (AUX-I and AUX-II) from *Clostridium histolyticum*. These collagenases are proteinases that can hydrolyze the triple-helical region of collagen under physiological conditions.
Pharmacodynamics	The PD effect of CCH in humans has not been characterized.
General Information Bioanalysis	AUX-I and AUX-II concentrations in human plasma were quantified using two separate validated enzyme-linked immunosorbent (ELISA) assays with the sensitivity of 5 ng/mL and 25 ng/mL, respectively.
PK model	The Applicant did not conduct any PK modeling and simulation analysis.
Healthy vs. patients	The Applicant characterized PK of CCH in adult women with EFP only.
Drug exposure at steady state	Systemic exposure to CCH was not detectable in all subjects evaluated.
Dose proportionality	Dose proportionality of CCH was not evaluated in this BLA.
ADME Absorption	Following SC injections at the recommended dose regimen, systemic exposures to AUX-I and AUX-II were below the LLOQ of 5 ng/mL and 25 ng/mL, respectively.
Distribution/elimination	Distribution and elimination of AUX-I/II are not clearly understood in humans.

Characteristics	Description
Immunogenicity Bioanalysis[1]	ADAs to either AUX-I or AUX-II were determined using validated ELISA bridging test methods. The sensitivity of the ELISA assay was 0.183 ng/mL for anti-AUX-I antibody, and 0.892 ng/mL for anti-AUX-II antibody. NAbs were determined using an enzymatic assay which measure the activity of either AUX-I or AUX-II in the presence of fluorescein-labelled collagen substrate.
Incidence	Among 383 evaluable subjects in the Phase 3 pivotal trials, the majority (>96%) of subjects developed ADAs for AUX-I and AUX-II after the second and third treatment visits. ADA titers suggested that ADAs were retained for up to 360 days after receiving the first recommended dose. By Day 71, approximately 68% and 83% of subjects who developed ADAs to AUX-I and AUX-II were classified as neutralizing, respectively.
Clinical impact	Antibodies to AUX-I and AUX-II including those classified as neutralizing were not associated with changes in clinical response or adverse reactions at injection site in Phase 3 trials.

[1] Two different assays or vendors were used for NAbs determination. Note that NAb analyses were only performed in ~50% of CCH-treated subjects in the Phase 3 trials.
Abbreviations: ADME = Absorption, Distribution, Metabolism and Excretion, AUX-I = Clostridial type I collagenase, AUX-II = Clostridial type I collagenase, BLA = biologics license application, CCH = collagenase clostridium histolyticum, ELISA = enzyme-linked immunosorbent, LLOQ = lower limit of quantitation, PD = pharmacodynamics, PK = pharmacokinetics

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

The clinical pharmacology program did not directly provide any efficacy data due to lack of systemic exposure to AUX-I and AUX-II in adult women with cellulite who received up to 3.36 mg of the to-be-marketed formulation of CCH in a single treatment visit (2-time higher than the recommended dose of 1.68 mg per treatment visit).

6.3.2.2. Is the Proposed Dosing Regimen Appropriate for the General Patient Population For Which the Indication is Being Sought?

Yes. Based on the efficacy and safety data from the Phase 3 trials, the proposed dosing regimen is appropriate for the treatment of moderate to severe cellulite in the buttocks of adult women.

6.3.2.3. Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

The effect of intrinsic and extrinsic factors was not evaluated by the Applicant in this BLA. Based on the efficacy and safety data from the Phase 3 trials, any dose adjustment will not be needed.

6.3.2.4. Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

Food-drug interaction study is not needed for biologic products with SC injection. Pharmacokinetic drug-drug interactions are unlikely as AUX-I and AUX-II are proteinases with the molecular weights of 113 to 114 kDa and systemic exposures to AUX-I and AUX-II were not detectable i.e., below LLOQ after treatment visits at the recommended dose regimen. There are potential safety concerns for pharmacodynamic effects of co-administration of antiplatelet or anticoagulant therapy in injection sites. See Section 9 for details.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Trials

To support the safety and efficacy of CCH for the treatment of moderate to severe cellulite in the buttocks of adult women, the Applicant conducted 11 clinical trials: three Phase 3 trials, four Phase 2 trials and four Phase 1 trials. A total of 964 subjects in the development program received CCH at the proposed dose (0.84 mg per treatment area).

Phase 3 Trials:

- EN3835-302: Randomized, double-blind, placebo-controlled, repeat dose (3) trial with administration of CCH (0.84 mg/area) to two areas (buttocks).
- EN3835-303: Randomized, double-blind, placebo-controlled, repeat dose (3) trial with administration of CCH (0.84 mg/area) to two areas (buttocks).
- EN3835-304: Open-label, long-term safety trial enrolling subjects who completed EN3835-302/ EN3835-303 with option for re-treatment with repeat doses (3) to 2 areas (buttocks)-ongoing 5 year trial.

Phase 2 Trials:

- AUX-CC-831: Randomized, double-blind, placebo-controlled, dose ranging trial (0.06, 0.48, and 0.84 mg) repeat dose (3) trial with administration of CCH to one area (buttock or thigh).
- EN3835-201: Randomized, double-blind, placebo-controlled, repeat dose (3) trial with administration of 0.84 mg CCH to one area (buttock or thigh).
- EN3835-202: Open-label, long-term safety trial enrolling subjects who completed EN3835-201 with option for re-treatment with repeat doses (3) to one area (buttocks).
- EN3835-205: Open-label, repeat dose (3) trial with administration of CCH to two areas (bilateral buttocks or bilateral thighs) to assess safety and treatment effect and characterize the onset and course of injection site bruising.

Phase 1 Trials:

- AUX-CC-830: Open-label, dose escalation trial to evaluate pharmacokinetics (PK), safety and effectiveness of CCH in 1 area (buttock or thigh)
- EN3835-102: Open-label, single-dose trial to evaluate PK and safety of CCH (0.84 mg) in 1 area (buttock or posterolateral thigh)
- EN3835-104: Open-label, single-dose trial to evaluate PK and safety of CCH (0.84 mg) in 2 areas (buttock-buttock, thigh-thigh, or buttock-thigh) (total dose 1.68 mg)
- EN3835-103: Open-label, single-dose trial to evaluate PK and safety of CCH (0.84 mg) in 4 areas (buttocks and thighs) (total dose 3.36 mg)

Table 9. Listing of Clinical Trials Relevant to BLA 761146

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/Route	Trial Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Trial Population	No. of Centers and Countries
Controlled Trials to Support Efficacy and Safety								
EN3835-302 CCH	NCT 03428750	Phase 3, randomized, DB,PC, repeat dose trial in bilateral buttocks	1.68 mg (0.84 mg per buttocks) or placebo administered in 12 SC injections/ buttock X 3 sessions 21 days apart	Efficacy: proportion of 2-level CR-PCSS/PR-PCSS multicomponent responders in the target buttock at Day 71 Safety: AEs, lab, vital signs, PE, immunogenicity	71 days	423 Randomized 210 Treated 213 Placebo 423 Safety 350 PP Completed: 378 Overall: 186 Treated 192 Placebo	Adult females with EFP - cellulite	26 US centers
EN3835-303 CCH	NCT 03446781	Phase 3, randomized, DB,PC, repeat dose trial in bilateral buttocks	1.68 mg (0.84 mg per buttocks) or placebo administered in 12 SC injections/ buttock X 3 sessions 21 days apart	Efficacy: proportion of 2-level CR-PCSS/PR-PCSS composite responders in the target buttock at Day 71 Safety: AEs, lab, vital signs, PE, immunogenicity	71 days	422 Randomized 214 Treated 206 Placebo 420 Safety 364 PP Completed: 377 Overall 186 Treated 191 Placebo	Adult females with EFP - cellulite	25 US centers
EN3835-201 Xiaflex	NCT 02724644	Phase 2, randomized (1:1), DB,PC, repeat dose trial in bilateral buttocks and bilateral thighs	0.84 mg per treatment session administered in 12 SC injections to one quadrant X 3 sessions 21 days apart	Efficacy: proportion of 2-level CR-PCSS/PR-PCSS composite responders in the target buttock at Day 71; Hexsel CSS, I-GAIS, S-GAIS Safety: AEs, lab, vital signs, PE, immunogenicity, injection site reactions	71 days	350 subjects	Adult females with EFP ≥1/ 4 sites with CR-PCSS +PR-PCSS 3 or 4; Hexel CSS <13	16 US centers

AUX-CC-831 Xiaflex	NCT 01987986	Phase 2a, randomized (5:5:5:3), DB,PC, dose ranging of repeat dose trial	Doses of 0.06 mg; 0.48 mg); 0.84 mg; or placebo administered in 12 SC injections to one quadrant X 3 sessions 21 days apart	Efficacy: GAIS-I, CSI, SGBA, SR-CIS, SR-CIS, SCTA, SGA-C, GAIS-C Safety: AEs, lab, vital signs, PE, immunogenicity,	73 days	150 subjects	Adult females with EFP	10 US centers
Trials to Support Long-Term Safety								
EN3835-304 CCH	NCT03526549	Phase 3b long-term, open-label, repeat exposure trial in bilateral buttocks enrolling subjects from Trials EN3835-302 and EN3835-303	No treatment or 1 course of treatment (1.68 mg (0.84 mg per buttocks) or placebo administered in 12 SC injections/ buttock X 3 sessions 21 days apart	Safety: AEs, lab, vital signs, PE, immunogenicity. Efficacy: CR-PCSS and PR-PCSS, PR-CIS, S-GAIS, SSRS, and Subject Satisfaction with Cellulite Treatment Assessment.	5 years Ongoing Data submitted from 04/26/2018-04/01/2019	617 completers from trials 302/303 agreed to participate and receive no drug; on Day 180: 198 subjects agreed to participate in open-label phase. 30 received retreatment	Adult women with EFP-	42 US centers
EN3835-202 Xiaflex	NCT 02942160	Phase 2 Open-label extension trial of CCH with the option of observation or treatment.	No treatment or up to 2 courses of treatment across 2 treatment areas (buttocks or posterolateral thighs)	Safety: AEs, lab, vital signs, PE, immunogenicity, injection site reactions Efficacy: PR-PCSS, CR-PCSS, Hexsel CSS, I-GAIS, S-GAIS	Up to 2 years	259 subjects from Trial-201 enrolled; 200 subjects received at least 1 dose	Adult females with EFP	15 US centers

Abbreviations: CR-PCSS = Clinician-Reported Photonumeric Cellulite Severity Scale, CSI = subject cellulite severity item, CSS = Hexsel Cellulite Severity Scale, DB = double-blind, EFP = edematous fibrosclerotic panniculopathy (cellulite), GAIS-C = global aesthetic improvement scale – cellulite, GAIS-I = investigators' assessment of aesthetic improvement, PC = placebo-controlled, PR-CIS = patient-reported cellulite impact scale, PR-PCSS = Patient-Reported Photonumeric Cellulite Severity Scale, SGA-C = subject global assessment – cellulite, S-GAIS = subject global aesthetic improvement scale, SCTA = subject satisfaction with cellulite treatment assessment, SGBA = subject global bother assessment, SR-CIS = subject-reported cellulite impact scale, SSRS = subject self-rating scale

7.2. Review Strategy

The sources of data used for the evaluation of the efficacy and safety of CCH for the proposed indication included final trial reports submitted by the Applicant, and datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)]. This application was submitted in electronic common technical document format and entirely electronic. The electronic submission included protocols, statistical analysis plans (SAPs), clinical trial reports, SAS transport datasets in Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM) format. The datasets were in the following network path:

Original submission: \\cdsesub1\evsprod\bla761146\0001\m5\datasets

8. Review of Safety

8.1. Safety Review Approach

The primary review of safety of CCH for the treatment of moderate to severe cellulite focused on the evaluation of pooled data from 2 randomized, double-blind, placebo-controlled, Phase 3 Trials EN3835-302 (302) and EN3835-303 (303) (Pool 1) which evaluated the safety, efficacy, and immunogenicity of CCH in adult female subjects with moderate or severe edematous fibrosclerotic panniculopathy (EFP or cellulite) in each buttock. Both Phase 3 trials were similar with regard to design, trial population, dosing regimen and key primary and secondary endpoints. Eligible subjects were randomized in a 1:1 ratio to receive either placebo or 0.84 mg of CCH per buttock (total dose of 1.68 mg for both buttocks). Subjects received injections of CCH or placebo in each buttock during 3 treatment sessions scheduled approximately 21 days apart, the proposed dosing regimen to be conveyed in labeling. The duration of each trial was 71 days.

The Applicant provided two additional pools of data to further characterize the overall safety profile. Data from the larger safety databases may capture potential reactions which occur at lower frequencies. However, due to differences in the trial populations, trial designs and durations, randomization ratios and trial product formulation, data from these trials was reviewed separately. The findings from other pools of data were used to confirm the safety conclusions from Trials 302/303.

The Applicant provided additional safety data in the 120-Day safety update report (SUR). The SUR included 6 months of long-term safety data from Trial EN3835 -304 (304) and additional pooled data as agreed in the pre-BLA meeting (Preliminary comments dated January 23, 2019). This review also provides a brief discussion of results of Trial EN3835 -830 which did not include an evaluation of the proposed dose of CCH (0.84 mg) and was not pooled with other trials.

The review team analyzed following types of pooled data: exposure, demographics and baseline characteristics, treatment-emergent adverse events (TEAEs), serious AEs (SAEs), AEs leading to discontinuation, AESIs and other abnormal findings observed on physical examination including vital signs and laboratory monitoring. The AESIs included the following adverse events which were observed with higher frequency during the development program or associated with the CCH which was administered for other indications:

- Adverse events (AEs) such as bruising, ecchymosis, hematomas, and contusions that occurred remote to the injection site.
- Any hypersensitivity reactions, including anaphylaxis.
- Local AEs associated with the injection site including acute (e.g., erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (e.g., skin thickening, fibrosclerosis, peau d'orange changes, atrophy) cutaneous AEs.

8.2. Review of the Safety Database

Overall Exposure

Overall, 964 adult female subjects with EFP received the proposed dose of CCH of 0.84 mg per treatment area (buttock or thigh). A total of 344 subjects completed 6 months of follow-up and 183 completed 1 year of follow-up. Among the 704 subjects who received the proposed dose for the proposed indication (EFP in the buttocks), 187 completed 6 months of follow-up and 110 completed 1 year of follow-up. A total of 18 subjects from Trial 202 with EFP in the buttocks received CCH and completed more than 1 year of follow-up.

Table 10. Overall Exposure to the Proposed Dose in the Development Program

Clinical Trial Groups	CCH 0.84 mg N	Placebo N
Pivotal controlled trials conducted for this indication (buttocks) EN3835-302/303	424	419
Other controlled trials conducted for this indication using the proposed dose (buttocks) EN3835-201/205; AUX-CC-831	111	105
Totals	535	524
Open-label, long-term, safety trials conducted for this indication (buttocks) (Not Phase 1) EN3835-205 EN3835-201→202 302/303→304[a]	136	0
Single dose trials (buttock) EN3835-102 EN3835-103[b] EN3835-104	33	0
Total	169	0

Clinical Trial Groups	CCH 0.84 mg N	Placebo N
Controlled trials conducted for other indications using the proposed dose (thigh only) AUX-CC-831; EN3835-201	118	105
Open-label, long-term, safety trials conducted for this indication (thigh only) (Not Phase 1) EN3835-201/202; EN3835-205	134	0
Single dose trials (thigh only) EN3835-102; EN3835-104	8	0
Total -all indications using the proposed dose	964	629[c]

Source: Reviewer's Table, data from SDN 30 dated May 7, 2020
[a] There were no new CCH-treated subjects in Trial EN3835-304.
[b] All subjects were treated in 4 treatment areas (right or left buttock or the right or left posterolateral thigh).
[c] Includes 112 placebo-treated subjects in Trial EN3835-201 who received CCH in Trial EN3835-202.
Abbreviations: CCH = Collagenase clostridium histolyticum, n = number of subjects

In Phase 3 Trials 302 /303, 424 adult female subjects with EFP in the buttocks received CCH and 419 received placebo. See summary table below. In Trial 304 (safety extension from Trial 302/303), 241 subjects completed 6 months of follow-up (observation period) at the time of the data cutoff (April 1, 2019).

Table 11. Phase 3 Trial Treatment Groups

Trial	Treatment Group	# of Subjects	Safety Population
302	CCH	210	423
	Placebo	213	
303	CCH	214	420
	Placebo	206	
Total			843

Source: Reviewer's table

The size of the overall safety database was consistent with ICH E1.

Relevant Characteristics of the Safety Population

Demographic characteristics of the subject population in the Phase 3 Trial 302/303 are presented in greater detail in Section 8.1.2 of this review. The Applicant excluded males from the from the development program because EFP is rare in males. ((Scherwitz and Braun-Falco 1978; Draelos and Marenus 1997; Avram 2004; Wanner and Avram 2008; Hexsel et al. 2009)). The low prevalence in males is a consequence of differences in estrogen/testosterone levels and structural differences in the collagen septal attachments. See Section 2.1 Analysis of the Condition of this review.

The safety population was comprised of females with a mean age of 47 years (range 18 to 78 years). A total of 39 subjects were 65 years or older (5%); of these, 24 subjects received CCH. The majority were white (78%) or African American (18%) and most were not Hispanic/Latino (79%). Approximately 80% of the subjects were either overweight (body mass index [BMI] 25 kg/m^2 to <30 kg/m^2, 32%) or obese (BMI ≥30 kg/m^2, 49%). There were 598 subjects (71%) who had a family history of EFP. The mean age of onset of EFP was 28 years. Only 3 subjects (<1%) had prior treatment for EFP. Demographic and baseline characteristics were generally

similar across treatment groups (CCH and placebo). In general, the trial population is representative of the patient population who presents with moderate to severe EFP.

Adequacy of the Safety Database:

The total exposure to CCH, 0.84 mg per treatment area which is administered to 2 treatment areas per visit with a course of treatment comprised of 3 visits occurring 21 days apart, provides adequate data for the evaluation of safety. The Applicant submitted additional safety data for multiple courses of treatment. The demographics of the trial population are sufficiently representative of the target population. Therefore, the safety database presented by the Applicant is sufficient to characterize the safety profile of CCH for the treatment of moderate to severe cellulite on the buttocks of adult women.

8.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of CCH. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

For both Phase 3 Trials, 302 and 303, the Applicant defined an AE as "any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (e.g., chemistry, electrocardiogram [ECG], X-ray, etc.), or worsening of a pre-existing condition associated temporally with the use of the study medication whether or not considered related to the study medication." AEs included any change in the general condition, sign, symptom offered by or elicited from the subject, clinically relevant laboratory abnormality or physical finding, or concurrent disease temporally associated with the use of a trial product or worsening in severity or frequency during the trial. Investigational staff will record all AEs in the electronic case report form. Treatment-emergent adverse event (TEAEs) form the primary basis of the safety review. As such, the Applicant defined TEAEs as any condition that was not present prior to treatment with trial medication but appeared following treatment, was present at treatment

initiation but worsened during treatment or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

In all clinical trials in the development of CCH, AEs were documented by system organ classes (SOCs) and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA). In the Phase 3 trials, the Applicant used MedDRA version 19.0. The coding of adverse events in this BLA submission appeared adequate to allow estimates of AE risk.

However, some PTs, such as nasopharyngitis and upper respiratory infection, were pooled during analyses to more effectively capture the incidence of the AEs.

Per 21 CFR 312.32, the Applicant defined a SAE as any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life threatening (subject is at risk of death at the time of the event)
- Results in or prolongs an inpatient hospitalization
- Results in permanent or substantial disability
- Is a congenital anomaly/birth defect
- Is considered an important medical event (e.g., events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes)

In addition, the Applicant did not categorized pregnancy or an uncomplicated, elective abortion as an AE. However, the Applicant did document any negative outcome associated with pregnancy (e.g., congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events as an SAEs. All potentially clinically important (PCI) AEs were followed until the condition resolved or stabilized.

Investigational staff queried subjects at each visit with non-leading questions to elicit AEs that have occurred since the last visit. Investigators categorized AE for relatedness to the trial drug, seriousness, intensity/severity (e.g., highest intensity observed), causality, duration, action taken with trial drug, corrective treatment and outcome.

The Investigational staff described the relationship of the AE to the trial drug as follows:

- Not related: the AE is definitely not related to the trial medication.
- Unlikely related: there are other, more likely causes and trial medication is not suspected
- Possibly related: there is evidence to suggest there is a reasonable possibility that the event was caused by the trial medication.
- Probably related: there is evidence suggesting a direct cause and effect relationship between the AE and the trial medication.

In the Phase 3 trials, causality of an AE was dichotomized to “related” to the trial product if the AE was “possibly related” or “probably related” or “not related” to the trial product if the AE was “unlikely related” or “not related.”

Investigators characterized the intensity or severity of AEs as mild, moderate or severe according to the following definitions:

- Mild: usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- Moderate: introduce a low level of inconvenience or concern to the subject and may interfere with daily activities but are usually ameliorated by simple therapeutic measures.
- Severe: interrupt a subject's usual daily activity and typically require systemic drug therapy or other treatment.

Other AEs of Clinical Interest Included:

- AESIs
  - Local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration
  - Hypersensitivity reactions including anaphylaxis
  - AEs such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration
- Special event reporting
  - Overdose: any accidental or intentional use of trial drug in an amount higher than the dose indicated by the protocol for that subject

Routine Clinical Tests

Safety monitoring occurred at all visits, Day 1, Day 22, Day 43, Day 71. The evaluation of safety consisted of AEs, clinical laboratory tests [screening and Day 71], vital signs [blood pressure, pulse, temperature, respiration, height (screening only), and weight], injection site reactions/local tolerability, pregnancy testing, concomitant medications and assessments of immunogenicity (Anti-AUX-I/anti-AUX-II antibody levels). See the previous section for the approach to recording adverse events. Additional assessments at screening included physical examinations, ECG and documentation of skin type using the Fitzpatrick scale. Investigational staff performed digital photography at screening and prior to injections (before and after marking injection sites on Days 1, 22, and 43) and on Day 71 to be used in some cellulite severity assessments.

8.4. Safety Results

Deaths

There were no deaths in Phase 3 trials 302/303. However, one subject who participated in the long-term, extension Trial 202 died in a motor vehicle accident on Day 461.

Serious Adverse Events

There were two serious adverse events (SAEs) in Trials 302/303. Both SAEs were unrelated to the trial drug. One subject received placebo and the other subject received CCH at 2 treatment visits. Brief narratives are below:

Colitis Ischemic
A 39-year-old white female subject (b) (6)) with a history of deep vein thrombosis, hemorrhoids and hysterectomy experienced ischemic colitis on Day 25. The subject completed 2 of 3 doses of placebo. She presented with bright red blood in her stool, severe abdominal cramping, nausea, and vomiting. The AE of ischemic colitis was documented as mild, and did not lead to discontinuation from the trial. The subject received her last dose of placebo.

Syncope, Hypokalemia, and Hypotension
A 54-year-old white female subject (b) (6) with a history of diabetes, chronic pain, hypertension, nerve disorder, posttraumatic stress syndrome experienced syncope, hypokalemia, and hypotension after receiving 1.68 mg of CCH. Concomitant medications included: Prazosin, lidocaine 5% transdermal patches, losartan, alprazolam, metformin, amlodipine, Vicodin 5 to 325 mg, doxepin, gabapentin, and baclofen. On Day 4 after her dose of CCH, the subject was hospitalized after losing consciousness and hitting her head. In the emergency room her blood pressure was 63/43, heart rate was 112 and potassium level was low (2.2 mEq/L). ECG, chest x-ray and computed tomography showed no clinically significant abnormalities. The subject was also diagnosed with concussion, dehydration, metabolic acidosis, nausea, and acute opioid overdose (treated with naltrexone). The AEs of syncope, hypokalemia, and hypotension were considered severe, and resulted in discontinuation from the trial. The temporal association of acute opioid overdose with these AEs supports causality.

Dropouts and/or Discontinuations Due to Adverse Effects

The majority of subjects (755 [89.3%]) completed Trials 302/303. The most common reasons for trial discontinuation were withdrawal of consent (37 [4%]) and lost to follow-up (28 [3%]). Among the subjects who received treatment, a total of 18 subjects [2%] experienced AEs which resulted in discontinuation from the trial. Two subjects who were randomized to placebo experienced AEs (herpes simplex lesions on the buttocks and hypertension) prior to dosing and withdrew from Trial 303. A greater proportion of subjects in the CCH group (17 subjects [4%]) discontinued the trial due to AEs compared to the placebo group (1 subject [<1%]).

The number of subjects who discontinued Trials 302/303 due to AEs was similar across trials. In Trial 302, a total of 9 (4%) subjects who received CCH and one (1%) subject who received placebo (b) (6) experienced TEAEs which resulted in discontinuation. One subject in each treatment group withdrew due to TEAEs which were assessed as not related to the trial drug ([placebo group: excessive cerumen] and [CCH group: 58-year-old white female with the onset (Day 8) of severe abscesses in the axilla, pubis and hamstring]). The remaining eight subjects

withdrew due to injection site reactions which were related to CCH (bruising, pain, hemorrhage, and nodules/ mass).

In Trial 303, two subjects experienced AEs which occurred after randomization but prior to dosing (43-year-old White female with herpes simplex lesions on the buttock (b) (6) and 47-year-old African American female with severe hypertension (b) (6)) and withdrew from the trial. Additionally, after receiving 2 doses of placebo, one 37-year-old White female subject (b) (6)] with a history of ectopic pregnancy withdrew from the trial due to pregnancy (not defined as an TEAE).

A total of 8 subjects withdrew from the trial and 3 withdrew the trial drug (b) (6) (b) (6)) due to AEs related to CCH (adverse reactions [ARs]). One subject experienced moderate pyrexia (b) (6) following each of two doses of CCH (1.68 mg x 2 sessions) which was assessed as possibly related to the trial drug. Ten subjects experienced injection site reactions including bruising, pain, hemorrhage, nodules, induration, and edema. These ARs are summarized below.

Most of the ARs occurred on Day 1 after the first injection of CCH. Discontinuations from the trial and drug product due to injection site reactions are tabulated below.

Table 12. Discontinuations Due to Injection Site Reactions With CCH

Subject ID	Demographics	Severity /Adverse Reaction(s) at Injection site	Onset Day (Session)	Total Dose
EN3835-302				
(b) (6)	70 yo W F	Moderate pain, mild warmth	Day 3 (1)	1.68 mg
	42 yo W F	Severe bruising	Day 1 (1)	1.68 mg
	64 yo W F	Mild bruising, pain	Day 1 (1)	1.68 mg
	53 yo W F[1]	Moderate bruising	Day 1 (1)	1.68 mg
	39 yo W F[2]	Mild hemorrhage, nodule	Day 1 (1)	1.68 mg
	62 yo W F[3]	Severe bruising	Day 1 (1)	1.68 mg
	62 yo AA F[4]	Moderate mass, severe bruising, pain	Day 1/2 (1)	1.68 mg
	48 yo AA F[5]	Moderate pain, mass, bruising	Day 1/2/7 (1)	1.68 mg

Subject ID	Demographics	Severity /Adverse Reaction(s) at Injection site	Onset Day (Session)	Total Dose
EN3835-303				
(b) (6)	63 yo W F[6]	Mild bruising, mass, pain	Day 1 (1)	1.68 mg
	45 yo W F	Moderate bruising	Day 1 (1,2)	1.68 mg x 2
	63 yo W F	Moderate bruising, pain, warmth, nodule	Day 3 (1)	1.68 mg
	54 yo W F	Severe bruising, pain	Day 1 (1)	1.68 mg
	39 yo W F[7]	Moderate induration, edema	Day 1 (1)	1.68 mg
	51 yo W F[8]	Severe hemorrhage, pain	Day 1 (1)	1.68 mg
	48 yo W F[9]	Mild bruising, nodule	Day 1 (1)	1.68 mg
	52 yo W F	Mild pain, bruising	Day 1,2 (1)	1.68 mg
	47 yo W F[10]	Moderate bruising	Day 1 (1,2)	1.68 mg x 2
	55 yo W F	Mild bruising, nodule, hemorrhage, pain	Day 1 (2)	1.68 mg x 2

Source: Reviewer's table
Additional history
[1] Resolved Day 23
[2] Resolved Day 18
[3] Concomitant Medications: sulindac and acetylsalicylic acid. Resolved Day 61
[4] Concomitant Medications: escitalopram oxalate. Resolved Day 49 and 23 respectively. Also, noted moderate nodules.5
[5] Concomitant Medications: vitamin E, fioricet
[6] Concomitant Medications: cortisone acetate 0.625 mg orally daily
[7] Additional AEs: discoloration
[8] Additional AEs: injection site dysesthesia (stinging), injection site erythema, injection site discoloration
[9] Concomitant Medications: ibuprofen prn
[10] Additional AEs: injection site atrophy, injection site nodule/mass, injection site pain
Abbreviations: CCH = Collagenase clostridium histolyticum, yo=year old

Significant Adverse Events

Refer to Section 8.5 Analysis of Submission-Specific Safety Issues of this review.

Treatment-Emergent Adverse Events and Adverse Reactions

Treatment-Emergent Adverse Events

The Applicant defined TEAEs as any AE with onset date on or after the treatment start date in each trial. Treatment-related AE, also called related TEAE, is defined as any AE with onset date on or after the treatment start date and with a relationship to trial medication of possible, probable, or missing in each trial.

In Phase 3 Trials 302 /303, there were 374 subjects (88%) who received CCH and experienced at least 1 TEAE. Of the 3342 TEAEs reported by these subjects, 2271 (68%) were mild, 825 (25%) were moderate, and 246 (7%) were severe. By comparison, there were 169 subjects (40%) who received placebo and experienced at least 1 TEAE. Of the 545 TEAEs reported by these subjects, 455 (84%) were mild, 88 (16%) were moderate, and 2 (<1%) were severe. The majority of common TEAEs were in the SOC of general disorders and administration site conditions. A total of 369 subjects (87%) who received CCH versus 125 subjects (30%) who received placebo experienced TEAEs in this class.

In order to characterize the frequency of common TEAEs which were reported under multiple preferred terms (PTs), the review team pooled similar PTs as indicated below:

- Bruising: injection site bruising, injection site hematoma, and injection site hemorrhage
- Pain: injection site pain and injection site discomfort
- Swelling: injection site swelling and injection site edema (no local swelling observations)
- Nodule: injection site mass and injection site nodule

In both treatment groups, the most common TEAEs among subjects who received CCH compared with placebo were injection site bruising [84% versus 22% of subjects], injection site pain [48% versus 9% of subjects], injection site nodule [33% versus 1% of subjects], and injection site pruritus {15% versus 1% of subjects].

A total of 5 subjects (1.2% of subjects) who received CCH and no subjects who received placebo experienced syncope. The majority of TEAEs were of mild (3/5) to moderate severity (1/5). Four of five subjects experienced syncope on the day of the injection, generally the first injection (3/4). One subject experienced syncope prior to any injections; one subject experienced syncope prior to the second treatment visit; one subject experienced a "vasovagal response" after completion of injections in both buttocks. One subject with persistent bruising and a history of anxiety, had 2 episodes of syncope approximately 3 weeks after her final session. Most had bruising (4/5) and pain (2/5) or nodule formation (1/5) concurrently. Most of these subjects completed the trial (4/5) and received additional doses of CCH (3/5); however, one subject (b) (6) using numerous concurrent medications experienced syncope and multiple SAEs and withdrew from the trial. See the discussion above under Serious Adverse Events in this review. There is no unconfounded data that suggests that syncope was a symptom of a hypersensitivity reaction or related to CCH. All TEAEs of syncope were assessed as not related by investigators.

The preferred terms included in the following two tables reflect pooling of related adverse events as follows:

- Bruising - injection site bruising, injection site hematoma, and injection site hemorrhage
- Pain - injection site pain and injection site discomfort
- Swelling - injection site swelling and injection site edema (no local swelling observations)
- Nodule- injection site mass and injection site nodule

Table 13. Treatment-Emergent Adverse Events in the Phase 3 Trials 302 /303

	EN3835-302 and EN3835-303	
Preferred Term or Pooled Term	**CCH N=424**	**Placebo N=419**
Injection site bruising	358 (84%)	90 (22%)
Injection site pain	204 (48%)	37 (9%)
Injection site nodule	141 (33%)	3 (1%)
Injection site pruritus	63 (15%)	4 (1%)
Injection site erythema	36 (9%)	21 (5%)
Injection site discoloration	33 (8%)	2 (1%)
Injection site swelling	29 (7%)	1 (<1%)
Injection site warmth	14 (3%)	0 (0%)
Injection site induration	10 (2%)	5 (1%)
Injection site dysesthesia	6 (1%)	3 (1%)
Syncope	5(1%)	0 (0%)

Source: Rebecca Hager, PhD, Statistical Reviewer
Note: As observed by the OSI reviewer, 2 investigators did not document all TEAE related to bruising. However, these deviations do not impact the number of subjects who experienced bruising because investigators documented bruising at other timepoints for these subjects.
Abbreviations: CCH = Collagenase clostridium histolyticum, N = number of subjects

Based on the high incidence of bruising associated with administration of CCH in the Phase 3 trials, the review team sought to fully characterize this TEAE. Phase 3 protocols excluded subjects with coagulation disorders or using anticoagulant or antiplatelet medications (except those taking ≤150 mg aspirin daily). However, a total of 65 subjects enrolled in these trials reported concomitant use of low dose aspirin (42 subjects who received CCH and 23 subjects who received placebo). Of these subjects, 20 subjects in the CCH group reported bruising while 3 in the placebo group reported bruising.

There was a wide variation in the time of onset and duration of bruising. However, more than 95% of events of bruising (1292/1340) and hemorrhage (94/98) occurred within the first 3 days following CCH injection. Most of the TEAE of injection site bruising (81.9%) and hemorrhage (71.4%) resolved within 21 days, before the next treatment session. The protocol did not specify evaluation procedures or photographic documentation of TEAEs related to bleeding. However, due to their concern about this TEAE, the Applicant conducted a dedicated trial for this purpose. (See the summary of Trial 205 in Section 8.5.)

Subjects who received CCH experienced multiple injection site adverse events more frequently than subjects who received placebo. The most common TEAEs observed together were bruising and injection site pain as summarized below.

Table 14. Subjects With Multiple Injection Site Adverse Events in the Phase 3 Trials 302 /303

	EN3835-302 & EN3835-303	
Safety Population (Pool 1)	**CCH N=424**	**Placebo N=419**
Bruising and pain	197 (47%)	18 (4%)
Bruising, pain, and nodule	83 (20%)	0
Bruising, pain, and induration	7 (2%)	1 (<1%)
Bruising, pain, nodule, and induration	3 (1%)	0
Bruising and erythema	34 (8%)	9 (2%)

	EN3835-302 & EN3835-303	
Safety Population (Pool 1)	**CCH N=424**	**Placebo N=419**
Bruising and discoloration	31 (7%)	0
Swelling and induration	5 (1%)	1 (<1%)
Swelling and nodule	18 (4%)	0
Swelling, nodule, and induration	1 (<1%)	0

Source: Rebecca Hager, PhD, Statistical Reviewer
Abbreviations: CCH = Collagenase clostridium histolyticum, N = number of subjects

Most of the subjects experienced TEAEs of mild to moderate severity. Among the subjects who received CCH in Trial 302/303, 73 subjects (17%) experienced TEAEs of severe severity compared with 1 subject who received placebo (<1%). Some subjects had more than one severe TEAE. Among the subjects with severe TEAEs who received CCH, 67 subjects had injection site bruising, 11 subjects had injection site pain, 5 subjects had injection site nodule, and 4 subjects each had injection site swelling, hemorrhage and pruritus. There were no other TEAEs of severe severity that were experienced by more than 1 subject.

Adverse Reactions

Most of the adverse reactions (AR; related TEAEs) which occurred during the Phase 3 Trials 302 and 303 involved the injection site. The majority of the injection site reactions were considered related to the trial product; therefore, the incidences of the common ARs are similar to the TEAEs. The following summary of ARs included additional pooling of similar, less common PTs: "swelling" included induration and "pain" included dysesthesia.

Table 15. Adverse Reactions in the Phase 3 Trials 302 /303

	EN3835-302 & EN3835-303 Pooled	
Safety Population (Pool 1)	**CCH N=424**	**Placebo N=419**
Injection site bruising	358 (84%)	88 (21%)
Injection site pain	205 (48%)	40 (1%)
Injection site nodule	141 (33%)	3 (1%)
Injection site pruritus	62 (15%)	4 (1%)
Injection site erythema	36 (9%)	21 (5%)
Injection site discoloration	33 (8%)	2 (1%)
Injection site swelling	34 (8%)	5 (1%)
Injection site warmth	14 (3%)	0

Source: Rebecca Hager, PhD, Statistical Reviewer
Abbreviations: CCH = Collagenase clostridium histolyticum, N = number of subjects

Definitions used in Table 15 above and discussions below:

- Bruising: injection site bruising, injection site hematoma, and injection site hemorrhage
- Pain: injection site pain, injection site discomfort, and injection site dysesthesia
- Swelling: injection site swelling, injection site edema, injection site induration
- Discoloration: injection site discoloration (no hyperpigmentation observations)
- Nodule: injection site mass and injection site nodule

As summarized above, the most common ARs reported by subjects in Trials 302/303 were injection site bruising, pain, nodule and pruritus. There was a substantial imbalance in the incidence of these ARs between treatment arms. There were 1707 events of bruising. Evaluable events (1659) had a median onset of Day 1 (range Day 1 to 43) and a median duration of 12 days (range 2 to 131 days). Subjects treated approximately 1% of the bruising reactions. Treatments included homeopathic preparations (35%), analgesics (26%), anti-inflammatory and anti-rheumatic products (26%), and ice therapy (9%).

There were 911 events of pain. Evaluable events (909) had a median onset of Day 1 (range Day 1 to 29) and a median duration of 6 days (range 1 to 70 days). Subjects treated approximately 11% of the pain reactions. Treatments included analgesics (60%), anti-inflammatory and anti-rheumatic products (22%), and ice therapy (8%).

There were 378 events of nodule. Evaluable events (367) had a median onset of Day 2 (range Day 1 to 25) and a median duration of 14 days (range 1 to 96 days). Subjects treated approximately 2% of the nodule reactions. Treatments included analgesics (67%), and anti-inflammatory and anti-rheumatic products (33%).

There were 182 events of pruritus. Evaluable events (182) had a median onset of Day 1 (range Day 1 to 12) and a median duration of 5 days (range 1 to 22 days). Subjects treated approximately 6% of the pruritus reactions. Treatments included antihistamines (67%). (See Supporting Document Number (SDN)28 dated April 21, 2020.)

The AR of discoloration was classified as an adverse event of special interest due to the potential for dermal pigmentation to be a long-term sequela of the administration of the trial product. There were 88 events of discoloration which occurred in 35 subjects. Of these, 33 subjects received CCH and 2 received placebo. Most of the subjects in both treatment arms experienced discoloration of mild severity (31 subjects). A total of 4 subjects who received CCH had discoloration of moderate severity. A majority of these ARs of discoloration represented hyperpigmentation (78/88, 86%). Evaluable events (31) had a median onset of Day 9 (range Day 1 to 34) and a median duration of 50 days (range 1 to 100 days). No treatment was reported. Another AR potentially related to long-term use was mild injection site atrophy experienced by one subject.

Most of the subjects experienced ARs of mild to moderate severity. Among the subjects who received CCH in Trial 302/303, 71 subjects (17%) experienced TEAEs of severe severity compared with 1 subject who received placebo (<1%). Some subjects had more than one severe AR. Among the subjects with severe ARs who received CCH, 67 subjects had injection site bruising, 11 subjects had injection site pain, 5 subjects had injection site nodule, and 4 subjects each had injection site swelling, hemorrhage and pruritus. There were no other ARs of severe severity that were experienced by more than 1 subject.

Laboratory Findings

Investigators conducted safety laboratory testing at baseline and end of treatment visit (Day 71). There were no clinically meaningful changes from mean baseline values in hematology parameters (hemoglobin, hematocrit, erythrocytes, leukocytes, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils) or chemistry parameters (glucose, sodium, potassium, calcium, chloride, bicarbonate, phosphate, urea nitrogen, creatinine, estimated glomerular filtration rate, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, bilirubin, albumin, alkaline phosphatase, and urate). The Applicant defined PCI laboratory values that exceeded the normal values. The definitions and numbers of subjects with PCI laboratory values by treatment group are summarized below.

Table 16. Potentially Clinically Important (PCI) Vital Sign Values by Treatment Arm-Trials 302 /303

Laboratory Analyte	Criteria	Statistic[a, b]	Study Drug	
			CCH 0.84 mg/ Treatment Area (N = 424)	Placebo (N = 419)
Hemoglobin (g/L)	PCI-: ≤100 g/L	n/N' (%)	8/393 (2.0)	6/386 (1.4)
	PCI+: ≥190 g/L	n/N' (%)	0/393 (0.0)	0/386 (0.0)
Hematocrit	PCI-: ≤0.3	n/N' (%)	3/393 (0.8)	2/386 (0.5)
	PCI+: ≥0.6	n/N' (%)	0/393 (0.0)	0/386 (0.0)
Platelets (10^9/L)	PCI-: ≤100 (10^9/L)	n/N' (%)	1/390 (0.3)	0/383 (0.0)
	PCI+: ≥650 (10^9/L)	n/N' (%)	0/390 (0.0)	0/383 (0.0)
ALT (U/L)	PCI+: ≥3×ULN	n/N' (%)	3/394 (0.8)	1/390 (0.3)
AST (U/L)	PCI+: ≥3×ULN	n/N' (%)	3/394 (0.8)	1/390 (0.3)
Creatinine (µmol/L)	PCI+: ≥300 (µmol/L)	n/N' (%)	0/394 (0.0)	0/390 (0.0)
BUN (mmol/L)	PCI+: ≥12 (mmol/L)	n/N' (%)	0/394 (0.0)	1/390 (0.3)

Source: 2.7.4 Summary of Clinical Safety, Table 41
[a] Safety Population: all enrolled subjects who received at least 1 injection of trial drug.
[b] Includes all post injection laboratory samples. If the subject had more than one clinically significant laboratory value for an analyte, the subject was counted only once.
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CCH = Collagenase clostridium histolyticum, N = number of subjects with at least 1 post injection laboratory test result for the analyte, PCI+ = potentially clinically important high, PCI = potentially clinically important low, ULN = upper limit of normal

Similar findings were observed across the development program.

Vital Signs

Investigators documented vital signs at pre-injection and 15 and 30 minutes post-injection on Days 1, 22, 43 and at the end of the trial on Day 71 in Trials 302/303. There were no clinically meaningful changes from mean baseline values in systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, or temperature values. The Applicant defined PCI vital sign values that exceeded the normal values. Shifts above and below the normal values were balanced for individual vital sign values. The definitions and numbers of subjects with PCI vital sign values by treatment group are summarized below.

Table 17. Potentially Clinically Important (PCI) Vital Sign Values by Treatment Arm-Trials 302 /303

Vital Sign	Criteria	Statistic[a, b]	Study Drug	
			CCH 0.84 mg/ Treatment Area (N=424)	Placebo (N=419)
Systolic Blood Pressure	PCI-: ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline	n/N' (%)	5/424 (1.2)	5/419 (1.2)
	PCI+: ≥180 mmHg and increase ≥20 mmHg from Baseline	n/N' (%)	1/424 (0.2)	1/419 (0.2)
Diastolic Blood Pressure	PCI-: ≤ 50 mmHg and decrease ≥15 mmHg from Baseline	n/N' (%)	3/424 (0.7)	1/419 (0.2)
	PCI+: ≥105 mmHg and increase ≥15 mmHg from Baseline	n/N' (%)	4/424 (0.9)	8/419 (1.9)
Pulse Rate	PCI-: ≤50 bpm and decrease ≥15 bpm from Baseline	n/N' (%)	5/424 (1.2)	4/419 (1.0)
	PCI+: ≥ 120 bpm and increase ≥ 15 bpm from Baseline	n/N' (%)	1/424 (0.2)	0/419 (0.0)
Respiratory Rate	PCI-: ≤8 brpm and decrease ≥ 7 brpm from Baseline	n/N' (%)	0/424 (0.0)	1/419 (0.2)
	PCI+: ≥ 25 brpm and increase ≥ 7 brpm from Baseline	n/N' (%)	0/424 (0.0)	0/419 (0.0)
Temperature	PCI+: ≥ 38.3 °C and increase ≥ 1.1 °C from Baseline	n/N' (%)	0/424 (0.0)	0/419 (0.0)

Source: 2.7.4 Summary of Clinical Safety, Table 42
[a] Safety Population: all enrolled subjects who received at least 1 injection of trial drug.
[b] Includes all post injection vital sign measurements. If the subject has more than one clinically significant value for a vital sign, the subject is counted only once N' is the number of subjects with at least 1 post injection vital sign measurement for the parameter.
Abbreviations: BPM = beats per minute, BRPM = breaths per minute, CCH = collagenase clostridium histolyticum, PCI+ = potentially clinically important high, PCI = potentially clinically important low

Similar findings were observed across the development program.

ECGs and QT

As CCH has no quantifiable systemic exposure after subcutaneous administration, the proposed product is not expected to prolong the QT interval or cause arrhythmias. Therefore, the Applicant did not conduct a thorough QT/QTc studies or perform cardiac safety monitoring. Investigators performed 12-lead ECGs at screening only in the Phase 3 trials.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The Applicant conducted immunogenicity testing as part of the safety monitoring in all 11 trials in the development program. In Phase 3 Trials 302/303, the Applicant conducted testing for ADAs at baseline, Day 22, Day 42 and Day 71 and for neutralizing antibodies (NAbs) at baseline and Day 71. By Day 22, approximately 53% (203/383) and 26% (101/383) of subjects who completed the first treatment visit in the Phase 3 trials developed anti-AUX-I and anti-AUX-II antibodies, respectively. After 2 treatment visits, most subjects (>96%) developed anti-AUX-I and anti-AUX-II antibodies which appeared to persist for up to 360 days after the first treatment.

Data from Trials 302/303 indicated no clear correlation between antibody titer and the development of TEAE or the severity of TEAE. At Day 22, the number of subjects with at least

one TEAE was 52% among subjects who were seropositive for anti-AUX-I antibodies and 53% among subjects who were seronegative for anti-AUX-I antibodies. Likewise, the number of subjects with at least one TEAE was 45% among subjects who were seropositive for anti-AUX-II antibodies and 55% among subjects who were seronegative for anti-AUX-II antibodies. A total of 74 (37%) seropositive anti-AUX-I subjects and 94 (38%) seronegative anti-AUX-I subjects experienced injection site bruising; a total of 30 (30%) of seropositive anti-AUX-II subjects and 113 (40%) seronegative anti-AUX-II subjects experienced injection site bruising. (See SDN 20 dated March 16, 2020.) The totality of the data suggested that antibody status did not have a clinically meaningful effect on the occurrence of injection site reactions.

A majority of subjects who developed ADA to AUX-I and AUX-II had NAbs to AUX-I and AUX-II. In Phase 3 Trials 302/303, the Applicant evaluated only a subset of subjects for neutralizing antibodies at Day 71. Among the 96 subjects who were tested for anti-AUX-I NAbs, 65 subjects (68%) were seropositive, and 31 subjects (32%) were seronegative.

The percentage of subjects who experienced at least one TEAE was 92% among seropositive subjects and 97% among seronegative subjects. The percentage of subjects who experienced injection site bruising was 85% among seropositive subjects and 81% among seronegative subjects. Among the 94 subjects who were tested for anti-AUX-II NAbs, 78 subjects (83%) were seropositive, and 16 subjects (17%) were seronegative. The percentage of subjects who experienced any TEAE was 89% among seropositive subjects and 81% among seronegative subjects. The percentage of subjects who experienced injection site bruising was 83% among seropositive subjects and 75% among seronegative subjects. (See SD 20 dated March 16, 2020.) However, a comparison of injection site reactions by neutralizing antibody status must be interpreted with caution since only a subset of subjects was evaluated for NAbs.

See Section 6 Clinical Pharmacology of this review for a discussion of the bioanalytical methods for testing anti-drug antibodies and neutralizing anti-drug antibodies and the immunogenicity findings from Trials 302/303.

Another concern associated with highly immunogenic drug products is the risk of hypersensitivity reactions. During the development of CCH for the treatment of moderate to severe EFP, there were no reports of serious hypersensitivity reactions among the 964 subjects who received CCH. Similarly, no subjects reported serious hypersensitivity reactions in the development program for Xiaflex (BLA 125338). However, the Applicant received multiple postmarketing reports of serious hypersensitivity reactions including anaphylaxis associated with the use of Xiaflex. Current labeling for Xiaflex contains a statement regarding the risk of anaphylaxis (WARNINGS AND PRECAUTIONS section of labeling revised December 6, 2013). For a discussion of hypersensitivity reactions reported in Phase 3 Trials 302/303, see Section 8.5 Adverse Events of Special Interest of this review.

8.5. Analysis of Submission-Specific Safety Issues

Adverse events of special interest included events in 3 categories: hypersensitivity reactions, events remote from the injection site, and injection site reactions related to CCH administration.

8.5.1. Hypersensitivity Reactions

Review of the Endo safety database for Xiaflex/Xiapex (European Union) indicated 15 reports of serious hypersensitivity reactions (including 12 reports of anaphylactic reaction or anaphylactic shock) during postmarketing surveillance. Therefore, the incidence of serious hypersensitivity reactions in the target population with cellulite was a key safety concern. In Phase 3 Trials 302/ 303, there were no TEAEs of anaphylaxis or other serious hypersensitivity reactions. However, two subjects who received CCH (0.5%) and 1 subject who received placebo (0.2%) experienced injection site urticaria; 63 subjects who received CCH (15%) and 4 subjects who received placebo (1%) experienced injection site pruritus. In addition, 2 subjects who received CCH experienced generalized pruritus or pruritus (0.5%) and one subject who received placebo experienced pruritus (0.2%).

8.5.2. Treatment-Emergent Adverse Events Remote From the Injection Site

As pharmacokinetic trials demonstrated no quantifiable systemic exposure to the drug product, AEs which occurred remote from the injection site were of clinical interest. Of particular interest, the Applicant focused on events of swelling, bruising, or contusion which were not associated with the administration site. In Phase 3 trials 302/ 303, there were 11 subjects [4 (0.9%)] who received CCH and 7 subjects [(1.7%)] who received placebo who reported 14 TEAEs of contusion that were located remote from the injection site. There were no subjects who received either trial product who reported bruising remote to the injection site and one subject who received placebo who reported swelling remote from the injection site. Most of the other TEAEs which occurred remote from the injection site or reflect systemic safety occurred in single subjects such as abscess, mild palpitations, paresthesia and spontaneous abortion (discussed under Human Reproduction and Pregnancy in Section 8.9). However, 3 subjects who received placebo reported rash and five subjects who received CCH reported syncope.

A total of 5 subjects (1.2% of subjects) who received CCH and no subjects who received placebo experienced syncope. The majority of events were of mild to moderate severity (4/5). Four of five subjects experienced syncope after their injection, generally the first injection (3/4). Most had bruising (4/5) and pain (2/5) or nodule formation (1/5) concurrently. One subject with persistent bruising and a history of anxiety, had syncope approximately 3 weeks after her final session. Most of these subjects (4/5) completed the trial; however, one subject (b) (6) using numerous concurrent medications experienced severe syncope and multiple SAEs and withdrew from the trial. See the discussion under Section 8.4 Serious Adverse Events in this review. All TEAEs of syncope were assessed as not related.

8.5.3. Injection Site Reactions Related to CCH Administration

Acute injection site reactions which were related to the trial product are discussed in Section 8.4 under Adverse Reactions in this review. Among the chronic TEAEs was one TEAE of injection site atrophy (there was an additional subject in Pool 3) and one AE of keloid scar in subjects who received CCH.

8.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There were no patient-reported outcome scales which measured safety parameters.

8.7. Safety Analyses by Demographic Subgroups

The review team evaluated TEAEs in Trials 302/303 by three demographic subgroups: age (<65 years and ≥65 years), race (white, African American and other) and body mass index (<25 and ≥25). The vast majority of subjects were <65 years old (total of 804 subjects [400 received CCH]) with a small number of subjects ≥65 years old (total of 39 subjects [24 received CCH]). The incidence of the two most common TEAEs in subjects receiving CCH, injection site bruising and injection site pain, were 85% and 49% in subjects <65 years old and 83% and 46% in subjects ≥65 years old. However, the incidence of nodule formation was 32% in subjects <65 years old and 54% in subjects ≥65 years old. Due to the size of the older subgroup, any comparison of subgroup safety should be viewed with caution.

Most of the subjects in Trials 302/303 were white (total of 661 [336 received CCH]) or African American (total of 151 [76 received CCH]). A total of 31 subjects {12 received CCH] were of other races. The incidence of the two most common TEAEs in subjects who received CCH, injection site bruising and injection site pain, were 87% and 53% in white subjects and 71% and 30% in African American subjects. The incidence of injections site pruritus and discoloration was 16% and 9% in white subjects and 12% and 5% in African American subjects.

Most of the subjects in Trials 302/303 were overweight or obese (BMI ≥25 kg/m^2) (a total of 677 [343 received CCH]) while a smaller number were of normal weight (BMI <25 kg/m^2) (a total of 165 [81 received CCH]). The incidence of the two most common TEAEs in subjects who received CCH, injection site bruising and injection site pain, were 84% and 49% in subjects with a BMI of ≥25 kg/$m^2$and 86% and 46% in subjects with a with a BMI of <25 kg/m^2. The incidence of nodule formation and discoloration was 35% and 9% in subjects with a BMI of ≥25 kg/m2 and 27% and 5% in subjects BMI of <25 kg/m.^{2}

See Appendix 15.3 for the summary tables of these comparisons.

8.8. Supportive Safety Studies/Clinical Trials

8.8.1. Safety Results From Other Trials

Phase 2

EN3835-831 (831)

Trial 831 was a randomized, double-blind, placebo-controlled, dose ranging trial to evaluate the safety and effectiveness of CCH when administered to a single treatment area (left or right buttock; left or right posterior thigh) in 150 adult females with EFP. Subjects were randomized to receive one of 3 doses of CCH (0.06 mg, 0.48 mg and 0.84 mg) or placebo in a 5:5:5:3 ratio into one eligible quadrant (e.g., left buttocks, right buttocks, left posterolateral thigh, and right posterolateral thigh). Subjects received a total volume of 3.6 mL per treatment visit which was administered as 12 injections. The duration of the Trial was 73 days Enrolled subjects had a Hexal photonumeric cellulite severity scale (CSS) score between 6 and 12 and at least one well defined dimple.

A majority of subjects had moderate EFP (51%). Most were white (91%),with a median age of 38 years (range 35 to 44 years) and a mean BMI of 25%. Of 150 subjects, 40 received the proposed dose (0.84 mg) of CCH and 17 had treatment in the buttocks. Among the subjects who received 0.84 mg of CCH, there were no deaths or SAEs and 85% (34/40) reported at least one TEAEs [injection site bruising 70%, injection site pain/discomfort 52% and injection site discoloration 15% compared with placebo 25%, 8% and 0%,respectively.] Two subjects (5%) who received 0.84 mg of CCH had severe injection site bruising and 2 subjects (5%) discontinued the trial due to TEAEs [(Subject (b) (6): 37-year-old white female with moderate injection site bruising and pain on Treatment Visit #1) and (Subject (b) (6): 34-year-old African American female with urticaria on Treatment Visit #2 which resolved with Benadryl and Zyrtec on the same day:]. ARs were reported by 83% (33/40), 78% (31/40) subjects reported injection site reactions and 1 subject reported urticaria.

EN3835-201 (201)

Trial 201 was a randomized, double-blind, placebo-controlled trial to evaluate the safety and effectiveness of CCH in adult females with EFP. Subjects were randomized in a 1:1 ratio to receive either CCH (0.84 mg) or placebo into one eligible quadrant (e.g., left buttocks, right buttocks, left posterolateral thigh, and right posterolateral thigh) which was randomly selected. Enrolled subjects had PR-PCSS and CR-PCSS scores of 3 or 4 and Hexsel CSS total score of no greater than 13. Subjects received a total volume of 3.6 mL per treatment visit which was administered as 12 injections. A course of treatment was 3 treatment visits separated by 21 days with a final assessment on Day 71.

Of 375 subjects, 189 subjects received CCH and 186 subjects received placebo. There were no deaths and one serious adverse event (0.5%). In the CCH treatment group 155 subjects (82%)

reported 712 TEAE; in the placebo group 50 subjects (27%) reported 77 TEAEs. The most frequently reported TEAEs were injection site bruising (142 subjects [75%] versus 25 subjects [13%]) and injection site pain (112 subjects [59%] versus 10 subjects [5%]). AR were experienced by 81% in the CCH group and 18% of the placebo group. The most frequently reported AR were injection site bruising (142 subjects [75.1%] versus 23 subjects [12.4%]) and injection site pain (112 subjects [59.3%] versus 10 subjects [5.4%]).

Serious Adverse Events (SAEs)

Spontaneous abortion: A 36-year-old white female subject (b) (6) with a history of ectopic pregnancy and spontaneous abortion became pregnant after receiving one course of treatment (total of 10.04 mg of CCH). The subject reported the occurrence of pregnancy approximately 3 weeks after her last dose. On Day 72, the subject experienced a spontaneous abortion at approximately 10 weeks of gestation. The TEAE of spontaneous abortion was assessed as severe and not related.

Discontinuations Due to Adverse Events

A total of seven subjects (3.7%) experienced TEAEs which lead to discontinuation in the active group and one subject (0.5%) in the placebo group. A 52-year-old African American subject (b) (6) who received CCH discontinued the trial due moderate arthralgia and lower back pain. The TEAEs of arthralgia and lower back pain were assessed as not related to the study trial. The remaining subjects discontinued the trial due to injection site reactions assessed as related to the trial drug. In addition, four additional subjects discontinued the trial drug but remained in the trial.

Table 18. Discontinuations Due to Treatment-Emergent Adverse Events (TEAEs)-Trial 201

Subject ID	Demographics	Severity /Adverse Reaction(s) at Injection Site Causing D/C	Onset	Total Dose	Outcome
(b) (6)	34yo W F	Moderate bruising, pain (thigh)[1]	Day 1	0.84 mg	d/c trial
	52 yo W F	Mild bruising, pain, induration (thigh)	Day 1	0.84 mg	d/c trial
	19 yo W F	Moderate bruising[2] (thigh)	Day 1	0.84 mg	d/c trial
	62 yo W F	Severe bruising; pain (thigh)	Day 1/3	0.84 mg	d/c trial
	59 yo AA F	Mild pain (thigh)	Day 1	0.84 mg	d/c trial
	53 yo WF	Moderate pain (thigh)	Day 1	0.84 mg	d/c trial
	42 yo WF	Moderate bruising, induration, pain (thigh)	Day 1	0.84 mg	d/c trial
	40 yo WF	Severe nodule	Day 1	0.84 mg	d/c drug
	38 yo WF Hispanic	Mild bruising, mass, pain, discoloration (thigh)	Day 1	0.84 mg	d/c drug
	44 yo WF	Moderate pain, bruising, mild pruritus, lipohypertrophy (thigh)[2]	Day 1	0.84 mg	d/c drug
	47 yo Asian F	Moderate pain, bruising, lipohypertrophy (thigh)[3]	Day 1	0.84 mg	d/c drug

[1] Subject also reported moderate swelling.
[2] Lipohypertrophy resolved on Day 22
[3] Lipohypertrophy resolved on Day 52
Abbreviations: AA = African American, D/C = discontinued, F = female, W = white, YO = year old

EN3835-205 (205)

Trial 205 was an open-label trial to evaluate the safety and effectiveness of CCH when administered to 2 treatment areas (i.e., bilateral buttocks or bilateral thighs) in adult females with EFP. The trial was comprised of 3 treatment visits, 21 days apart followed by a 90-day observation period. Investigators conducted a final safety evaluation on Day 180. The safe and effective dose, 0.84 mg per treatment area, was established in Trial 201. Enrolled subjects had a CR-PCSS of at least mild (score of ≥2) and a Hexsel CSS score of ≤13. A photographic sub-study documented injection site reactions at predose (baseline) and post dose Day 1, 3, 6, 13 and 22. Other subjects had postdose safety assessments by telephone (Day 1, 4, 8, 14). Investigators measured effectiveness using CR-PCSS for buttock or thigh, Subject Satisfaction with Cellulite Treatment Assessment – Buttocks (separate scale for the thigh) and Hexsel Cellulite Severity Scale (Hexsel CSS).

Among 158 enrolled subjects, 69 received CCH in the buttocks. Most subjects were white with a mean of 45 years (range 19 to 74). Results of the sub-study (N=37) indicated that Injection site bruising was most severe at 3 and 6 days after each treatment visit, generally resolved before the next treatment visit (approximately 21 days later), and tended to diminish over the treatment visits.

In Trial EN3835-205, there was one serious adverse event and no deaths.

Serious Adverse Events (SAEs)
Chronic obstructive pulmonary disease (COPD): A 62-year-old white female subject (b) (6) (b) (6) with a history of Chronic obstructive pulmonary disease (COPD), anxiety, chronic pain and post-traumatic stress disorder experienced an exacerbation of COPD on Day 33 after she received a total of 1.68 mg of CCH to her thighs. Prior to the exacerbation of COPD, the subject experienced bronchitis (Day 23) and influenza (Day 32). The AE of COPD was assessed as severe, not related and led to discontinuation of CCH. In addition, on Day 2 the subject reported injection site tenderness and mild injection site bruising. The injection site tenderness resolved on Day 10 and injection site bruising resolved on Day 21. The AEs of injection site tenderness and bruising were assessed as mild and related.

Discontinuations due to Adverse Events

After receiving 2 doses of CCH (1.68 mg x 2 sessions -total dose of 3.36 mg), a 30-year-old African American, female subject (b) (6) with no relevant medical history withdrew from the trial due to pregnancy on Day 43. The subject reported a normal pregnancy and delivered a full-term healthy baby with 2 months of postnatal follow-up. In addition, a total of 5 subjects withdrew due to injection site reactions.

Table 19. Discontinuations Due to Treatment-Emergent Adverse Events (TEAEs)-Trial 205

Subject ID	Demographics	Severity /Adverse Reaction(s) at Injection Site Causing D/C	Onset	Total Dose	Outcome
(b) (6)	48yo W F	Mild bruising (thigh)[1]	Day 3	1.68 mg	d/c trial
	74 yo W F	Mild bruising, pain (buttocks)	Day 3	1.68 mg	d/c trial
	24 yo W F	Mild bruising[2] (thigh); Mild bruising, pain (thigh)	Day 1	1.68 mg x 2 sessions	d/c trial
	62 yo W F	Mild bruising; mod pain(thigh)	Day 1	1.68 mg	d/c trial
	33 yo AA F	Moderate pain, bruising, swelling (thigh)	Day 1	1.68 mg	d/c trial

[1] Also, mild injection site discoloration (Day 32)
[2] Concomitant medications: ibuprofen; also, pain, erythema pruritus; bruising resolved after 20 and 22 days respectively
Abbreviations: AA = African American, D/C = discontinued, F = female, W = white, YO = year old

Long Term Safety and Safety After Repeat Dosing

EN3835-202 (202)

Trial 202 was an open-label trial to evaluate long-term safety up to 2 years, durability of response and the safety and efficacy of retreatment (dosing in a previously treated area) or redosing (dosing in a naïve treatment area). Subjects who received 2 courses of treatment were also evaluated for tolerance (a loss of ability to respond to a subsequent doses of CCH). After subjects completed Day 71 of Trial 201 and sign the informed consent, they were eligible for enrollment in this Trial 202. Subjects underwent up to 4 observation-only visits at 3-month intervals until the blind was broken. After unblinding of the treatment received in Trial 201, eligible subjects could choose to receive CCH treatment or observation only. Subjects who received CCH in Trial 201 could choose to receive one additional course of treatment (3 treatment visits) in a new treatment area (re-dosing) or the previously treated area (re-treatment).

To qualify for treatment in previously treated area, the quadrant had to have CR-PCSS and PR-PCSS scores equal to or greater than Trial 201 baseline scores and a Hexsel CSS score ≤13. Subjects who received placebo in Trial 201 qualified for treatment if the selected quadrant had a score of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS, and a Hexsel CSS score ≤13. After completing the first treatment course, subjects who received placebo in Trial 201 may choose to have a second treatment course (3 treatment visits) in a qualifying quadrant in Trial 202.

Subjects who selected observation-only were followed for safety and cellulite severity assessments at 3-month intervals through month 12 or more. Durability of response was assessed for 2 years in subjects who received CCH in Trial 201 and showed at least a 1-level multicomponent PR-PCSS/CR-PCSS improvement in cellulite severity (Long-term Durability Phase in double-blind treated subjects). Durability of response was defined as subjects who were CR-PCSS and PR-PCSS responders and maintained this response (i.e., lack of complete loss, did not return to baseline or worse) in a CCH-treated area.

Results
Of the 259 subjects who received treatment in the thigh or buttocks and enrolled in Trial 202, 121 received CCH in Trial 201 and 138 received placebo in Trial 201. Among the subjects who received CCH, 48 of these subjects were redosed in the other buttock and 4 subjects were retreated in the same buttock. Among the subjects who received placebo, 52 subjects received the first treatment with CCH in the buttock. and 42 of these subjects received the second treatment in the other buttock (redosed) and 2 subjects received the second treatment course in the same buttocks (retreated).

In Trial 202, there were four serious adverse events and one death.

Death
A 31-year-old, white female subject (b) (6) with no relevant medical history died in a motor vehicle accident on Day 461. She received one course of CCH (total dose of 2.52 mg) administered into the thighs. She also reported moderate to severe bruising with each injection which resolved after 7 to 10 days. The AE of death from internal injuries was assessed as severe and not related to the trial drug.

Serious Adverse Events (SAEs)
Appendicitis: A 23-year-old white female subject (b) (6) with no relevant medical history experienced appendicitis following one dose of CCH (0.84 mg). The subject missed the following 2 scheduled doses. Approximately, 6 months later, the subject presented to the hospital with abdominal pain and vomiting. After admission, an appendectomy was performed. The subject did not provide medical records. The AE of appendicitis was assessed as severe and not related to CCH. The subject was lost to follow-up.

Breast cancer: A 45-year-old African American, female subject (b) (6) with a history of mammoplasty and use of noregestimate /ethinyl estradiol contraceptives received the diagnosis of invasive ductal carcinoma of the breast (Stage IIA) 5 days after completing her second course of CCH (total dose of 2.52 mg). The ductal carcinoma was treated with lumpectomy and radiation. The AE of breast cancer was assessed as moderate in severity and not related to CCH. Other AEs reported by the subject during treatment were mild concussion, moderate cervicalgia, moderate sciatica, depression and moderate insomnia.

Spontaneous abortion: A 41-year-old white female subject (b) (6) with a history of miscarriage and hypothyroidism experienced a spontaneous abortion at approximately 8 weeks after receiving one dose of placebo. Concomitant medications included a norgestimate /ethinyl estradiol contraceptives and levothyroxine. The AE of spontaneous abortion was assessed as severe and not related to the trial product. In addition, one day after receiving 0.84 mg of CCH, the subject experienced a generalized rash which resolved with intermittent use of Benadryl on Day 43. CCH was discontinued. The TEAE of generalized rash was assessed as mild in severity, a TEAE of special interest and probably related to CCH. The subject withdrew from the trial.

Hypertension: A 57-year-old white, female subject (b) (6) with a history of anxiety, gastroesophageal reflux disease (GERD), asthma and headaches experienced a hypertensive crisis after receiving one course of CCH (total of 2.52 mg). On Day 170 of the trial, the subject noted pain shooting up her right arm. Her blood pressure was 217/94 and her ECG was normal. The subject received clonidine and lisinopril. The AE of hypertensive crisis was assessed as severe and not related to CCH.

Discontinuations Due to TEAEs

Adverse events resulting in discontinuation included eosinophilia and pregnancy. A 50-year-old white female subject (b) (6) with no relevant medical history experienced mild eosinophilia on Day 8 after receiving one dose of placebo. The AE of eosinophilia was assessed as mild and not related to the trial product. Two subjects (b) (6) discontinued Trial 202 due to pregnancy and refused to provide follow-up. Both subjects used condoms with spermicide as their contraceptive methods. Refer to Human Reproduction and Pregnancy in Section 8.9 of this review for a discussion of the data regarding the impact of CCH on reproduction.

Three subjects withdrew from the trial due to ARs (injection site bruising, pain and nodule).

Table 20. Discontinuations Due to Treatment-Emergent Adverse Events (TEAEs)-Trial 202

Subject ID	Demographics	Severity /Adverse Reaction(s) at Injection Site	Onset	Total dose	Outcome
(b) (6)	61 yo W F	Moderate bruising[1]	Day 2	0.84 mg to thigh	d/c trial
	33 yo AA F	Moderate bruising, nodule, pain[2]	Day 2	0.84 mg	d/c drug
	49 yo W F	Mild bruising, pain[3]	Day 1	0.84 mg	d/c drug

[1] Resolved in 21 days
[2] Resolved in16 days
[3] Resolved in 18 days
Abbreviations: AA = African American, D/C = discontinued, F = female, W = white, YO = year old

Safety of Retreatment

Only 6 subjects elected to receive retreatment in the same buttocks. Of these, 5 subjects (83%) experience 10 TEAEs. The most common TEAEs were injection site bruising (5 subjects) and Injection site pain (2 subjects). All other injection site reactions (discoloration, nodule, urticaria) were reported by one subject each.

Safety of Redosing

A total of 74 subjects elected to be redosed in the other buttock. Among these subjects, 66 subjects (89%) reported at least one TEAE. The most common TEAEs were: injection site bruising (64 subjects [87%]), injection site pain (42 subjects [57%]), injection site pruritus (13 subjects [18%]), injection site nodule (11 [15%]), injection site swelling (7 subjects [10%]), injection site discoloration (5 subjects [7%]) and injection site urticaria (3 subjects [4%]).Two subjects (3%) experienced vertigo, one subject experienced syncope (1%) two subjects each experienced alanine aminotransferase increased (3%)and aspartate aminotransferase increased (3%).

Safety in Subjects who Declined Retreatment

A total of 17 subjects who received treatment with CCH in the buttocks during Trial 201 declined treatment in Trial 202. Two of these subjects (12%) experienced 3 adverse events (cholelithiasis, tooth abscess, back pain).

EN3835-304 (304)

Trial 304 was a multicenter, open-label trial to evaluate long term safety and efficacy after re-treatment. The trial was conducted in 2 periods: a 180 -day observation period without treatment followed by an unblinded open-label period with retreatment of eligible subjects. In order to enroll in Trial 304, subjects must have completed the safety and efficacy assessments at Day 71 in Phase 3 trials 302/ 303. From Day 71 through Day 180 (Observational Period), subjects and investigational staff remained blinded to the treatment assignment in Trial 302/ 303.

After unblinding at Day 180, 238 subjects who received placebo during Trials 302/ 303 were withdrawn and 198 of 241 subjects who received CCH were enrolled in the open-label retreatment period of Trial 304. Enrolled subjects were classified into one of three categories:

Category I: 1-Level Composite Responders in either (or both) buttock(s) – 84 subjects

Category II: 2-Level Composite Responders in at least one buttock – 19 subjects

Category III: Non-Composite Responders (did not meet criteria to be included in Category I or II) – 95 subjects

The following enrolled subjects were eligible for retreatment (3 treatment visits):

- Category I responders were eligible for retreatment on Day 180 in up to two buttocks. After retreatment and completion of efficacy and safety assessments at the last treatment visit, investigators will observe subjects every 6 months for 2 years and then annually until Day 1800 (5 years after Day 71).
- Category II responders were eligible for retreatment during Trial 304 at Months 12, 18, 24, 36, and 48, with loss of 2-level composite response on either or both buttocks AND at least a 1-level composite response reduction compared to Day 71 in Trial 302/303. Investigators will observe subjects every 6 months for 2 years and then annually until Day 1800 (5 years after day 71).
- Category III subjects were not eligible for retreatment and will be evaluated for safety every 6 months for 2 years and annually for up to 5 years (Day 1800).

The dosing regimen during the retreatment period was the same as for Trials 302/ 303).

Investigators will evaluate multiple measures of durability of response. Per Applicant, durability of response is the lack of complete loss of response in which cellulite severity

returns back to baseline levels (Day 1 of the double-blind trials on both the PR-PCSS and CR-PCSS)

Safety Results
Observation Period

A total of 479 subjects participated in the 180-Day Observational Period of Trial 304. Among the 479 subjects, 241 subjects received CCH and 238 subjects received placebo during Trials 302/303.

During the Observation Period, there were no deaths and three serious adverse events which were assessed as severe and unrelated to the trial product.

- A 53-year-old white female subject (b) (6) with diabetes who received CCH in Trials 302/303, experienced viral meningitis and discontinued Trial 304 when she developed a clostridium difficile infection.
- A 51-year-old African American female subject (b) (6) with hypertension who received placebo in Trials 302/303, experienced severe hypertension (BP: 222/115) and discontinued Trial 304 as a screening failure.
- A 50-year-old white female subject (b) (6) with depression who received placebo in Trials 302/303, sustained a hip fracture and worsening depression and was lost to follow-up.

Other AEs which led to withdrawal of subjects from Trial 304 included: mild contusion due to an intramuscular iron injection, severe bilateral discoloration of the buttocks in an African American female subject, mild bilateral discoloration in a white subject and moderate bruising in a white subject who all received CCH in Trial 302/303. Two subjects withdrew from Trial 304 due to pregnancy which occurred after Day 71 and prior to retreatment. Both pregnancies were ongoing at the time of the cut-off date. The pregnancies are discussed under Human Reproduction and Pregnancy in Section 8.9.

Of the 241 subjects who received CCH, 57 (24%) subjects experienced 131 AEs; of the 238 subjects who received placebo, 26 subjects (11%) experienced 45 AEs. The majority of the AEs were mild or moderate (98%). Among the subjects who reported AEs, 30 subjects (12%) in the CCH group and 12 (5%) in the placebo group were still experiencing ongoing events which occurred during the Phase 3 trials (302/303 up to Day 71). In the CCH group, most of these events were in the General disorders and administration site conditions SOC. The most common preferred terms were injection site bruising, discoloration, nodule and mass. A total of 25 subjects in the CCH group and no subjects in the placebo group experienced adverse reactions.

When ongoing TEAEs from Trials 302/303 were excluded, the most frequently reported AEs in subjects who received CCH (in Trials 302/303) were in the SOCs of Infections and Infestations

(11 subjects [5%], 15 events) and Musculoskeletal and Connective Tissue Disorders (6 subjects [3%], 7 events). The most frequently reported TEAE in subjects treated with placebo were in the SOCs of Infections and Infestations (6 subjects [3%] 6 events) and Musculoskeletal and Connective Tissue Disorders (6 subjects [3%], 9 events). None of these TEAEs were considered to be late findings of previous treatment with CCH or placebo. Therefore, there were no new ARs identified during this period (except ongoing AR). There were no clinically meaningful laboratory abnormalities or changes in vital signs during the Observation Period.

Open-label, Retreatment Period

A total of 198 subjects signed a consent and entered the 5-year open-label period. Prior to retreatment, there were no deaths, no serious adverse events and 15 (8%) subjects experienced a total of 23 AEs.

At the time of the data cut-off (April 1, 2019), 30 subjects received retreatment including 13 subjects who completed 3 treatment visits, and 20 subjects completed 2 treatment visits. One subject discontinued the trial due to the AE of severe injection site discoloration after retreatment. There were no serious hypersensitivity events but there were 11 events of injection site pruritus. Among the retreated subjects, 17 (57%) subjects reported 79 TEAEs. Most of these TEAEs (17 [57%] subjects with 74 events) were considered related to CCH. One subject experienced 2 severe TEAEs. TEAEs reported by more than 1 subject included: injection site bruising (14/30 subjects, 47%), injection site pruritus (3/30 subjects, 10%), injection site discoloration (2/30 subjects, 7%), injection site hemorrhage (2/30 subjects, 7%) and injection site pain (2/30 subjects, 7%). All injection site reactions were considered to be related to CCH while all other TEAEs (upper respiratory tract infection, urinary tract infection, and vomiting) which were reported by one subject each were considered unrelated to CCH.

There were no clinically meaningful laboratory abnormalities or changes in vital signs during the open-label phase after retreatment.

Refer to Appendix 15.3.3 for a brief review of the safety findings from the Phase 1 development program.

8.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

As CCH has no quantifiable systemic exposure after subcutaneous administration, the proposed product is not expected to promote carcinogenicity. The Applicant did not conduct any dedicated nonclinical or clinical studies to evaluate carcinogenic potential.

Human Reproduction and Pregnancy

The Applicant did not conduct any adequate and well-controlled trials of CCH in pregnant females. Requirements for females of childbearing potential who were enrolled in the CCH development program included the use of effective forms of contraception, a negative serum pregnancy test at screening and negative urine pregnancy testing prior to each injection of the trial product. Investigators withdrew subjects who became pregnant from the trial and, where feasible, followed them until conclusion of the pregnancy. The protocol did not require that pregnancies or elective abortions be considered as AEs; however, the protocol did require that negative outcomes such spontaneous abortion, stillbirth, and congenital anomalies or other serious complications associated with the pregnancy be managed as SAEs.

Multiple pharmacokinetic trials indicated that systemic levels of CCH were not quantifiable with the available assays up to a total dose of 3.36 mg/ treatment visit. In the Xiaflex development program (BLA 125338), nonclinical studies showed no effects of collagenase clostridium histolyticum or persistent ADAs on reproduction or embryo-fetal development. See the discussion of the nonclinical findings in Section 5 of this review.

The Applicant reported 11 pregnancies in the development program of CCH for the treatment of moderate to severe cellulite. Investigators identified two pregnant subjects at screening and excluded them from enrollment. Six subjects received CCH prior to the pregnancy (total doses ranging from 0.84 to 5.04 mg) and the outcomes were: one each 1) premature birth of a healthy neonate in a subject with diabetes mellitus, 2) induced abortion, 3) healthy neonate, 4) unknown outcome and 5&6) two spontaneous abortions (one subject with a history of ectopic pregnancy and one subject with premature separation of the placenta at approximately 4 weeks of gestation). Three subjects received placebo prior to the pregnancy and the outcomes were: two healthy neonates and one unknown outcome. Pregnancies occurring in subjects who received collagenase clostridium histolyticum for other indications included: one subject who received CCH for adhesive capsulitis of the shoulder (unknown outcome) and 3 female partners of subjects who received CCH for Peyronie's disease (two normal births and one unknown outcome). There were no reported findings of congenital malformations in neonates whose mothers were exposed CCH in the development program for moderate to severe cellulite.

Jane Liedtka, MD, Maternal Health Division of Pediatric and Maternal Health (DPMH), evaluated the pregnancy data and provided labeling recommendations. Dr. Liedtka evaluated information from the Pharmacovigilance Database (PVDB), reviewed the medical literature, and consulted teratology and lactation references [Briggs' *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*, Micromedex, TERIS (Teratogen Information System), Medications and Mothers' Milk and, LactMed database]. Dr. Liedtka concluded that due to lack of quantifiable systemic exposure to CCH detected in the clinical pharmacology studies "CCH is not expected to result in fetal exposure to the drug" and "breastfeeding is not expected to result in the exposure of the child to CCH." On this basis, there was no need to conduct a clinical lactation

study, or require contraception or pregnancy testing. (See the DPMH review by Dr. Jane Liedtka dated April 1, 2020)

Regarding the labeling for CCH, Dr. Liedtka recommended omitting Section 8.3 and provided the following language for Section 8.1 and 8.2:

> 8.1 Pregnancy
>
> Risk Summary
>
> There are no available data on collagenase clostridium histolyticum use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Following subcutaneous injection, the systemic concentrations for Qwo were below the bioanalytical assay limit of quantification *[see Clinical Pharmacology (12.3)].*
>
> In animal reproduction studies, intravenous administration of collagenase clostridium histolyticum to pregnant rats during organogenesis at doses up to 0.13 mg/rat revealed no evidence of harm to the fetus.
>
> The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.
>
> 8.2 Lactation
>
> Risk Summary
>
> There are no data on the presence of CCH in human milk, the effects of CCH on the breastfed child or on milk production. Following subcutaneous injection, the systemic concentrations for Qwo were below the bioanalytical assay limit of quantification *[see Clinical Pharmacology (12.3)].* The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CCH and any potential adverse effects on the breastfed child from CCH, or from the underlying maternal condition.

Pediatrics and Assessment of Effects on Growth

During drug development, the Applicant did not evaluate the safety and efficacy of CCH in the pediatric population. The product triggered the Pediatric Research Equity Act (2003) (21 U.S.C. 355c) as a new indication for collagenase clostridium histolyticum. Per the Food and Drug Administration Safety and Innovation Act, the Applicant submitted an Initial Pediatric Study Plan (iPSP) on April 6, 2017. (Agreement Letter issued August 14, 2017).

In the Agreed iPSP, Endo requested a full waiver of the requirement to provide data from pediatric studies (<18 years of age) of EN3835 (CCH) for the treatment of EFP. The regulatory justification was that necessary studies would be impossible or highly impracticable because the estimated number of patients with EFP less than an age of 18 years was extremely small (Section 505B (a)(4)(B)(i) of the Act). Endo supported this request with marketing data from plastic surgeons, literature related to the age of onset of EFP, survey data from the national center for health statistics and discussions of the psychological aspects of aesthetic procedures for pediatric patients and limited potential benefit of evaluating CCH in this population. In view of full waiver request, a deferral of pediatric studies was not requested.

In the BLA application, Endo submitted a request for a full waiver of required pediatric studies. The Pediatric Review Committee concurred with the recommendation by the Division to grant a full waiver of pediatric assessments for CCH for the treatment of moderate to severe cellulite in the buttocks of adult women (Meeting conducted on April 7, 2020).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

Per Applicant, no overdoses occurred in the CCH development program for the treatment of cellulite. There is no available information on overdose with CCH.

Drug Abuse Potential/ Withdrawal and Rebound

In view of the mechanism of action and lack of systemic exposure, there is no reason to anticipate any potential for abuse or dependency. The Applicant did not evaluate abuse potential and did not design or conduct trials to evaluate subjects for withdrawal or rebound. Therefore, the review team did not consult with the Controlled Substance Staff.

120-Day Safety Update Report

No new safety signals were identified in the safety update report (SUR: SDN 11 dated December 19, 2019). The cut-off date for inclusion of safety data was September 9, 2019. In the SUR, the Applicant submitted additional safety data from the ongoing, long-term safety extension, Trial 304. Other data provided in the submission were SAEs which occurred in the ongoing trials in development program for EFP of the thigh (Trials EN3835-209 and EN3835-219), hypersensitivity reactions with the moiety and pregnancies which occurred during the reporting period.

Two pregnancies occurred during the ongoing Trial 304. These pregnancies are included in the discussion in Section 8.9.

During the reporting period, the Applicant received 4 reports of serious hypersensitivity reactions in patients treated with Xiaflex for Dupuytren's contracture: 2 reports of anaphylactic reactions from Denmark and Canada; 1 report with signs consistent with angioedema from the

United States (swelling of the lips and face); 1 report of an "unspecified life-threatening allergic reaction" from Sweden.

- A 52-year-old male (MedWatch number 2019-1051292) of unknown race and with no personal or family history of atopy, or allergic reactions to medications, foods or other allergens experienced angioedema, bronchospasm, hypotension and dizziness approximately 30 minutes after injection of Xiaflex into his left hand. He received Solu-Medrol and adrenalin (×2) in the intensive care unit. He responded rapidly and was released on the same day. The patient tolerated previous administrations of Xiaflex well. There were no other suspect medications.
- A 65-year-old male (MedWatch number 2019-107994) of unknown race and unknown medical history experienced diffuse rash, flushing, nausea and hypotension (Blood Pressure 65/35) approximately 15 minutes after his second treatment visit. In the emergency room the patient received epinephrine (X 4), cortisone, and diphenhydramine. Medical staff observed the patient overnight. The other suspect medication was the predose anesthesia (Xylocaine and epinephrine). The event was assessed as possibly related.
- A 60-year-old male (MedWatch number 2019-104182) of unknown race and unknown medical history experienced swelling of his upper lip and face on the same day as his first injection of Xiaflex 0.58 mg. The patient denied hives, pruritus or shortness of breath. The patient received IV fluids, corticosteroids and antihistamines in the emergency room and the event resolved by the following day. The reporter assessed the event as unrelated to Xiaflex but related to an unknown cause.
- A 66-year-old male (MedWatch number 2019-103578) of unknown race and unknown medical history experienced an "allergic reaction" at the time of his third injection of 0.25 mL of Xiaflex. Signs and symptoms of the reaction and treatment were not reported. The patient recovered and no further injections were administered.

The Applicant included narratives of two serious adverse events occurring in Trial EN3835-209, an open-label, exploratory trial to evaluate the safety and effectiveness of different injection techniques, which was not conducted to support approval of the BLA.

- A 51-year-old African American female (b) (6)) with a history of asthma, diabetes mellitus, chronic obstructive pulmonary disease (COPD), congestive heart failure, hypothyroidism, pulmonary hypertension and smoking experienced an upper respiratory tract infection and asthma exacerbation approximately 14 days after her first treatment of CCH (total dose of 1.68 mg) for EFP of the buttocks. These events were assessed as not related to CCH.
- A 43-year-old African American female (b) (6) with a history of HIV, hypertension, depression, and anxiety was hospitalized for "worsening of preexisting medical

condition, unspecified." No other information is included in the report and the hospitalization is not considered to be related to CCH. The subject was lost to follow-up.

Trial 304
Unblinded (Open-label) Retreatment Period (Following Day 180 of the Observational Period)

Up to the cut-off date, a total of 45 subjects received retreatment with CCH. Of these, 45 subjects completed one treatment visit, 43 subjects completed two treatment visits and 42 subjects completed three treatment visits. Of the 45 subjects who received any retreatment, 80% (36/45 subjects) experienced at least 1 TEAE. The majority of subjects had TEAEs in the SOC of general disorders and administration site conditions (73.3%, 33/45 subjects). The most frequently experienced TEAEs (≥5% of subjects) were injection site bruising (64%, 29/45 subjects), injection site pruritus (18%, 8/45 subjects), injection site pain (18%, 8/45 subjects), and injection site erythema (9%, 4/45 subjects). The most common AR reported by the retreated subjects were: injection site bruising (64%, 29/45 subjects), injection site pruritus (18%, 8/45 subjects), injection site pain (18%, 8/45 subjects), and injection site erythema (9%, 4/45 subjects).

The Applicant indicated that no subject experienced a TEAE suggestive of an autoimmune disorder. However, five subjects experienced 11 local injection site AEs that were potentially suggestive of chronic panniculitis. These subjects ranged in age from 37 to 51 years old and were white (4/5) or African American (1/5). All subjects developed a nodule or mass which was graded as mild in severity and resolved in 46 to 150 days. A majority (3/5) had associated bruising, hemorrhage or discoloration.

In addition, one subject each reported increased alanine aminotransferase, gamma-glutamyl transferase increased and skin hypertrophy. The TEAE of skin hypertrophy occurred in a 62-year-old African American subject on one buttock after three treatment visits. The TEAE was graded as mild in severity, probably related and resolved in approximately 4 weeks.

There were 201 subjects in the open-label period of Trial 304 who did not yet receive retreatment. Among these subjects, 26 (13%) experienced 45 AEs. The most common AEs were urinary tract infection (1%, 2/201 subjects) and insomnia (1%, 2/201 subjects). No AE were considered as long term sequelae of treatment. Therefore, there were no ARs.

8.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Although CCH is not marketed in any jurisdiction, the same mixture of collagenases is marketed as Xiaflex for the treatment of adult patients with DC with a palpable cord (BLA 125338 approved February 2, 2010) and for the treatment of adult men with PD with a palpable plaque and curvature deformity of at least 30 degrees (S-061 approved December 6, 2013). Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of this

formulation of collagenases. The potential for hypersensitivity reactions will be communicated to providers through labeling.

In addition, the Applicant is developing CCH for the treatment of cellulite of the thigh of adult females. Ongoing studies may inform safety in the postmarket setting.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the safety data for CCH identified no safety signals. There are no safety concerns that are expected to change the favorable benefit/ risk assessment or demonstrate increased risk with administration of CCH in the postmarket setting.

8.11. Integrated Assessment of Safety

The safety profile for CCH was adequately characterized during the drug development program. The primary review of safety of CCH for the treatment of moderate to severe EFP focused on the evaluation of pooled data from Phase 3 Trials 302 and 303. These trials included 424 subjects exposed to the proposed dose of 0.84 mg of Qwo per treatment area as 12 subcutaneous injections.

Treatment with CCH did not appear to increase the risk of mortality. There was one death in the development program which occurred during the long term safety Trial 202 on Day 461. This death from a motor vehicle accident was not causally related to the trial product. There were two SAEs in Trials 302/303. Neither SAE can be assessed as causally related to the trial product. One 39-year-old subject who received placebo experienced ischemic colitis on Day 25; another 54-year-old subject who received CCH experienced syncope, hypokalemia, and hypotension on Day 4. The latter subject had a complex medical history which included diabetes, chronic pain, and hypertension, and used multiple medications which included Prazosin, lidocaine 5% transdermal patches, losartan, alprazolam, metformin, amlodipine, and Vicodin.

A greater proportion of subjects in the CCH group (17 subjects [4%]) discontinued the trial due to TEAEs compared to the placebo group (1 subject [<1%] with excessive cerumen). The majority of these TEAEs were injection site reactions which were assessed as related to CCH. Most of these subjects reported bruising/hemorrhage and /or pain within the first three days following administration of CCH. Time to resolution of the TEAE was variable but generally occurred within approximately 60 days. Similar findings regarding injection site reactions were reported across all the trials in the development program.

In the Phase 3 Trials 302 /303, there were 374 subjects (88%) who received CCH and experienced at least 1 TEAE. By comparison, there were 169 subjects (40%) who received placebo and experienced at least 1 TEAE. Overall, the majority of TEAEs were in the SOC of general disorders and administration site conditions. A total of 369 subjects of 424 (87%) who received CCH versus 125 subjects of 419 (30%) who received placebo experienced TEAEs in this class. In both treatment groups, the most common TEAEs in subjects who received CCH

compared with placebo were injection site bruising [84% versus 22% of subjects], injection site pain [48% versus 9% subjects], injection site nodule [33% versus 1% of subjects], and injection site pruritus {15% versus 1% of subjects]. In addition, a disproportionate number of subjects who received CCH compared to placebo reported syncope (5 subjects [1.2%] who received CCH and 0 subjects [0%] who received placebo. However, there is no unconfounded data that suggests that syncope was a symptom of a hypersensitivity reaction or related to CCH.

The majority of the TEAEs which were localized to the treatment site were considered related to the trial drug. The most common adverse reactions (ARs) reported by subjects in Trials 302/303 were injection site bruising, pain, nodule and pruritus. The same imbalance between treatment arms was observed for ARs as for TEAEs. Adverse reactions, occurring in ≥1% and observed more frequently in subjects who received CCH compared to placebo through Day 71 included: injection site bruising (84% versus 21%), injection site pain (48% versus 10%), injection site nodule (33% versus 1%), injection site pruritus (15% versus 1%), injection site erythema (9% versus 5%), injection site discoloration (8% versus 1%), injection site swelling (8% versus 1%), and injection site warmth (3% versus 0%). This data will be conveyed in the product labeling (6.1 Clinical Trials Experience).

Other specific safety considerations included immunogenicity, hypersensitivity reactions, and adverse events associated with multiple administrations of CCH or potential long term effects.

The Applicant conducted immunogenicity testing as part of the safety monitoring in all trials in the development program. In Trials 302/303, most subjects (>96%) developed anti-AUX-I and anti-AUX-II antibodies by Day 71. The ADAs appeared to persist for up to 360 days after the first treatment but did not appear to impact the occurrence of injection site reactions. In addition, the majority of subjects who developed ADA to AUX-I and AUX-II and were evaluated for NAbs to AUX-I and AUX-II were seropositive. Among the subset of subjects evaluated for neutralizing antibodies, neutralizing antibody status did not appear to have a clinically meaningful effect on the occurrence of injection site reactions. No serious hypersensitivity reactions occurred among the 964 subjects who received CCH during development. However, there was an imbalance in the incidence of injection site pruritus in the CCH group and some events of injection site urticaria which are suggestive of less severe hypersensitivity reactions.

Examination of long term effects of CCH administration did not identify a safety signal. In Trial 302/303, there was one report of injection site atrophy and one report of keloid scar. In the trials which included at least 6 months of follow-up (Trials 202,205,304), investigators identified no autoimmune disorders that were potentially related to CCH. However, there is persistence of discoloration (predominantly hyperpigmentation) in some subjects (up to 150 days) which will be monitored during the 5 year long term safety Trial 304.

In Trials 202 and 304, a total of 53 subjects received more than one treatment course (comprised of 3 treatment visits each) with CCH in the same anatomic site in the buttocks. In these subjects, the frequency of most AEs decreased with the second treatment course

(bruising, pain, nodule/mass) except injection site pruritus which increased (9% versus 15%). Fewer subjects experienced severe AEs during the second course of treatment (17% versus 6%).

There were no clinically meaningful changes in vital signs or laboratory parameters with administration of CCH among subjects who received one or two courses of CCH.

The submitted data support the safety of CCH for the treatment of moderate to severe cellulite in the buttocks of adult women. Postmarketing risk management will include professional labeling, and routine pharmacovigilance. Long term risks and sequalae from multiple exposures will be assessed during the 5-year open-label extension Trial 304.

9. Statistical and Clinical Evaluation

9.1. Review of Relevant Individual Trials Used To Support Efficacy

9.1.1. Trial Design and Endpoints

Trial Design

The Applicant conducted two identically-designed, randomized, double-blind, placebo-controlled trials (EN3835-302 and EN3835-303, hereinafter referred to as Trials 302 and 303) comparing up to 3 treatments 21 days apart of CCH (also referred to as EN3835) versus placebo in the treatment of adult females with moderate to severe EFP, otherwise known as cellulite, in the buttocks. The trials were conducted at centers in the United States. Trial EN3835-302 was conducted between February 5, 2018 and September 26, 2018. Trial EN3835-303 was conducted between February 8, 2018 and September 26, 2018.

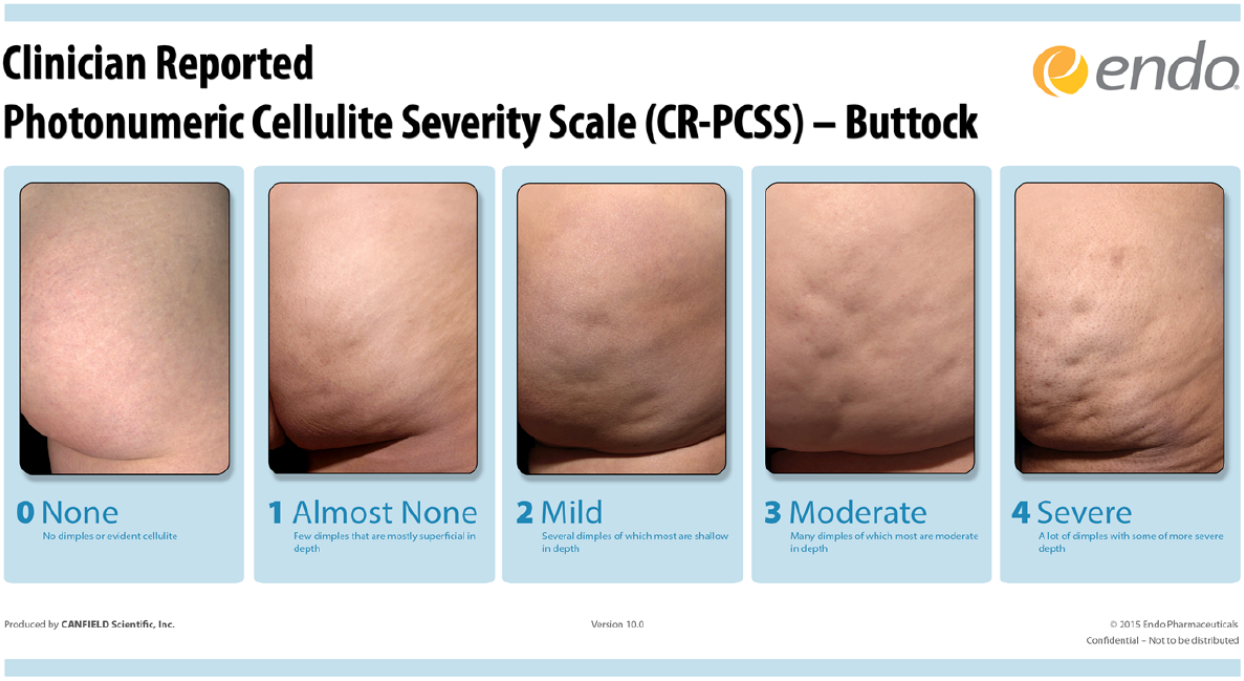
Cellulite severity was evaluated by both the clinician and subject on the CR-PCSS and the PR-PCSS presented in Figure 1 and Figure 2 respectively. The clinician ratings were based on live assessments of each buttock, and the patient ratings were assessed while viewing the digital images of each of their buttocks on a standardized computer monitor.

Other patient assessments (Subject Global Aesthetic Improvement Scale [S-GAIS], Patient-Reported Cellulite Impact Scale [PR-CIS], and the Subject Self-Rating Scale [SSRS]) and clinician assessments (I-GAIS) that were administered are presented in Patient-Reported Outcome Scales

Figure 10 through Figure 13 in Section 15.4.1. The global aesthetic improvement scales evaluate the appearance of treated cellulite from -3 (very much worse) to +3 (very much improved). The PR-CIS scale consists of 6 questions evaluating the visual and emotional impact of cellulite (happy, bothered, self-conscious, embarrassed, looking older, or looking overweight or out of shape). Each question was rated on a numerical rating scale from 0 (not at all) to 10

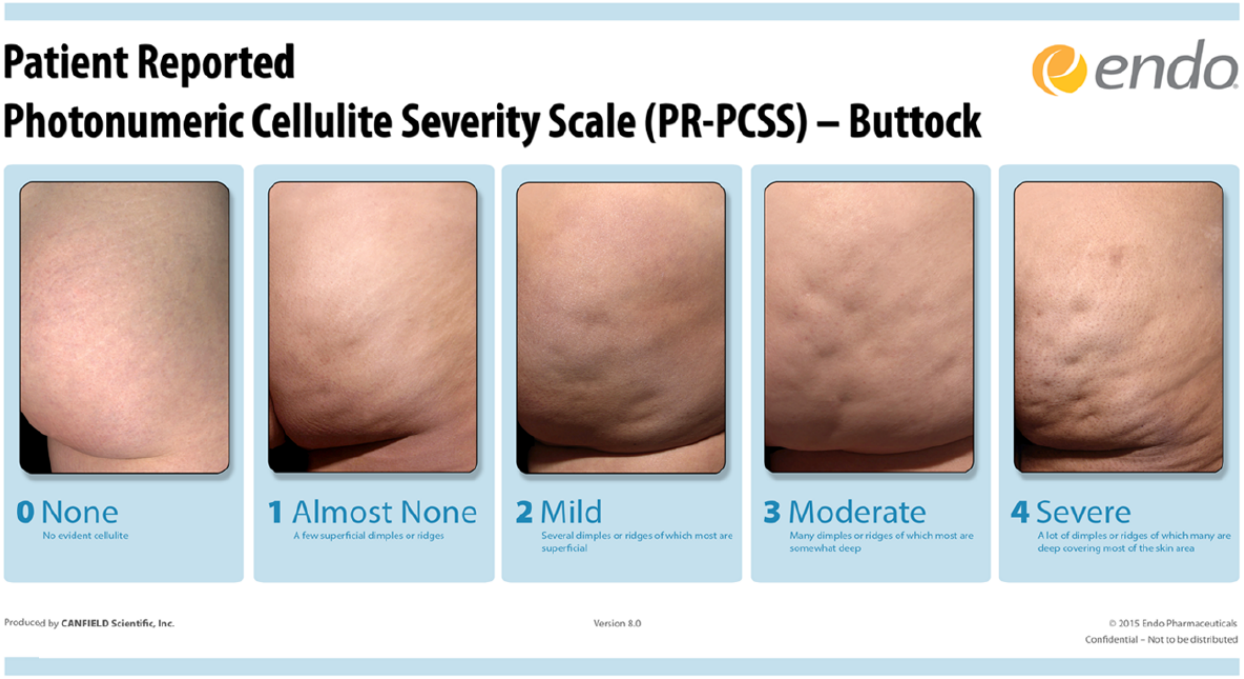
(extremely), so the total score ranges from 0 to 60. The SSRS evaluates subject satisfaction with appearance on a scale ranging from 0 (extremely dissatisfied) to 6 (extremely satisfied). For the SSRS assessment, no photographs or reference to previous ratings or evaluations were to be used.

Figure 1. Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS)



Source: Applicant's Appendix C of protocol

Figure 2. Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS)



Source: Applicant's Appendix B of protocol

The following were the key inclusion criteria for enrollment into the trials:

- Female ≥18 years of age
- At the screening and Day 1 visit, have 2 bilateral buttocks with each buttock having:
  - a score of 3 or 4 (moderate or severe) as reported by the subject (PR-PCSS), and
  - a score of 3 or 4 (moderate or severe) as reported by the investigator (CR-PCSS)

Prior to treatment, one buttock (right or left) was randomly selected as the target buttock, while the other buttock was considered the non-target buttock. The protocols specify that subjects, investigators, site personnel and Applicant personnel were blinded to the assignment of the target/non-target buttock. Eligible subjects were randomized in a 1:1 ratio stratified by investigational site to CCH or placebo. Each subject received up to 3 treatment sessions separated by 21 days (Days 1, 22, and 43). The protocols specify that the selection of dimples to be treated was at the discretion of the investigator, and each treatment consisted of 12 injections (0.3 mL per injection of CCH 0.07 mg/injection or placebo; 0.84 mg in 3.6 mL per buttock) in each of the two buttocks for a total volume of 7.2 mL (1.68 mg). An end of trial visit was planned on Day 71.

At each treatment visit, each buttock was to be photographed before and after marking dimples and injection sites while the subject was in a standardized relaxed standing pose. Subject and investigator assessments were to be conducted prior to marking. The protocols specify that subject assessments should always be completed prior to and independently of the investigator assessments. Subjects assessed a pre-marking photographic image of each buttock

using the PR-PCSS at each visit. At all post-treatment visits, subjects completed the S-GAIS. On Day 1 and Day 71, subjects also completed the PR-CIS and SSRS assessments. Subsequent to the patient assessments, the clinician conducted a live assessment of each buttock using the CR-PCSS at each visit. At each post-treatment visit, the clinician also completed the I-GAIS.

Trial Endpoints

The protocols specify that the primary endpoint is the proportion of 2-level "composite responders" at Day 71 of the target buttock defined as subjects with:

- an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS as assessed live by the investigator of the target buttock, AND
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock.

As success on this endpoint requires achieving 2-level improvement on both the clinician and patient scales, this endpoint will subsequently be referred to as 2-level multicomponent responders to align with the terminology in guidance for industry, Multiple Endpoints in Clinical Trials {January, 2017 #45}.

The SAPs specify 8 key secondary endpoints grouped into 3 families:

Family 1

- Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of the target buttock at Day 71 compared to Day 1
- Proportion of 2-level PR-PCSS responders defined as subjects with ≥2-level improvement in PR-PCSS severity rating of the target buttock at Day 71 compared to Day 1
- Proportion of 1-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of the target buttock) at Day 71 compared to Day 1
- Proportion of 2-level composite responders (subsequently referred to as 2-level multicomponent responders) of the non-target buttock at Day 71 compared to Day 1

Family 2

- Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied (i.e., SSRS rating of slightly satisfied [4], very satisfied [5] or extremely satisfied [6]) with her appearance of the cellulite on her buttocks at Day 71
- Change from baseline (Day 1) of the PR-CIS total score at Day 71

Family 3

- Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (i.e., improved, much improved, or very much improved) in the S-GAIS assessment of the target buttock at Day 71
- Proportion of 2-level S-GAIS responders defined as subjects with ≥2-level improvement (much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71

Protocol Amendments

There was one protocol amendment submitted after initiation of the trials. This amendment was dated June 5, 2018 for both trials and clarified that subjects would view digital images of their buttocks when responding to a subject satisfaction with cellulite treatment assessment, added additional subject and investigator training requirements regarding the assessment scales, and clarified the per protocol (PP) population exclusions.

9.1.2. Statistical Methodologies

The protocols define the following analysis populations:

- Intent-to-treat (ITT) population – all randomized subjects who received at least one injection of trial medication
- Modified intent-to-treat (mITT) population – all ITT subjects with a baseline and at least one post-injection evaluation of both the CR-PCSS and PR-PSS for each buttock
- PP population – subjects in the mITT population who were considered compliant with the protocol. The SAPs specify that subjects are excluded from the PP population if they meet any of the following criteria:
  - Placebo-assigned subject receives CCH treatment
  - CCH-assigned subject receives placebo treatment only throughout the trial
  - Any subject receives protocol-prohibited medications
  - Subject missing PR-PCSS and/or CR-PCSS assessment at Day 71
  - Subject with a buttock not receiving all three treatment sessions without medical reasons (e.g., adverse events or CR-PCSS rated as 0)
  - Subject who did not meet all inclusion and exclusion criteria
- Safety population: all enrolled subjects who have at least 1 injection of trial medication

The protocols and SAPs specify analyzing the primary endpoint and the dichotomous secondary endpoints using a Cochran-Mantel-Haenszel (CMH) test adjusted for analysis center at a significance level of 0.05 based on the ITT population. The SAPs specify analyzing the change from baseline in the PR-CIS total score at Day 71 using analysis of covariance with a factor of treatment group and analysis center adjusting for baseline value.

The SAPs state that sites with a small number of subjects are combined into analysis centers for the analyses. Any site with at least 8 subjects per treatment arm stands alone as an analysis center. The SAPs state that the smallest sites are pooled together until the analysis center has at least 8 subjects per treatment arm. The next larger sites are then pooled together to reach at least 8 subjects per treatment arm, etc. until all analysis centers have at least 8 subjects per treatment arm. If the last pooled analysis center does not have at least 8 subjects per treatment arm, it is pooled into the previously pooled analysis center. If two or more small sites enrolled the same number of subjects in the trial, the following was used to break the tie:

- The site with the lowest number of subjects in either treatment group will be pooled first.
- In the event the sites have the same lowest number of subjects in either treatment group, then the site with the lower site ID will be pooled first.

Consistency of the treatment response across analysis centers for the primary endpoint will be assessed by plotting the proportion of responders in the CCH arm versus the proportion of responders in the placebo arm by center. Additionally, variability between sites and analysis centers will be assessed by the Breslow-Day test.

The SAPs specify a hierarchical gatekeeping strategy to test the secondary endpoints. The key secondary efficacy analyses in Family 1 are performed only if the primary efficacy analysis is significant at a level ≤0.05. Within a family of key secondary efficacy endpoints, Bonferroni's method is used to reallocate unused alpha for testing each endpoint to ensure an overall error rate of 0.05. The Family 2 key secondary efficacy analyses are performed only if at least one of the 4 key secondary efficacy endpoints in Family 1 is significant at a level ≤0.0125. Unused alpha (0.05, 0.0375, 0.025, 0.0125 corresponding to 4, 3, 2, or 1 of the key secondary endpoints in Family 1 being statistically significant, respectively) from the Family 1 tests are carried over to the inference of the 2 key secondary endpoints in Family 2. The inference for each of 2 key secondary endpoints in Family 2 are based on the raw p-value, unused alpha, and the Bonferroni method for alpha spending. The Family 3 key secondary efficacy analyses are performed only if at least one of the 2 key secondary efficacy endpoints in Family 2 is significant (i.e., the raw p-value is less than half of the unused alpha from Family 1). The unused alpha from Family 2 is carried over to the inference of the 2 key secondary endpoints in Family 3.

For the primary and binary secondary endpoints, the SAPs specify that subjects who do not have an assessment at Day 71 are considered non-responders. Subjects without a PR-CIS evaluation at Day 71 have their observation imputed as the baseline value for the analysis.

The SAPs specify that a tipping point analysis examines under what conditions the conclusion of the trial remains unchanged, even if the missing data mechanism depends on the unobserved missing values (i.e., data are missing not at random). Missing values of the multicomponent primary efficacy endpoint are assigned based on treatment group and analysis center. The SAPs define the following variables:

- m_p = the number of subjects in the placebo group with missing primary efficacy endpoint data
- m_t = the number of subjects in the CCH group with missing primary efficacy endpoint data

The tipping point analysis consists of an m_p-by-m_t grid with m_t values along the x-axis and m_p values along the y-axis. The SAPs specify that each grid point (i,j) contains a summary statistic s_{ij} corresponding to the result of the primary analysis with random responder assignment of missing data such that there are i additional responders in the CCH group and j additional responders in the placebo group. First, the data are analyzed under the "worst case" conditions, i.e., all subjects in the placebo group with missing primary efficacy endpoint are assumed to be responders and all subjects in the CCH group are assumed to be non-responders. The "worst case" dataset is analyzed using the same methodology for the primary endpoint (i.e., CMH test adjusted for analysis center). If the analysis of the "worst case" dataset reverses the conclusion of the main trial analysis, then the analysis proceeds by performing responder assignment based on treatment group and analysis center, and calculating summary statistics s_{ij} for additional grid points (i,j).

For the responder assignment, datasets D_{ijz} will be generated taking analysis center into account, where the range of z depends on the number of subjects with missing data at specific analysis centers. Each dataset D_{ijz} is analyzed using the same methodology as that for the primary endpoint, and the results over all D_{ijz} datasets are summarized using a pooled p-value from the datasets, based on the method of Wilson-Hilferty transformation. The pooled p-value from this set of datasets is the summary statistic s_{ij} for grid location (i,j). If any summary statistic, $s_{ij,}$ is not less than 0.05, and therefore reverses the conclusion of the primary analysis of the trial, then that point represents one condition of the tipping point.

Additionally, the SAPs specify the following sensitivity analyses for the primary and key secondary endpoints:

- ITT subjects with missing data handled by MI approach
- ITT subjects with missing data handled by an LOCF approach
- mITT subjects with missing data handled by an LOCF approach
- Observed data only (no missing data imputed)
- PP subjects with missing data handled by an LOCF approach if 10% or more subjects are excluded in the PP population from mITT population

For the multiple imputation analyses, the SAPs specify that 100 datasets are generated using a linear regression model for the PR-CIS scores and a logistic regression model for all other scale scores by using PROC MI in SAS. The SAPs specify that the missing individual components (PR-PCSS and CR-PCSS) of the multicomponent endpoints (e.g., two-level composite responders of the target buttock at Day 71) will be imputed separately on the original 5-level ordinal scales (rating 0 to 4) within each treatment group. The following variables are included in the model:

baseline value, value at previous visit, age, baseline BMI, Fitzpatrick skin type (I-III versus IV-VI), and number of treatments received. Once the missing data are imputed, each imputed data set will be analyzed, and the resulting statistics will be combined using Proc MIANALYZE. For each of the binary efficacy endpoints, the values of the general association test statistic from the CMH analysis will be transformed using the Wilson-Hilferty transformation prior to being combined.

9.1.3. Trial Results

Compliance with Good Clinical Practices

The Applicant stated that the trials in the development program were designed and monitored in accordance with their own standard procedures which complied with the ethical principles of Good Clinical Practice (GCP) as required by the regulatory authorities and in accordance with the Declaration of Helsinki. The Institutional Review Board (IRB), reviewed and approved the protocol, any amendments and the informed consent form (ICF). All subjects received information regarding the nature and risks of participation in the trial and provided written informed consent prior to participation in the trials.

Financial Disclosure

The Applicant submitted the required certification and disclosure information for participating investigators (Form 3454 and 3455). Refer to Section 15.2 Financial Disclosure of this review for a discussion of the investigators with disclosable financial arrangements and interests and procedures to minimize bias.

Patient Disposition

In Trial EN3835-302 (302), 423 subjects were randomized, 210 to CCH and 213 to placebo. In Trial EN3835-303 (303), 422 subjects were randomized, 214 to CCH and 208 to placebo; however, the Study Report states that 2 subjects did not receive trial drug because of adverse events (hypertension and herpes simplex lesion left buttock) at the planned time of dosing. Therefore, the ITT population for Trial EN3835-303 comprises of 420 subjects, 214 in the CCH group and 206 in the placebo group.

Table 21 presents the reasons for discontinuation as classified by the Applicant. The majority of subjects discontinued due to withdrawal by subject or lost to follow-up. In both trials, a greater number of subjects discontinued in the active arm than in the placebo arm, with a more pronounced difference in Trial EN3835-303. One subject was administratively discontinued in Trial 302 as the trial was closing before the subject was available to come in. One subject in each trial (placebo arm in Trial 302 and CCH arm in Trial 303) withdrew consent due to lack of efficacy. See Section 8.4 for further details regarding the discontinuations due to adverse events.

Table 21. Disposition of ITT Population in Trials EN3835-302 and EN3835-303

	EN3835-302		EN3835-303	
ITT Population	CCH N=210	Placebo N=213	CCH N=214	Placebo N=206
Discontinued	24 (11.4%)	21 (9.9%)	28 (13.1%)	15 (7.3%)
Withdrawal by subject	11 (5.2%)	10 (4.7%)	9 (4.2%)	7 (3.4%)
Lost to follow-up	3 (1.4%)	9 (4.2%)	11 (5.1%)	5 (2.4%)
Adverse event	9 (4.3%)	1 (0.5%)	8 (3.7%)	0
Administrative	0	1 (0.5%)	0	0
Protocol noncompliance	1 (0.5%)	0	0	3 (1.4%)

Source: Reviewer's analysis (same as Applicant's analysis)
Abbreviations: CCH = Collagenase clostridium histolyticum, ITT = intent-to-treat

Protocol Violations/Deviations

Protocol deviations were defined as accidental or unintentional changes to, or noncompliance with, the trial protocol and were divided into 2 categories:

- Major protocol deviations: Accidental or unintentional changes to, or noncompliance with the trial protocol that increased risk or decreased benefit or; had a significant effect on the subject's rights, safety or welfare and/or on the integrity of the data.
- Minor protocol deviations: Accidental or unintentional changes to, or noncompliance with the research protocol that did not increase risk or decrease benefit or; did not have a significant effect on the subject's rights, safety or welfare and/or on the integrity of the data.

The majority of minor protocol deviations in both Trial 302 and 303 were out of window / missed visits. Other minor protocol deviations included incorrect form completion, laboratory tests / vital signs not obtained, missing/ incorrect photographs, Day 1 visit conducted under the incorrect ID number, missed assessments of treatment effect, and sample processing error.

In Trial 302, a total of 7 subjects had major protocol deviations (3 subjects in the CCH group and 4 subjects in the placebo group). The deviation in all 7 subjects was categorized as "assessment not performed per protocol." Most of these deviations were related to failure to document CR-PCSS or PR-PCSS at Day 71. In addition, one subject was enrolled without completion of all screening laboratory testing.

In Trial 303, a total of 20 subjects had at least 1 major protocol deviation (8 subjects in the CCH group and 12 subjects in the placebo group). The major protocol deviations in the CCH treated group were categorized as assessment not performed per protocol (3), trial drug noncompliance (3), eligibility (1), and failure to adhere to visit schedule (1). In the placebo treated subjects the major protocol deviations included assessment not performed per protocol (5), trial drug noncompliance (5), and eligibility (2). In both groups, the major deviations included administration of fewer than 12 injections, subjects enrolled who did not meet the exclusion criteria (2 subjects had a history of cancer), failure to document CR-PCSS or PR-PCSS

at Day 71, patient-reported outcomes incorrectly performed/documented and subjects dosed with the wrong treatment kit.

Two of these subjects were randomized to the placebo arm and received placebo in one buttocks and CCH in the other buttock at one treatment visit due to the use of the incorrect kit number. Both subjects completed the trial. To preserve the randomization, the data from these subjects was analyzed as if they received the planned treatment. Brief narratives are below.

- A 47-year-old white female (Subject (b) (6)) with a BMI of 28 and no relevant medical history except prior use of botulinum toxin type A and hyaluronic acid received both placebo and CCH during the first treatment visit. The subject experienced no AEs and developed Anti-AUX I antibodies after the second treatment visit.
- A 47-year-old white female (Subject (b) (6)) with a BMI of 29 and history of endometriosis treated with hysterectomy and levothyroxine received both placebo and CCH during the second treatment visit. The subject experienced injection site bruising after the second treatment visit and developed anti-AUX I antibodies. The subject developed anti-AUX II antibodies after the third treatment visit.

Demographic Characteristics

Table 22 presents the demographic characteristics of subjects in Trials 302 and 303. All subjects were female, and the majority of subjects were white, not Hispanic nor Latino, and between 45 and 64 years of age. Demographics were generally consistent across the treatment arms and across the trials.

Table 22. Demographic Characteristics of ITT Population in Trials EN3835-302 and EN3835-303

	EN3835-302		EN3835-303	
ITT Population Demographics	**CCH N=210**	**Placebo N=213**	**CCH N=214**	**Placebo N=206**
Age				
Mean (SD)	47.9 (10.3)	45.8 (9.8)	47.7 (10.6)	45.7 (11.2)
Median	48	46	48	46
Range	21, 70	22, 70	20, 78	18, 72
<35 Years	23 (11%)	27 (12.7%)	23 (10.7%)	34 (16.5%)
35-44 Years	53 (25.2%)	66 (31%)	53 (24.8%)	56 (27.2%)
45-64 Years	125 (59.5%)	115 (54%)	123 (57.5%)	106 (51.5%)
≥65 Years	9 (4.3%)	5 (2.3%)	15 (7%)	10 (4.9%)
Sex				
Female	210 (100%)	213 (100%)	214 (100%)	206 (100%)
Race				
White	157 (74.8%)	161 (75.6%)	179 (83.6%)	164 (79.6%)
Black or African American	47 (22.4%)	43 (20.2%)	29 (13.6%)	32 (15.5%)
Asian	0	2 (0.9%)	0	1 (0.5%)
American Indian or Alaska Native	1 (0.5%)	2 (0.9%)	3 (1.4%)	5 (2.4%)
Native Hawaiian/Pacific Islander	0	1 (0.5%)	0	0
Multiple	3 (1.4%)	4 (1.9%)	2 (0.9%)	2 (1%)
Other	2 (1%)	0	1 (0.5%)	2 (1%)

	EN3835-302		EN3835-303	
ITT Population Demographics	**CCH N=210**	**Placebo N=213**	**CCH N=214**	**Placebo N=206**
Ethnicity				
Hispanic or Latino	31 (14.8%)	41 (19.2%)	46 (21.5%)	58 (28.2%)
Not Hispanic or Latino	179 (85.2%)	172 (80.8%)	168 (78.5%)	148 (71.8%)
Weight (kg)[a]				
Mean (SD)	83.9 (21.6)	84.0 (19.7)	82.2 (17.9)	83.7 (19.8)
Median	80.85	81.5	79.1	81.3
Range	49.9, 181.3	52.6, 175.7	51.8, 154.8	48.5, 171.7
BMI (kg/m^2)a				
Underweight (<18.5)	1 (0.5%)	0	0	0
Normal Weight (18.5 – <25)	42 (20%)	41 (19.2%)	38 (17.8%)	43 (20.9%)
Overweight (25 – <30)	69 (32.9%)	62 (29.1%)	74 (34.6%)	61 (29.6%)
Obese (≥30)	98 (46.7%)	109 (51.2%)	102 (47.7%)	102 (49.5%)
Skin phototype				
Type I	5 (2.4%)	4 (1.9%)	6 (2.8%)	8 (3.9%)
Type II	50 (23.8%)	48 (22.5%)	74 (34.6%)	54 (26.2%)
Type III	69 (32.9%)	75 (35.2%)	50 (23.4%)	64 (31.1%)
Type IV	40 (19%)	35 (16.4%)	53 (24.8%)	47 (22.8%)
Type V	33 (15.7%)	27 (12.7%)	15 (7%)	18 (8.7%)
Type VI	13 (6.2%)	24 (11.3%)	16 (7.5%)	15 (7.3%)

Source: Reviewer's analysis (similar to Applicant's analysis).
[a] One placebo subject in Trial EN3835-302 has missing weight data
Abbreviations: SD = standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Table 23 presents the baseline disease characteristics of subjects in Trials 302 and 303. Approximately 60% of subjects had moderate cellulite according to the clinician assessment (CR-PCSS) and approximately 40% of subjects had moderate cellulite according to the patient assessment (PR-PCSS), indicating that subjects tended to rate their cellulite severity as more severe than clinicians. For the SSRS assessment (Figure 13 in Section 15.4.1), subjects were instructed to answer the following question on Day 1 (baseline): "Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time?" on a scale ranging from 0 (extremely dissatisfied) to 6 (extremely satisfied). The PR-CIS (Figure 12 in Section 15.4.1) total score, the sum of the responses from the 6 questions, ranges from 0 to 60. For the purpose of calculating the total score, scores for Item #1 on the PR-CIS asking how happy the subject is about their appearance of cellulite were reversed by subtracting the subject's score from 10 to make it directionally consistent with the other questions (assessing bother, self-consciousness, embarrassment, looking older, or looking overweight or out of shape).

Table 23. Baseline Disease Characteristics of ITT Population in Trials EN3835-302 and EN3835-303

	EN3835-302		EN3835-303	
ITT Population	**CCH N=210**	**Placebo N=213**	**CCH N=214**	**Placebo N=206**
CR-PCSS				
3 - Moderate	127 (60.5%)	127 (59.6%)	130 (60.8%)	132 (64.1%)
4 - Severe	83 (39.5%)	86 (40.4%)	84 (39.3%)	74 (35.9%)

	EN3835-302		EN3835-303	
ITT Population	CCH N=210	Placebo N=213	CCH N=214	Placebo N=206
PR-PCSS				
3 – Moderate	88 (41.9%)	83 (39.0%)	91 (42.5%)	85 (41.3%)
4 – Severe	122 (58.1%)	130 (61.0%)	123 (57.5%)	121 (58.7%)
SSRS[a]				
0 – Extremely dissatisfied	120 (57.1%)	128 (60.1%)	114 (53.3%)	98 (47.8%)
1 – Dissatisfied	70 (33.3%)	64 (30.1%)	63 (29.4%)	79 (38.5%)
2 – Slightly dissatisfied	11 (5.2%)	15 (7.0%)	26 (12.2%)	15 (7.3%)
3 – Neither satisfied nor dissatisfied	4 (1.9%)	1 (0.5%)	6 (2.8%)	4 (2.0%)
4 – Slightly satisfied	4 (1.9%)	4 (1.9%)	3 (1.4%)	6 (2.9%)
5 – Satisfied	1 (0.5%)	0	2 (0.9%)	2 (1.0%)
6 – Extremely satisfied	0	1 (0.5%)	0	1 (0.5%)
PR-CIS[b]				
Mean (SD)	51.1 (8.9)	51.6 (9.8)	52.4 (9.0)	51.6 (9.4)
Median	53	55	55	55
Range	18, 60	10, 60	14, 60	16, 60

Source: Reviewer's analysis
[a] One placebo subject in Trial EN3835-303 is missing a baseline SSRS assessment. Results are based on 205 subjects in the placebo group.
[b] One CCH subject and 4 placebo subjects in Trial EN3835-303 are missing a baseline PR-CIS assessment. Results are based on 213 and 202 subjects in the CCH and placebo groups respectively.
Abbreviations: CCH = Collagenase clostridium histolyticum, CR-PCSS = Clinician-Reported Photonumeric Cellulite Severity Scale, PR-CIS = Patient-Reported Cellulite Impact Scale, PR-PCSS = Patient-Reported Photonumeric Cellulite Severity Scale, SSRS = Subject Self-Rating Scale

Table 46 in Section 15.4.2 presents a cross-tabulation of the scores on the right and left buttocks for each the CR-PCSS and the PR-PCSS assessments at baseline. The right and left buttocks tended to have same severity score. Table 47 in Section 15.4.2 presents the percentage of subjects whose target buttock was randomly assigned to be the left versus right side. As expected, due to random assignment, these probabilities are around 50%.

A cross-tabulation the CR-PCSS and PR-PCSS scores for the target buttock at baseline are presented in Table 24 for each of the treatment arms in both trials. Subjects tended to rate the cellulite severity of their target buttock as more severe than the clinicians. These ratings and this pattern are consistent across the treatment arms and across trials.

Table 24. Comparison of CR-PCSS and PR-PCSS Scores at Baseline for the Target Buttock of ITT Population in Trials EN3835-302 and EN3835-303

	EN3835-302						EN3835-303					
	CCH (N=210)			Placebo (N=213)			CCH (N=214)			Placebo (N=206)		
	PR-PCSS			PR-PCSS			PR-PCSS			PR-PCSS		
CR-PCSS	3	4	Total	3	4	Total	3	4	Total	3	4	Total
3	71	56	127	71	56	127	71	59	130	71	61	132
4	17	66	83	12	74	86	20	64	84	14	60	74
Total	88	122	210	84	130	213	91	123	214	85	121	206

Source: Reviewer's analysis
Abbreviations: CCH = Collagenase clostridium histolyticum, CR-PCSS = Clinician-Reported Photonumeric Cellulite Severity Scale, ITT = intent-to-treat, PR-PCSS = Patient-Reported Photonumeric Cellulite Severity Scale

Treatment Compliance and Concomitant Medications

Compliance
As the trial product was not self-administered, there was limited treatment non-compliance in the Phase 3 trials. The Applicant reported that one subject (0.2%) who received CCH and 3 subjects (0.7%) who received placebo were not compliant.

Concomitant and Prior Medications
The Applicant defined prior medication is any medication with a stop date prior to the date of the first dose of trial drug. All prior medications and concomitant medications were coded by drug class and standard term using the WHO Drug Dictionary (March 1, 2016 version). Among subjects in Phase 3 Trials 302/303, the most commonly used prior medications were nonsteroidal anti-inflammatory drug and antibiotics. Six subjects (0.7%) received botulinum toxin for cosmetic indications or headache; four subjects (0.5%) received injectable fillers and two subjects (0.2%) received central acting obesity drugs.

The Applicant defined a concomitant medication as any medication with a stop date on or after the date of the first dose of trial drug or any medication reported as ongoing. The entry criteria excluded subjects using anticoagulant (warfarin, heparin, direct thrombin inhibitors, Factor X inhibitors) or antiplatelet medications (aspirin ≥150 mg/day and P2Y12 inhibitors, such as clopidogrel) and topical products to prevent or mitigate EFP (e.g., Celluvera™, TriLastin®).

A total of 331 subjects (78%) who received CCH and 320 subjects (76%) who received placebo used at least one concomitant medication during the trials. Some of the most common concomitant medications and their indications were: thyroid hormones (menopause or hypothyroidism), vitamin D and analogs and calcium (osteoporosis), selective serotonin reuptake inhibitors and other antidepressants (depression), proton pump inhibitors and H2-receptor antagonists (gastrointestinal reflux disease), 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors and other lipid modifying agents (elevated low density lipoprotein [LDL] cholesterol and lipids), angiotensinogen-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (high blood pressure), centrally acting sympathomimetics (weight loss), and benzodiazepines and related drugs (anxiety) and contraceptives (birth control). The proportions of subjects who received concomitant medications of various pharmacologic classes were similar across treatment groups.

9.1.4. Results for the Primary and Secondary Efficacy Endpoints

The number and percentage of subjects who have missing assessments at Day 71, the timepoint at which the primary and secondary endpoints are assessed, are presented in Table 25.

Table 25. Missing Assessments at Day 71 for ITT Population in Trials EN3835-302 and EN3835-303

	EN3835-302		EN3835-303	
ITT Population	CCH N=210	Placebo N=213	CCH N=214	Placebo N=206
PR-PCSS	28 (13.3%)	24 (11.3%)	29 (13.6%)	16 (7.8%)
CR-PCSS	28 (13.3%)	24 (11.3%)	29 (13.6%)	16 (7.8%)
SSRS	26 (12.4%)	23 (10.8%)	28 (13.1%)	15 (7.3%)
PR-CIS	26 (12.4%)	23 (10.8%)	28 (13.1%)	15 (7.3%)
S-GAIS	26 (12.4%)	23 (10.8%)	28 (13.1%)	15 (7.3%)

Source: Reviewer's analysis
Abbreviations: CCH = Collagenase clostridium histolyticum, CR-PCSS = Clinician-Reported Photonumeric Cellulite Severity Scale, ITT = intent-to-treat, PR-CIS = Patient-Reported Cellulite Impact Scale, PR-PCSS = Patient-Reported Photonumeric Cellulite Severity Scale, S-GAIS = Subject Global Aesthetic Improvement Scale, SSRS = Subject Self-Rating Scale

Table 26 presents the results for the multicomponent primary endpoint, the proportion of subjects who are 2-level multicomponent responders at Day 71 of the target buttock, and its components, i.e., proportion of subjects with 2-level improvement of the target buttock on the PR-PCSS and CR-PCSS assessments respectively. For the primary endpoint, the response rates are fairly low with a treatment difference around 5 to 6%. The response rates and treatment effects are higher when looking at 2-level improvement on the PR-PCSS and CR-PCSS assessments separately. There tended to be a higher rate of responders according to the patient assessments, but the treatment effects did not have a clearly differential trend from that of the clinician assessments.

The proportion of subjects who are 1-level multicomponent responders at Day 71 of the target buttock, and its components are also presented in Table 26. These results show a larger treatment effect, i.e., approximately 20 to 30%, than the 2-level improvement.

Some of the endpoints in Table 26 are secondary endpoints and are denoted by [b] in the table. Table 27 depicts the results from the remaining secondary endpoints that are not presented in Table 26. All primary and secondary endpoints were statistically significant according the prespecified hierarchal gatekeeping method, except for the secondary endpoint of the proportion of subjects who are 2-level multicomponent responders at Day 71 in the non-target buttocks in Trial 303. While the p-value is nominally less than 0.05, this endpoint was allocated an alpha of 0.0125 according to the method specified to account for testing multiple endpoints. The treatment differences were numerically similar for the target and non-target buttocks for the proportion of 2-level multicomponent responders at Day 71.

Table 26. Results for the Composite Primary Endpoint and Components (Target Buttock) for ITT Population in Trials EN3835-302 and EN3835-303

	EN3835-302			EN3835-303		
Endpoints	**CCH N=210**	**Placebo N=213**	**P-Value**	**CCH N=214**	**Placebo N=206**	**P-Value**
2-Level improvement						
Multicomponent[a]	16 (7.6%)	4 (1.9%)		12 (5.6%)	1 (0.5%)	
Adj Trt Diff (95% CI)	5.7% (1.6%, 9.7%)		0.006	5.1% (1.9%, 8.3%)		0.002
PR-PCSS[b]	51 (24.3%)	26 (12.2%)		45 (21.0%)	12 (5.8%)	
Adj Trt Diff (95% CI)	11.9% (4.7%, 19%)		0.002	15.3% (9%, 21.6%)		<0.001
CR-PCSS	35 (16.7%)	12 (5.6%)		32 (15.0%)	3 (1.5%)	
Adj Trt Diff (95% CI)	11.1% (5.2%, 17%)		<0.001	13.4% (8.4%, 18.5%)		<0.001
1-Level improvement						
Multicomponent	78 (37.1%)	38 (17.8%)		89 (41.6%)	23 (11.2%)	
Adj Trt Diff (95% CI)	19.1% (10.8%, 27.5%)		<0.001	30.6% (22.9%, 38.4%)		<0.001
PR-PCSS[b]	114 (54.3%)	77 (36.2%)		124 (57.9%)	61 (29.6%)	
Adj Trt Diff (95% CI)	17.9% (8.5%, 27.3%)		<0.001	28.6% (19.7%, 37.6%)		<0.001
CR-PCSS	107 (51.0%)	62 (29.1%)		121 (56.5%)	52 (25.2%)	
Adj Trt Diff (95% CI)	21.7% (12.6%, 30.7%)		<0.001	31.4% (22.6%, 40.2%)		<0.001

Source: Reviewer's analysis of ADaM datasets. Non-responder imputation used to handle missing data. P-values calculated with a Cochran-Mantel-Haenszel (CMH) test stratified by analysis center. Adjusted difference in proportions is the weighted average of the treatment differences across the analysis centers using CMH weights along with the associated CI.

[a] Primary endpoint

[b] Secondary endpoints in Family 1

Abbreviations: Adj Trt Diff = Adjusted Treatment Difference, CCH = Collagenase clostridium histolyticum, CI = confidence interval, CR-PCSS = Clinician-Reported Photonumeric Cellulite Severity Scale, PR-PCSS = Patient-Reported Photonumeric Cellulite Severity Scale

For the SSRS assessment on Day 71, subjects were instructed to respond to the question "Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time whether or not in your judgment it is due entirely to treatment with EN3835?" using a scale ranging from 0 (extremely dissatisfied) to 6 (extremely satisfied) depicted in Figure 13 in Section 15.4.1. Approximately a 26 to 27% more subjects in the CCH group compared to the placebo group were at least Slightly Satisfied (score of 4) according to the SSRS assessment at Day 71.

In Trial-303, there were 5 subjects, 1 in the CCH group and 4 in the placebo group, with missing PR-CIS assessments at baseline; therefore, these subjects are not included in the results in Table 27 for the endpoint evaluating the change from baseline in PR-CIS score.

Table 27. Secondary Endpoint Results at Day 71 for ITT Population in Trials EN3835-302 and EN3835-303

	EN3835-302			EN3835-303		
Secondary Endpoints	**CCH N=210**	**Placebo N=213**	**P-Value**	**CCH N=214**	**Placebo N=206**	**P-Value**
Family 1 (not in **Table 26**)						
2-level multicomponent improvement (nontarget)	16 (7.6%)	2 (0.9%)		13 (6.1%)	4 (1.9%)	
Adj Trt Diff (95% CI)	6.5% (2.7%, 10.3%)		<0.001	4.1% (0.4%, 7.8%)		0.03[b]
Family 2						
SSRS rating ≥4 (target)	102 (48.6%)	48 (22.5%)		90 (42.1%)	31 (15.1%)	
Adj Trt Diff (95% CI)	25.7% (16.9%, 34.5%)		<0.001	27.2% (19%, 35.4%)		<0.001
Change from baseline PR-CIS[a], mean (SD)	-10.9 (12.5)	-5.9 (11.6)		-11.5 (12.7)	-6.5 (11.7)	
Adj Trt Diff (95% CI)	-5.1 (-7.3, -2.9)		<0.001	-4.7 (-7.0, -2.5)		<0.001
Family 3						
1-level S-GAIS (target)	135 (64.3%)	82 (38.5%)		126 (58.9%)	46 (22.3%)	
Adj Trt Diff (95% CI)	25.8% (16.5%, 35%)		<0.001	36.5%(27.8%, 45.3%)		<0.001
2-level S-GAIS (target)	49 (23.3%)	13 (6.1%)		38 (17.8%)	9 (4.4%)	
Adj Trt Diff (95% CI)	17.2% (10.6%, 23.7%)		<0.001	13.4% (7.6%, 19.3%)		<0.001

[a] 5 subjects (1 randomized to CCH and 4 randomized to placebo) in Trial EN3835-303 had missing PR-CIS assessments at baseline, so these subjects are not included in the analysis.
[b] This endpoint was not statistically significant according to the prespecified hierarchal gatekeeping method
Source: Reviewer's analysis of ADaM datasets. Non-responder imputation used to handle missing data. P-values for binary endpoints are calculated with a Cochran-Mantel-Haenszel (CMH) test stratified by analysis center. Adjusted difference in proportions is the weighted average of the treatment differences across the analysis centers using CMH weights along with the associated CI. P-values and CIs for the change from baseline in the PR-CIS total score at Day 71 are calculated using ANCOVA with a factor of treatment group and adjusted for analysis center and baseline value.
Abbreviations: Adj Trt Diff = Adjusted Treatment Difference; ANCOVA = analysis of covariance, CI = confidence interval, PR-CIS = Patient-Reported Cellulite Impact Scale, S-GAIS = Subject Global Aesthetic Improvement Scale, SSRS = Subject Self-Rating Scale

Sensitivity Analyses and Missing Data

Possible Unblinding

The Study Report for Trial 302 states that, "One site coordinator from each of 2 sites and 1 Endo clinical trial manager received potentially unblinding e-mails containing information regarding investigational product orders, due to a privilege unintentionally assigned to them in the IWRS." The Applicant states that all 3 individuals were removed from the trial staff, and the unused trial product kits that were potentially unblinded were not to be utilized. There were 13 subjects whose treatment could have possibly been unblinded, 12 (6 CCH, 6 placebo) subjects from site 1350 and 1 placebo subject from site 1366. Site 1350 randomized 26 subjects total, 13 in each treatment arm; Site 1366 randomized 15 subjects total, 7 to CCH and 8 to placebo.

To investigate the impact of this possible unblinding, the primary endpoint results were examined for Trial 302 excluding sites 1350 and 1366 which were affected. These results are presented in Table 28, and the conclusions from this analysis are similar to that of the primary analysis including all sites. Therefore, it is unlikely that the possible unblinding affect the conclusions about the efficacy of the product.

Table 28. Post Hoc Sensitivity Analysis: Results for the Primary Endpoint and Components for ITT Population in Trial EN3835-302 Excluding Sites 1350 and 1366

	EN3835-302		
Primary Endpoint Results	**CCH N=190**	**Placebo N=192**	**Adj Trt Diff (95% CI)**
2-Level improvement			
Multicomponent success	15 (7.9%)	3 (1.6%)	6.3% (2%, 10.5%)
PR-PCSS success	50 (26.3%)	23 (12.0%)	14.1% (6.5%, 21.7%)
CR-PCSS success	32 (16.8%)	10 (5.2%)	11.7% (5.5%, 17.8%)

Source: Reviewer's analysis of ADaM datasets. Non-responder imputation used to handle missing data. Adjusted difference in proportions is the weighted average of the treatment differences across the analysis centers with the Cochran-Mantel-Haenszel weights along with the associated
Abbreviations: Adj Trt Diff = Adjusted Treatment Difference, CCH = Collagenase clostridium histolyticum, CR-PCSS = Clinician-Reported Photonumeric Cellulite Severity Scale, PR-PCSS = Patient-Reported Photonumeric Cellulite Severity Scale

Pre-Specified Sensitivity Analyses

Table 29 presents results for the prespecified sensitivity analyses of the primary endpoint. These analyses investigate different methods for handling missing data (e.g., MI, LOCF) and different analysis populations. The LOCF analysis for the ITT population had the same results as the non-responder imputation analysis for the ITT population (i.e., no subject with missing data at Day 71 had 2-level multicomponent improvement in the target buttock at their last observed assessment). The results of these sensitivity analyses support the conclusions of the primary analysis in Table 26.

Table 29. Sensitivity Analyses for Handling Missing Data on the Primary Endpoint in Trials EN3835-302 and EN3835-303

	EN3835-302			EN3835-303		
Primary Endpoint	**CCH**	**Placebo**	**Adj Trt Diff (95% CI)**	**CCH**	**Placebo**	**Adj Trt Diff (95% CI)**
ITT population	N=210	N=213		N=214	N=206	
NRI[a]	7.6%	1.9%	5.7% (1.6%, 9.7%)	5.6%	0.5%	5.1% (1.9%, 8.3%)
MI	7.9%	2.2%	5.7% (1.3%, 10.1%)	6.2%	0.6%	5.6% (1.9%, 9.3%)
mITT population	N=201	N=205		N=209	N=201	
LOCF	8.0%	2.0%	6.0% (1.7%, 10.2%)	5.7%	0.5%	5.2% (1.9%, 8.5%)
PP Population	N=172	N=178		N=180	N=184	
LOCF	9.3%	1.7%	7.6% (2.9%, 12.4%)	6.1%	0.5%	5.7% (2%, 9.3%)
Observed	N=182	N=189		N=185	N=190	
No Imputation	8.8%	2.1%	6.7% (2.1%, 11.3%)	6.5%	0.5%	6.1% (2.4%, 9.8%)

Source: Reviewer's analysis of ADaM datasets. Adjusted difference in proportions is the weighted average of the treatment differences across the analysis centers with the Cochran-Mantel-Haenszel weights along with the associated CI.
[a] Pre-specified primary analysis.
Abbreviations: CCH = Collagenase clostridium histolyticum, ITT = intent-to-treat, LOCF = last observation carried forward, MI = multiple imputation, mITT = modified intent-to-treat, NRI = non-responder imputation, PP = per protocol

Pre-Specified Tipping Point Analysis of the Primary Endpoint

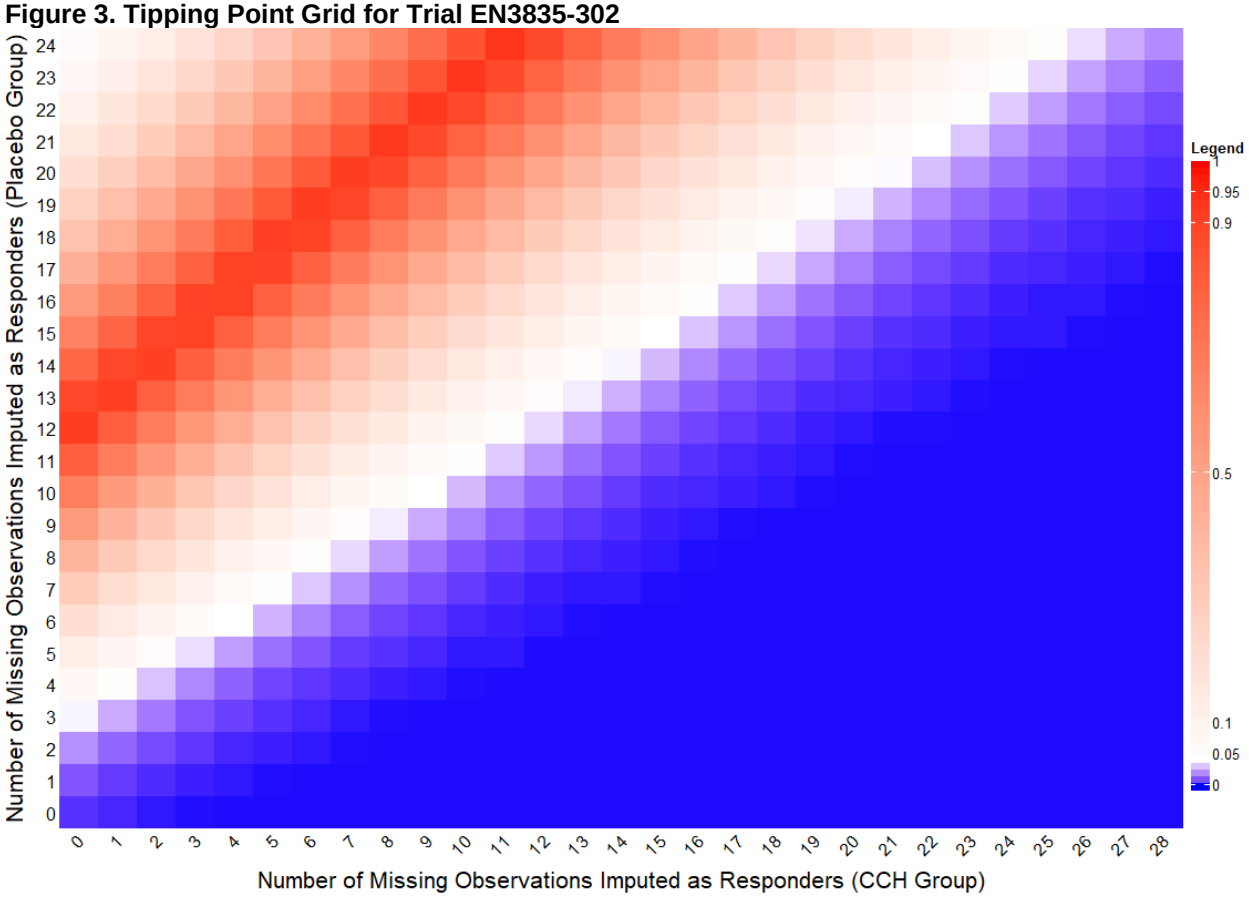
As described in Section 9.1.2, the Applicant prespecified a tipping point analysis for the primary endpoint to examine under what conditions the conclusion of the trial remains unchanged. Depictions of the tipping point grid for Trial 302 and 303 are displayed in Figure 3 and Figure 4 respectively.

The x-axis represents the number of missing observations that are imputed as responders in the CCH arm and the y-axis represents the number of missing observations that are imputed as responders in the placebo arm. The color indicates the resulting p-value based on the analysis at each point on the graph. White indicates a p-value of 0.05. Shades of blue indicate p-values less than 0.05 down to 0, with darker blue indicating a smaller p-value; shades of red indicate p-values greater than 0.05 up to 1, with darker red indicating a larger p-value. Note that the light red to white in the upper left corner of the figures indicate smaller p-values in favor of the placebo arm compared to the CCH arm. The white diagonal points on the grid separating the blue from the red indicate where our conclusions would change regarding the efficacy of CCH.

In Trial 302, recall that there were 28 (13.3%) and 24 (11.3%) subjects with missing assessments at Day 71 in the CCH and placebo groups respectively. If imputing 0 subjects in the CCH arm as responders and imputing 4 subjects in the placebo group as responders, this results in a situation for which the p-value is greater than 0.05, and we would not be able to conclude the efficacy of CCH compared to placebo. As only 4 subjects were observed to be responders on the primary endpoint in the placebo group, it seems highly unlikely that 4/24 (16.7%) subjects with missing data in the placebo arm would be responders. The remainder of the scenarios along the diagonal also seem implausible, as those situations are where more than 4 subjects with missing data in the placebo arm are responders. As the situations where one would reverse the conclusions about the efficacy of CCH are considered implausible, this provide support of our conclusion about the efficacy of CCH compared to placebo.

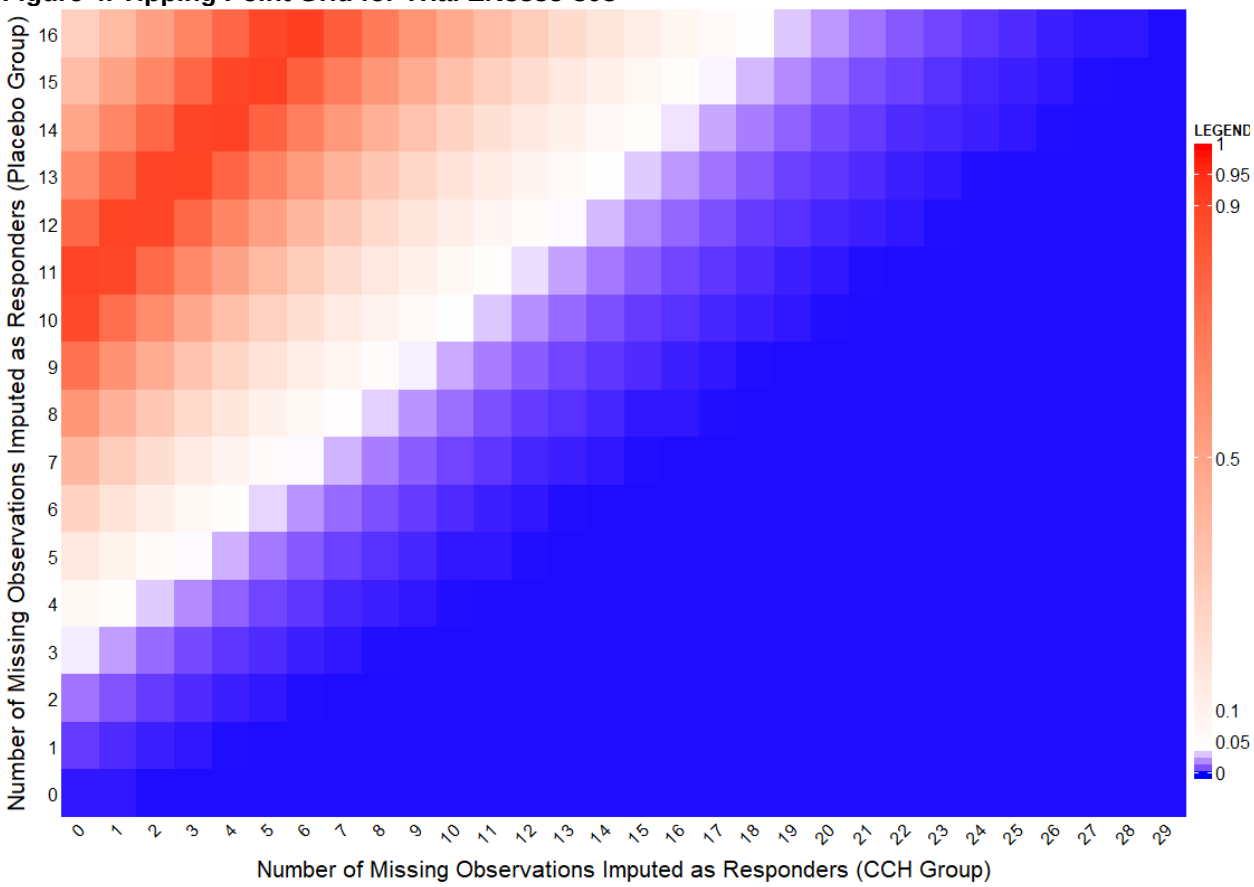
In Trial 303, recall that there were 29 (13.6%) and 16 (7.8%) subjects with missing assessments at Day 71 in the CCH and placebo groups respectively. Just as in Trial 302, if imputing 0 subjects in the CCH arm as responders and imputing 4 subjects in the placebo group as responders, this results in a situation for which the p-value is greater than 0.05, and we would not be able to conclude the efficacy of CCH compared to placebo. As only 1 subject was observed to be a responder on the primary endpoint in the placebo group, it seems highly unlikely that 4/16 (25%) subjects with missing data in the placebo arm would be responders. The remainder of the scenarios along the diagonal also seem implausible. As the situations where one would reverse the conclusions about the efficacy of CCH are considered implausible, this provide support of our conclusion about the efficacy of CCH compared to placebo.

Figure 3. Tipping Point Grid for Trial EN3835-302



Source: Statistical analyst's figure based on Applicant's calculated p-values.
Note that the light red to white in the upper left corner indicates smaller p-values in favor of the placebo arm compared to the CCH arm.

Figure 4. Tipping Point Grid for Trial EN3835-303

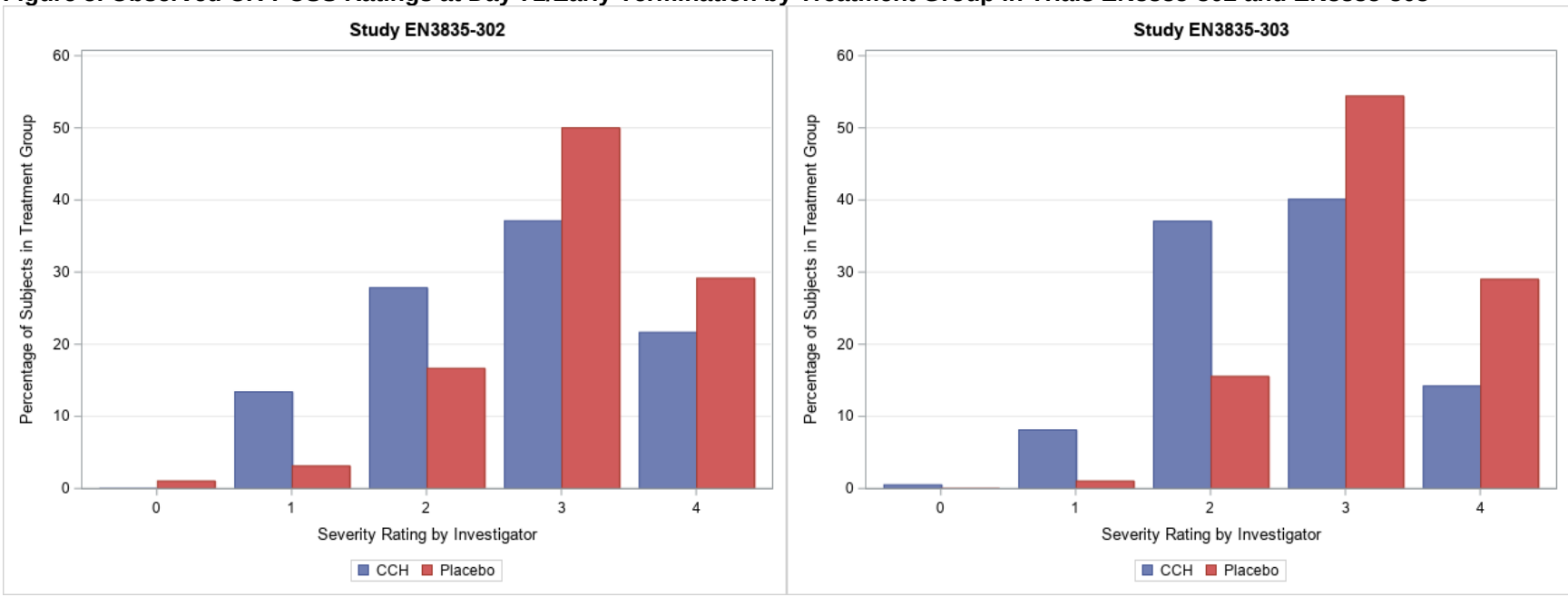


Source: Statistical analyst's figure based on Applicant's calculated p-values.
Note that the light red to white in the upper left corner indicates smaller p-values in favor of the placebo arm compared to the CCH arm.

Further Descriptive Results on the PR-PCSS and CR-PCSS Assessments

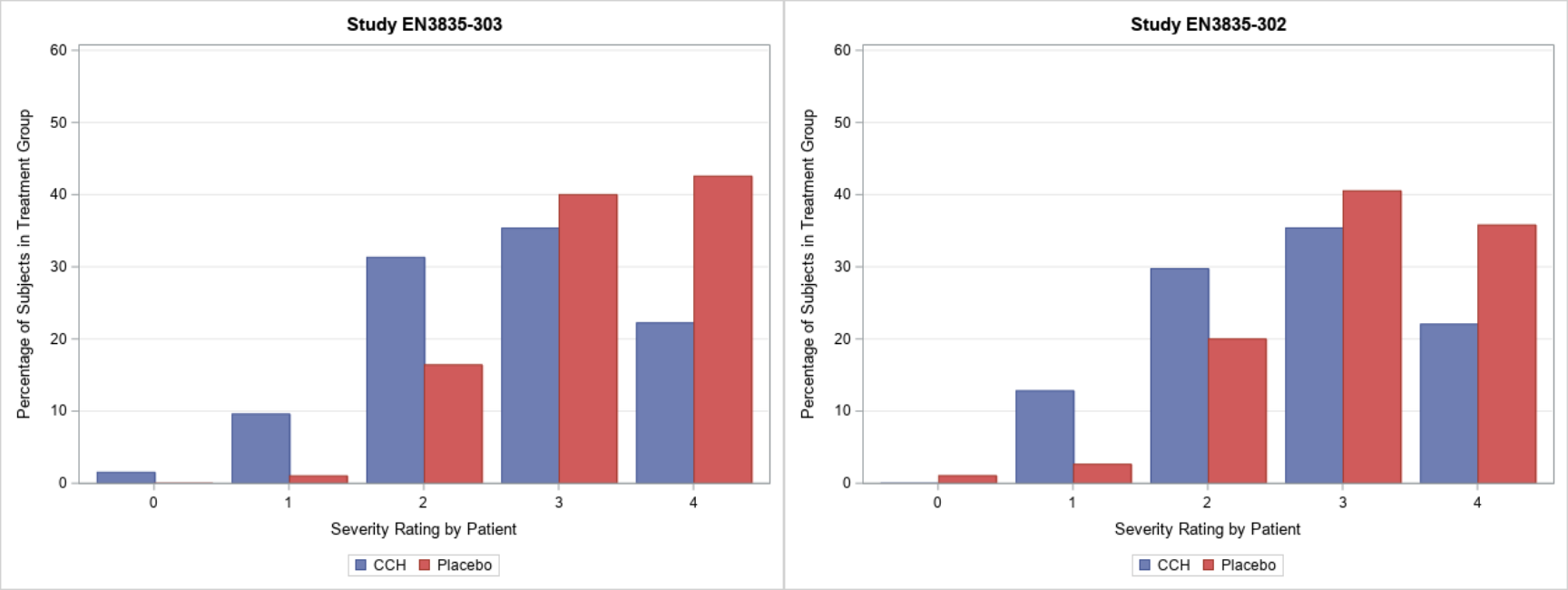
To provide further details regarding the CR-PCSS and PR-PCSS results, Figure 5 depicts the observed CR-PCSS ratings at the Day 71/Early Termination visit by treatment group for each trial. Similarly, Figure 6 depicts the observed PR-PCSS ratings at the Day 71/Early Termination visit by treatment group for each trial. The blue bars indicate the results for the CCH group and the red indicates the results for the placebo group. The figures support the conclusions of the prespecified analyses that there is a treatment effect of CCH compared to placebo.

Figure 5. Observed CR-PCSS Ratings at Day 71/Early Termination by Treatment Group in Trials EN3835-302 and EN3835-303



Source: Reviewer's analysis

Figure 6. Observed PR-PCSS Ratings at Day 71/Early Termination by Treatment Group in Trials EN3835-302 and EN3835-303



Source: Reviewer's analysis

Comparison of Clinician and Patient Assessments

While one would not expect the clinician and patient to always agree on the cellulite severity rating, it is of interest to assess how the ratings differed. The results in Table 30 investigate the agreement, separated by treatment group, between the CR-PRCSS and PR-PCSS observed assessments at the Day 71/Early Termination visit pooled across Trials 302 and -303. A total of 41/390 (10.5%) subjects in the pooled CCH group and 21/383 (5.5%) subjects in the pooled placebo group had PR-PCSS and CR-PCSS scores differ by more than 1 category.

Table 30. Crosstabulation of CR-PCSS and PR-PCSS Scores at Day 71/Early Termination Visit in Pooled Trials EN3835-302 and EN3835-303 (Observed Cases; Target Buttock)

	CCH Subjects (N=390)						Placebo Subjects (N=383)					
	PR-PCSS						PR-PCSS					
CR-PCSS	0	1	2	3	4	Total	0	1	2	3	4	Total
0	0	0	1	0	0	1	0	0	1	1	0	2
1	1	16	15	8	2	42	0	2	3	1	2	8
2	1	20	52	41	12	126	0	3	22	32	5	62
3	0	6	43	66	36	151	2	2	37	95	64	200
4	1	2	8	23	36	70	0	0	7	25	79	111
Total	3	44	119	138	86	390	2	7	70	154	150	383

Source: Reviewer's analysis
Abbreviations: CCH = Collagenase clostridium histolyticum, CR-PCSS = Clinician-Reported Photonumeric Cellulite Severity Scale, PR-PCSS = Patient-Reported Photonumeric Cellulite Severity Scale

To further evaluate this, Table 31 presents the cross-tabulation of the change from baseline in the CR-PRCSS and PR-PCSS observed assessments at the Day 71/Early Termination visit pooled across treatment group. Table 52 in Section 15.4.2 presents these results by treatment group. While the majority of the assessments agree in terms of whether the severity improved, stayed the same, or got worse, there were some assessments for which the clinician assessments indicated improvement while the patient assessments indicated no change, or vice versa. The results tended to occur around a 1-level improvement from baseline. For instance, when looking at the results for the pooled treatment groups, 100/268 (37%) subjects who were rated as having a 1-unit improvement on the CR-PCSS had no change or worsening according to the PR-PCSS. Similarly, 110/249 (44%) of subjects who were rated as having a 1-unit improvement on the PR-PCSS had no change or worsening according to the CR-PCSS. As there is a continuous outcome of cellulite severity underlying these categorical scales, a small change on the continuous outcome can translate to a 1-level improvement (or worsening) on the categorical scale. Thus, we do not expect precision in results for 1-level improvement. Therefore, a 1-level improvement on one assessment is not indicative of improvement on the other assessment.

Table 31. Crosstabulation of Change From Baseline in CR-PCSS and PR-PCSS Scores at Day 71/Early Termination Visit in Pooled Trials EN3835-302 and EN3835-303 and Pooled Treatment Arms (Observed Cases; Target Buttock)

	Change in PR-PCSS						
Change in CR-PCSS	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**Total**
-4	0	0	0	0	0	0	0
-3	0	1	2	1	3	0	7
-2	0	7	23	30	15	1	76
-1	0	9	51	108	97	3	268
0	3	2	35	105	231	17	393
1	0	0	2	5	21	1	29
Total	3	19	113	249	367	22	773

Source: Reviewer's analysis

Descriptive Results on the SSRS

In regard to the SSRS, on face, the evaluation for satisfaction of the appearance of cellulite is appropriate. The Applicant conducted cognitive interviews where subjects found the item and response options of the SSRS to be clear and easy to answer. In reviewing the other measurement properties of the SSRS, the data showed that the test-retest reliability was acceptable for the SSRS, the convergent validity showed acceptable association with the SSRS and PR-PCSS, and the responsiveness showed acceptable correlation with the SSRS and S-GAIS. Therefore, the evidence provided for the measurement properties of the SSRS was adequate. Overall, the evidence to support the SSRS was sufficient to determine that the instrument was fit-for-purpose in this target population.

Table 32 presents the full response rates on the SSRS assessment at Day 71. This supports the results in Table 27 that subjects in the CCH arm tended to be more satisfied with the appearance of their cellulite at Day 71 than those in the placebo arm. Additional results on the PR-CIS and S-GAIS are in Table 48 and Table 49 in Section 15.4.2.

Table 32. SSRS Results at Day 71 in ITT Population in Trial EN3835-302

	EN3835-302		EN3835-303	
SSRS at Day 71	**CCH N=210**	**Placebo N=213**	**CCH N=214**	**Placebo N=206**
0 – Extremely dissatisfied	32 (15%)	65 (31%)	32 (15%)	55 (27%)
1 – Dissatisfied	39 (19%)	47 (22%)	41 (19%)	46 (22%)
2 – Slightly dissatisfied	14 (7%)	15 (7%)	17 (8%)	35 (17%)
3 – Neither satisfied nor dissatisfied	23 (11%)	38 (18%)	34 (16%)	38 (18%)
4 – Slightly satisfied	47 (22%)	29 (14%)	46 (22%)	18 (9%)
5 – Satisfied	42 (20%)	15 (7%)	38 (18%)	13 (6%)
6 – Extremely satisfied	13 (6%)	4 (2%)	6 (3%)	1 (<1%)

Source: Reviewer's analysis

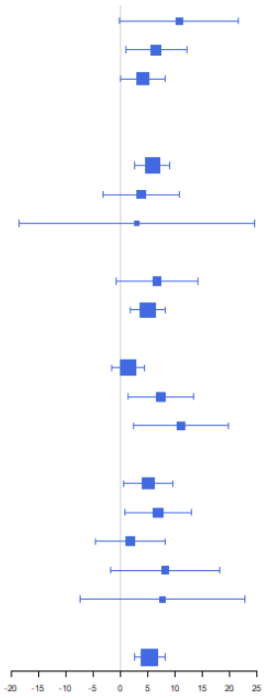
9.1.5. Findings in Special/Subgroup Populations

9.1.5.1. Sex, Race, Age, and Baseline Disease Severity

Figure 7 depicts subgroup results for the primary endpoint for age group, race, ethnicity, BMI group, and skin phototype based on the pooled data from Trials 302 and 303. The treatment difference and response rate tended to be smaller for older subjects and heavier subjects.

Figure 7. Primary Endpoint Results by Age, Race, Ethnicity, BMI, and Skin Phototype (ITT Population; Pooled Trials EN3835-302 and EN3835-303)

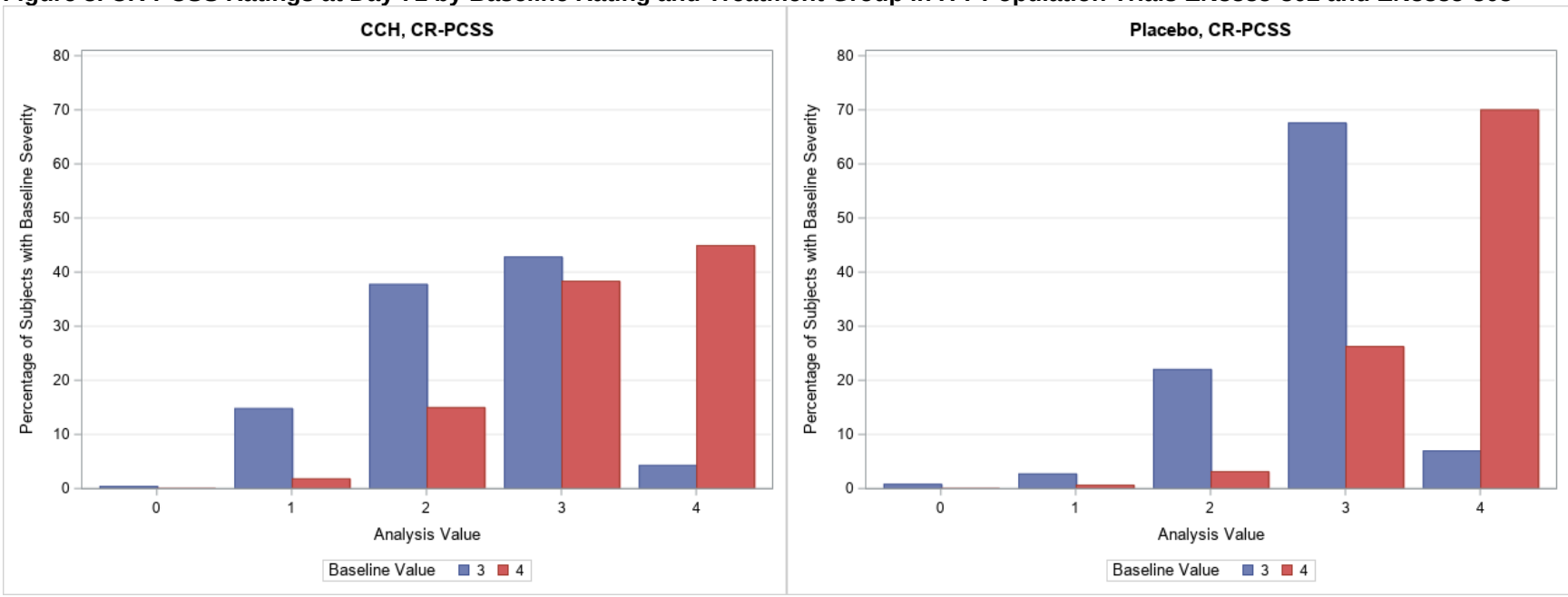
Subgroups	(n[C],n[P])	Treatment	Placebo	Difference
Age				
<35 Years	(46, 61)	10.9%	0%	10.9%
35-44 Years	(106, 122)	6.6%	0%	6.6%
45-64 Years	(248, 221)	6.5%	2.3%	4.2%
>= 65 Years	(24, 15)	0%	0%	0%
Race				
White	(336, 325)	6.8%	0.9%	5.9%
Black or African American	(76, 75)	5.3%	1.3%	3.9%
Other	(12, 19)	8.3%	5.3%	3.1%
Ethnicity				
Hispanic or Latino	(77, 99)	7.8%	1%	6.8%
Not Hispanic or Latino	(347, 320)	6.3%	1.2%	5.1%
BMI				
Obese (>= 30 kg/m2)	(200, 211)	2.5%	0.9%	1.6%
Overweight (25 - < 30 kg/m2)	(143, 123)	9.1%	1.6%	7.5%
Under/Normal Weight (< 25 kg/m2)	(81, 84)	12.3%	1.2%	11.2%
Skin Phototype				
Type I or II	(135, 114)	5.2%	0%	5.2%
Type III	(119, 139)	8.4%	1.4%	7%
Type IV	(93, 82)	4.3%	2.4%	1.9%
Type V	(48, 45)	8.3%	0%	8.3%
Type VI	(29, 39)	10.3%	2.6%	7.8%
Overall	(424, 419)	6.6%	1.2%	5.4%



Source: Statistical analyst's figure. Treatment difference and 95% confidence intervals depicted.
Abbreviations: BMI = body mass index, ITT = intention-to-treat, n[C] = number of subjects in the CCH group, n[P] = number of subjects in the placebo group

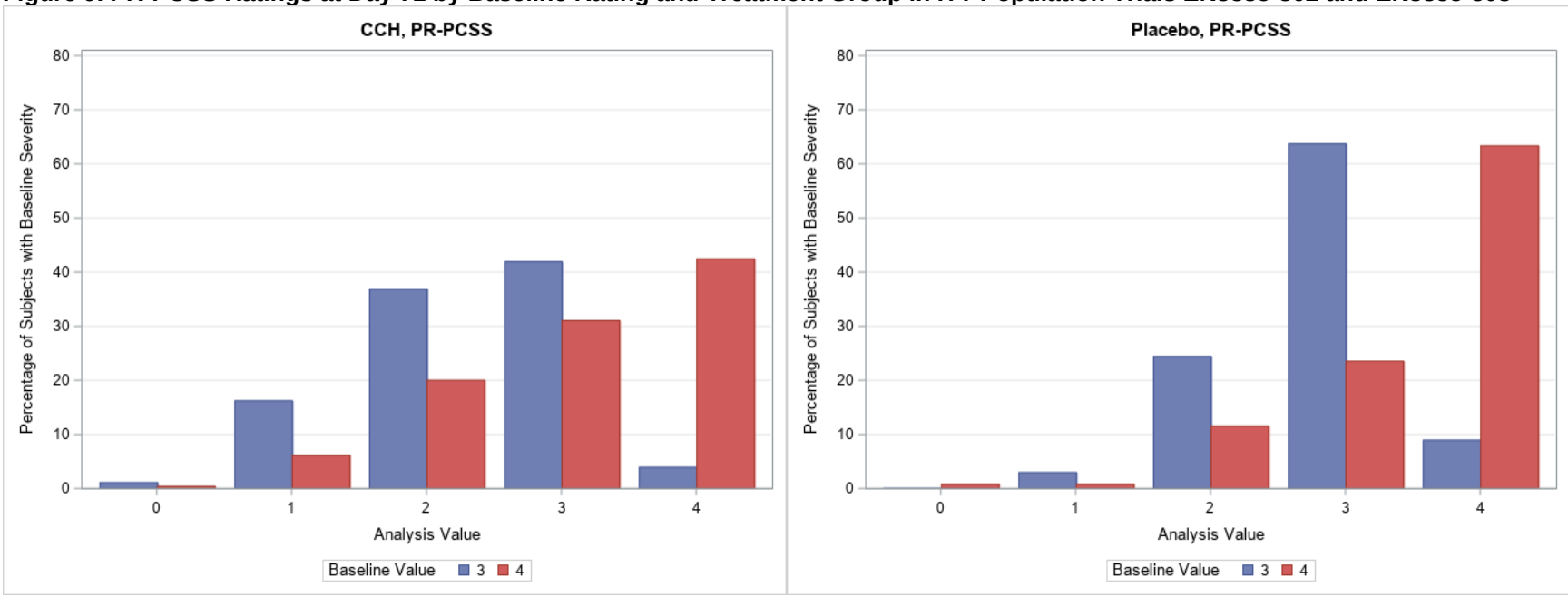
Efficacy was also investigated by baseline disease severity for the pooled trials based on the CR-PCSS and PR-PCSS assessments in Figure 8 and Figure 9 respectively. Further results broken down by trial on the CR-PCSS and PR-PCSS by baseline disease severity are in Table 50 and Table 51 respectively in Section 15.4.2. On both the CR-PCSS and PR-PCSS assessments and in both treatment groups, the distribution of results appears similar but shifted by 1 unit for the different subgroups of subjects evaluated as moderate (3) and severe (4) at baseline.

Figure 8. CR-PCSS Ratings at Day 71 by Baseline Rating and Treatment Group in ITT Population Trials EN3835-302 and EN3835-303



Source: Reviewer's figure

Figure 9. PR-PCSS Ratings at Day 71 by Baseline Rating and Treatment Group in ITT Population Trials EN3835-302 and EN3835-303



Source: Reviewer's figure

9.1.5.2. Center

The SAPs specified performing the Breslow-Day test to test for differential effects on the primary endpoint between sites and also between pooled analysis centers. This test results in p-value=0.4364 in Trial 302 and a p-value=0.7653 in Trial 303 when evaluating sites. This test results in p-value=0.4756 in Trial 302 and a p-value=0.7487 in Trial 303 when evaluating pooled analysis centers.

Table 53 and Table 54 in Section 15.4.2 present further investigation into the results by sites with at least 15 subjects total. The tables present the total number of subjects, the number of subjects in each treatment group, the response rate in the active arm, the response rate in the placebo arm, and the treatment effect. This is presented for the proportion of subjects who are 2-level multicomponent responders, 2-level CR-PCSS responders, and 2-level PR-PCSS responders. Overall, it does not appear that any one center drove the efficacy results.

Durability of Response

Durability of a Multicomponent Response

The Applicant evaluated multiple measures of durability of response in extension Trial 202 (Trial 201→202) and extension Trial 304 (Trial 302/303→304). The Applicant considered a durable response to be one in which subject cellulite severity in the treatment area did not return to baseline or worse than baseline severity at a specified timepoint.

In the 180-day Observation Phase of Trial 304, there were 241 enrolled subjects who had received CCH in the buttocks in Trials 302/303. The Applicant evaluated durability of response by multicomponent response category (1-level multicomponent responders [category I], 2-level multicomponent responder [category II] and non-multicomponent responders [category III]). Among subjects who received CCH, there were 99 subjects who were 1-level multicomponent responders and 24 subjects who were 2-level multicomponent responders at Day 71. On Day 180, 61 subjects (62%) maintained the 1-level multicomponent response and 9 subjects (38%) maintained the 2-level multicomponent response. No subjects had a 2-level multicomponent loss of response by Day 180 of the observation period. These results are summarized below.

Table 33. Trial 302/303 – Multicomponent Responders During the Observation Period of Trial 304 Among Subjects Who Received CCH

	Category I [a] N=99		Category II[b] N=24		Category III[c] N=118	
	Number of Responders	%	Number of Responders	%	Number of Responders	%
At least 1-level multicomponent response						
Day 71	99	100	24	100	0	0
Day 180	61	62	19	79	21	18

	Category I [a] N=99		Category II[b] N=24		Category III[c] N=118	
At least 2-level multicomponent response						
Day 71	0	0	24	100	0	0
Day 180	9	9	9	38	1	<1

Source: SDN 30 dated May 30, 2020
[a] CH-treated subjects: exactly 1-level multicomponent responders at Day 71 in Trials 302/303.
[b] CCH-treated subjects: ≥2-level composite responders at Day 71 in Trials 302/303
[c] CCH-treated subjects: non-responders in Trials 302/303.
[d] Percentages are based on the total number of subjects (N) in each category.
Abbreviations: CCH = Collagenase clostridium histolyticum, N = total number of subjects

In the Observation Phase of Trial 202, there were 34 subjects who had received CCH in the buttocks in Trial 201 and achieved at least a 1-level multicomponent response at Day 71. Loss of durable response was defined as return to baseline ratings from Trial 201 or worse on both CR-PCSS and PR-PCSS. Although 50% of subjects lost their multicomponent response, only 2 subjects (6%) had complete loss of response with return to baseline severity or worse at Day 180. Of the 29 evaluable subjects from this group, 2 subjects (7%) had complete loss of response at Day 360. There were 14 subjects who received CCH in the buttocks and achieved at least a 2-level multicomponent response at Day 71. Although 64% of subjects lost their multicomponent response, there were no subjects with complete loss of response at Day 180 or 360.

9.2. Statistical Issues

The response rates and the treatment effects on the primary endpoint were small in both trials, so further sensitivity analyses and descriptive analyses were conducted to better understand the results. The tipping point analyses (Section 9.1.4) indicated that the conclusion of efficacy of CCH over placebo would only be overturned under implausible scenarios regarding the missing data, thus providing confidence in the primary analysis conclusions. There were some subjects for whom the clinician assessment (CR-PCSS) indicated improvement while the patient assessment (PR-PCSS) indicated no change, or vice versa, and this tended to occur around a 1-level improvement from baseline. As there is a continuous outcome of cellulite severity underlying these categorical scales, a small change on the continuous outcome can translate to a 1-level improvement (or worsening) on the categorical scale, so we do not expect precision in the results for 1-level improvement. Additionally, there were strong results for efficacy on both assessments separately. Results on the secondary endpoints, including additional patient-reported outcomes, supported the conclusion that CCH is efficacious compared to placebo.

9.3. Conclusions and Recommendations

To establish the efficacy of CCH, the Applicant conducted two-identically designed, multi-center, randomized, double-blind, placebo-controlled trials (EN3835-302 and EN3835-303). The trials enrolled female subjects 18 years of age and older with moderate (4) to severe (4) cellulite as assessed on both the clinician assessment (CR-PCSS) and the patient assessment (PR-PCSS). Both scales were 4-levels ranging from 0 (none) to 4 (severe). The primary endpoint

was the proportion of 2-level multicomponent responders at Day 71 of the target buttock defined as subjects with:

- an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS as assessed live by the investigator of the target buttock, AND
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock.

In both trials, CCH was statistically superior to placebo for the primary endpoint, and thus demonstrated efficacy compared to placebo.

The efficacy and safety of CCH for the treatment of moderate to severe cellulite was supported by data from two randomized, double-blind, placebo-controlled, Phase 3 Trials 302 and 303.

To establish the safety of CCH for the treatment of moderate to severe cellulite, the Applicant evaluated adverse events, vital signs, laboratory parameters, immunogenicity and concomitant medications during the Phase 3 Trials and throughout the development program. As CCH levels were not quantifiable with the available assays, the key findings concerned local safety. Compared to placebo, subjects who received CCH experienced injection site reactions such as bruising/hematoma, nodule/mass, pain, pruritus, erythema with much greater frequency. The rate of development of antidrug antibodies was high but did not appear to impact efficacy or the incidence of injection site reactions. Although no subjects experienced serious hypersensitivity reactions during the CCH development program for the treatment of cellulite, patients have reported anaphylaxis with postmarketing use of collagenase clostridium histolyticum for other indications. The Applicant provided adequate overall exposures to support the conclusion that this benefit /risk analysis is sufficient for approval of the application.

10. Advisory Committee Meeting and Other External Consultations

The Agency conducted no Advisory Committee Meeting regarding this application because collagenase clostridium histolyticum is an approved product for other indications. The safety profile in the target population with EFP was expected to be similar to the safety profile in the populations for which the product is approved. Additionally, there were no novel or

complex regulatory issues that required discussion in a public forum.

11. Pediatrics

This product triggered Pediatric Research Equity Act considerations as a new Indication. The Applicant submitted and followed the plan for pediatric assessments as indicated in their agreed-upon initial Pediatric Study Plan. The Applicant requested a full waiver of pediatric studies, because studies are impossible or highly impracticable since the estimated number of patients with EFP less than age 18 years is extremely small. The Pediatric Review Committee agreed (Meeting Minutes dated April 24, 2020). The request for a full waiver of pediatric studies is acceptable. No pediatric studies are required/ recommended.

Refer to Section 8.9 under the heading Pediatrics and Assessment of Effects on Growth for a discussion of the Pediatric Study Plan.

Labeling recommendations for Section 8.4 Pediatric Use are the following:

8.4 Pediatric Use

The safety and effectiveness of Qwo have not been established in pediatric patients (b) (6).

12. Labeling Recommendations

12.1. Prescription Drug Labeling

Prescribing Information

The Applicant submitted proposed prescribing information (PI) for Qwo. The review team provided recommendations regarding PI which are provided throughout this review. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI, proposed patient information and the carton/container. These comments are reflected in final labeling. Refer to the OPDP review by Laurie Buonaccorsi PharmD dated May 13, 2020.

Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis provided comments regarding the proposed labeling and labels for areas that may lead to medication errors (Review dated March 18, 2020). In a review of the revised container labels and carton labeling received on June 5, 2020, Dr. Patel noted that the Applicant had implemented all of the recommendations (Review dated June 12, 2020.) Labeling negotiations are currently ongoing.

The members of the team who provided recommendations regarding PI are tabulated below.

Table 34. Summary of Significant High-Level Labeling Changes

Section	Location of Reviewer Comments on Proposed Labeling
1 INDICATIONS AND USAGE	Clinical Team Section 1.1, 2
2 DOSAGE AND ADMINISTRATION	Product Quality Team Section 4.2
3 DOSAGE FORMS AND STRENGTHS	Product Quality Team Section 4.2
4 CONTRAINDICATIONS	Clinical Team Section 8.5.
5 WARNINGS AND PRECAUTIONS	Clinical Team Section 8.5
6 ADVERSE REACTIONS	Clinical Team/ DPV Section 8.4, 12.1
7 DRUG INTERACTIONS	Clinical Pharmacology Team Section 6, Appendix 20.6
8 USE IN SPECIFIC POPULATIONS	Nonclinical Team/DPMH Section 5, 8.9 Appendix 20.5
11 DESCRIPTION	Product Quality Team Section 4.2
12 CLINICAL PHARMACOLOGY	Clinical Pharmacology Team Section 6, Appendix 20.6
13 NONCLINICAL TOXICOLOGY	Nonclinical Team Section 5, Appendix 20.5
14 CLINICAL STUDIES	Statistical Team/ COA Team Section 9, Appendix 20.4, 20.8
16 HOW SUPPLIED	Product Quality Team Section 4.2
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling, Sections 4, 5, 6 and 14.

Source: Reviewer's Table

Other Prescription Drug Labeling

The Applicant submitted proposed patient package insert for Qwo (collagenase clostridium histolyticum) Injection, for subcutaneous use. The Division of Medical Policy Programs (DMPP) and OPDP reviewed and provided comments on the patient package insert. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Shawna Hutchins, MPH, BSN, RN and Laurie Buonaccorsi, PharmD (dated May 14, 2020).

Postmarketing ARs

To inform the postmarketing adverse reactions section of labeling, the Division of Dermatology and Dentistry consulted with the Division of Pharmacovigilance. Jessica Weintraub, PharmD, BCPS conducted an evaluation of Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) reports and the literature for adverse reactions reported with the use of Xiaflex (collagenase clostridium histolyticum) for injection. The proposed formulation of collagenase clostridium histolyticum has minor differences from Xiaflex (BLA 125338). Dr. Weintraub concluded the following:

> "Hypersensitivity reactions, including anaphylaxis and cases reporting hospitalization, have been reported with Xiaflex use, and are likely to be relevant to the cellulite treatment population… Other adverse reactions not labeled for Xiaflex, including necrosis, skin exfoliation, and vascular occlusion, can be monitored postmarketing for CCH…"

See the Division of Pharmacovigilance review by Jessica Weintraub dated February 11, 2020 for her findings and specific labeling recommendations.

13. Risk Evaluation and Mitigation Strategies (REMS)

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling are not warranted at this time. The benefits of treatment with CCH were demonstrated in adequate and well controlled trials. With limited systemic exposure, the risks are predominantly local injection site reactions.

Approval of intralesional Xiaflex for the treatment of adult patients with DC with a palpable cord required the implementation of a REMS. The REMS assessment plan focused on the potential for tendon rupture and serious hypersensitivity reactions. With approval of intralesional Xiaflex for the treatment of adult men with Peyronie's disease (PD), the FDA modified the REMS to include elements to assure safe use (ETASU) to ensure that the benefits of treatment with Xiaflex outweighed the risks of corporal fracture and other serious penile injuries. No serious risks related to the subcutaneous injection site of collagenase clostridium histolyticum-aaes were observed. Risks including the potential for hypersensitivity reactions can be managed with labeling and routine pharmacovigilance. See Section 12 Labeling Recommendations.

14. Postmarketing Requirements and Commitment

Based on review of the data in the submission, the review team recommended no clinical postmarketing requirements.

However, see Section 4.2 Product Quality for the recommendation regarding Phase 4 (Postmarketing) Commitments from the Office of Product Quality.

- Conduct a drug product (DP) transport qualification study shipping 5 mL and 10 mL vials of CCH Mannitol DP from (b) (4) to the (b) (4) packaging site (b) (4).
  - Target completion date: June 30, 2021
- The target (b) (4) volume (b) (4) was not achieved for one of the test (b) (4) (lot number: R6EA67189) in the bacterial retention study (b) (4) (b) (4). Conduct a bacterial retention study to simulate the target (b) (4) volume (b) (4) throughout the study duration (b) (4).
  - Target completion date: June 30, 2021
- The validation runs (b) (4) (b) (4)

(b) (4) In response to the Agency's Information Request dated May 6, 2020, (b) (4) (b) (4) (b) (4) . Provide data summaries from recent validation runs (b) (4) (b) (4)

– Target completion date: June 30, 2021

15. Appendices

15.1. References

Avram, MM, 2004, Cellulite: a review of its physiology and treatment, J Cosmet Laser Ther, 6(4):181-185.

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Wanner, M and M Avram, 2008, An evidence-based assessment of treatments for cellulite, J Drugs Dermatol, 7(4):341-345.

15.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical trials for CCH. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical trials as defined in 21 CFR 54.2(e) were Trial 302 and Trial 303 which provided the primary data to establish effectiveness and safety of this product. Refer to Section 9.1 for the trial designs.

One investigator from Trial 302 and one investigator with one sub-investigator from Trial 303 had disclosable financial interests and arrangements which are tabulated below. In addition, the Applicant provided a list of sub-investigators who left investigational sites (Trial 302: 2 sub-investigators and Trial 303: 3 sub-investigators) without completing financial disclosure forms.

The Applicant adequately disclosed financial interests involving clinical investigators. Because the number of investigators with financial disclosures was limited and assessments were blinded, the strategies employed by the Applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

Table 35. Covered Clinical Trial 302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 26		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator 0 Sponsor of covered study: Auxilium/Endo		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Table 36. Covered Clinical Trial 303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 25		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 2 Significant equity interest held by investigator 0 Sponsor of covered study: Auxilium/Endo		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Table 37. Investigators With Financial Disclosure Forms 3455 for Trials 302 /303

Investigator (b) (6)	Trial/Site	Country	Percent of Enrollment	Description of Disclosure
	EN3835-302/ (b) (4)	USA	1.9% (b) (4)	Significant Payments of Other Sorts: Amount: $63,230.00 Comment: $63,230.00 for consultation fees in 2018 and 2019.
	EN3835-303/ (b) (4)	USA	0.2% (b) (4)	Proprietary Interest: Comment: These investigators developed a technology related to CCH for the treatment of cellulite, hold a patent application related to this use, and are party to a licensing agreement with (b) (4) (b) (4) for royalties related to the sale of CCH.

Source: Reviewer's Table using data from Form 3455

15.3. Additional Clinical Information

15.3.1. Investigational Sites

The following two tables provide the site numbers, principal investigator names and the number of subjects who were enrolled and completed for Trials 302 and 303.

Table 38. Clinical Site List for Trial 302

Site	Principle Investigator	Randomized	Completed
1279	Sadick	8	6
1280	Young	12	10
1321	Clark	40	39
1324	Lain	11	10
1326	Zook	8	6
1327	Bass	17	17
1338	Fabi	6	4
1340	Venkat	14	13
1342	Heller	30	24
1344	Smith	30	28
1346	Ali	14	13
1348	Bank	14	13
1350	Katz	26	24
1352	Jackson	25	21
1354	Kaminer	8	8
1356	Martin	40	35
1358	Weiss	21	19
1360	Kuohung	4	2
1362	Noss	12	11
1364	Rivkin	1	0
1366	Chiong	15	13
1368	Kempers	7	5
1370	Schlessinger	31	30
1372	Rendon/Lucas	9	8
1374	Jacob	10	9
1376	Peterson/Couvillion	10	10

Source:BLA 761146 SD 10 dated December 19, 2020

Table 39. Clinical Site List for Trial 303

Site	Principle Investigator	Randomized	Completed
1277	Dagum	1	1
1278	Goldman	5	5
1299	Gold	37	36
1320	Kaufman-Janette	40	40
1323	Joseph	22	21
1325	Thiele	6	2
1329	Meadows	38	35
1341	DuBois	11	8
1343	Marchand/Dakour	38	35
1345	Geronemus	4	4
1347	Downie	13	8
1349	Coleman	23	22
1351	Lupo	4	4
1353	Cohen	17	15
1355	Grekin	4	3
1357	Pehoushek	9	8
1359	Bruce	25	22
1361	Yoelin	13	12
1363	Nutt	32	26
1365	Baumann	10	9
1367	Hanke	10	10
1369	Taylor	17	12
1371	Petrus	12	12
1373	Harris	29	26
1375	Fixler	2	1

Source:BLA 761146 SD 10 dated December 19, 2020

15.3.2. Treatment-Emergent Adverse Events by Demographic Subgroup

This section provides the tables which are the basis for the discussion (Section 8.7 of this review) of the TEAEs by demographic subgroup (data from SDN 28 dated April 21, 2020).

For all of the tables in this section, the following preferred terms were pooled:

- Bruising: injection site bruising, injection site hematoma, and injection site hemorrhage
- Pain: injection site pain, injection site discomfort, and injection site dysesthesia
- Swelling: injection site swelling, injection site edema, injection site induration
- Discoloration: injection site discoloration
- Nodule: injection site mass and injection site nodule

The tables below include TEAEs ≥1% by preferred term compared to placebo by demographic subgroup (age, race, body mass index [BMI]) for Trials 302/303.

Table 40. Treatment-Emergent Adverse Events in ≥1% CCH Treated Subjects <65 Years Old

Body System	Preferred Term	Statistic	CCH N=400	Placebo N=404
General disorders and administration site conditions	Bruising [a]	n (%)	338 (84.5)	87 (21.5)
	Discoloration [b]	n (%)	32 (8.0)	2 (0.5)
	Injection site erythema	n (%)	35 (8.8)	21 (5.2)
	Injection site pruritus	n (%)	59 (14.8)	4 (1.0)
	Injection site warmth	n (%)	12 (3.0)	0 (0.0)
	Nodule[c]	n (%)	128 (32.0)	3 (0.7)
	Pain[d]	n (%)	194 (48.5)	37 (9.2)
	Swelling [e]	n (%)	33 (8.3)	5 (1.2)
Infections and infestations	Urinary tract infection	n (%)	5 (1.3)	8 (2.0)
Nervous system disorders	Syncope	n (%)	5 (1.3)	0 (0.0)

Source: BLA 761146, SDN 28 dated April 21, 2020
Abbreviations: CCH = Collagenase clostridium histolyticum

Table 41. Treatment-Emergent Adverse Events in ≥1% CCH Treated Subjects ≥65 Years Old

Body System	Preferred Term	Statistic	CCH N=24	Placebo N=15
General disorders and administration site conditions	Bruising[a]	n (%)	20 (83.3)	3 (20.0)
	Discoloration[b]	n (%)	1 (4.2)	0 (0.0)
	Injection site erythema	n (%)	1 (4.2)	0 (0.0)
	Injection site pruritus	n (%)	4 (16.7)	0 (0.0)
	Injection site warmth	n (%)	2 (8.3)	0 (0.0)
	Nodule[c]	n (%)	13 (54.2)	0 (0.0)
	Pain[d]	n (%)	11 (45.8)	3 (20.0)
	Swelling[e]	n (%)	1 (4.2)	0 (0.0)

Source: BLA 761146, SDN 28 dated April 21, 2020
Abbreviations: CCH = Collagenase clostridium histolyticum

Table 42. Treatment-Emergent Adverse Events in ≥1% CCH Treated White Subjects

Body System	Preferred Term	Statistic	CCH N=336	Placebo N=325
General disorders and administration site conditions	Bruising[a]	n (%)	293 (87.2)	78 (24.0)
	Discoloration[b]	n (%)	29 (8.6)	1 (0.3)
	Injection site erythema	n (%)	30 (8.9)	19 (5.8)
	Injection site pruritus	n (%)	53 (15.8)	4 (1.2)
	Injection site warmth	n (%)	14 (4.2)	0 (0.0)
	Nodule[c]	n (%)	112 (33.3)	3 (0.9)
	Pain[d]	n (%)	177 (52.7)	27 (8.3)
	Swelling[e]	n (%)	25 (7.4)	2 (0.6)
Infections and infestations	Urinary tract infection	n (%)	3 (0.9)	5 (1.5)
Nervous system disorders	Syncope	n (%)	4 (1.2)	0 (0.0)

Source: BLA 761146, SDN 28 dated April 21, 2020
Abbreviations: CCH = Collagenase clostridium histolyticum

Table 43. Treatment-Emergent Adverse Events in ≥1% CCH Treated African American Subjects

Body System	Preferred Term	Statistic	CCH N=76	Placebo N=75
General disorders and administration site conditions	Bruising[a]	n (%)	54 (71.1)	6 (8.0)
	Discoloration[b]	n (%)	4 (5.3)	1 (1.3)
	Injection site erythema	n (%)	4 (5.3)	0 (0.0)
	Injection site pruritus	n (%)	9 (11.8)	0 (0.0)
	Nodule[c]	n (%)	26 (34.2)	0 (0.0)
	Pain[d]	n (%)	23 (30.3)	8 (10.7)
	Swelling[e]	n (%)	7 (9.2)	2 (2.7)
Infections and infestations	Urinary tract infection	n (%)	1 (1.3)	3 (4.0)
Nervous system disorders	Syncope	n (%)	1 (1.3)	0 (0.0)

Source: BLA 761146, SDN 28 dated April 21, 2020
Abbreviations: CCH = Collagenase clostridium histolyticum

Table 44. Treatment-Emergent Adverse Events in ≥1% CCH Treated Subjects With a BMI <25 Kg/M²

Body System	Preferred Term	Statistic	CCH N=81	Placebo N=84
General disorders and administration site conditions	Bruising[a]	n (%)	70 (86.4)	24 (28.6)
	Discoloration[b]	n (%)	4 (4.9)	0 (0.0)
	Injection site erythema	n (%)	6 (7.4)	3 (3.6)
	Injection site pruritus	n (%)	6 (7.4)	0 (0.0)
	Nodule[c]	n (%)	22 (27.2)	0 (0.0)
	Pain[d]	n (%)	37 (45.7)	6 (7.1)
	Swelling[e]	n (%)	7 (8.6)	0 (0.0)
Infections and infestations	Urinary tract infection	n (%)	2 (2.5)	2 (2.4)
Nervous system disorders	Syncope	n (%)	2 (2.5)	0 (0.0)

Source: BLA 761146, SDN 28 dated April 21, 2020
Abbreviations: CCH = Collagenase clostridium histolyticum

Table 45. Treatment-Emergent Adverse Events in ≥1% CCH Treated Subjects With a BMI ≥25 Kg/M²

Body System	Preferred Term	Statistic	CCH N=343	Placebo N=334
General disorders and administration site conditions	Bruising[a]	n (%)	288 (84.0)	66 (19.8)
	Discoloration[b]	n (%)	29 (8.5)	2 (0.6)
	Injection site erythema	n (%)	30 (8.7)	18 (5.4)
	Injection site pruritus	n (%)	57 (16.6)	4 (1.2)
	Injection site warmth	n (%)	14 (4.1)	0 (0.0)
	Nodule[c]	n (%)	119 (34.7)	3 (0.9)
	Pain[d]	n (%)	168 (49.0)	34 (10.2)
	Swelling[e]	n (%)	27 (7.9)	5 (1.5)
Infections and infestations	Urinary tract infection	n (%)	3 (0.9)	6 (1.8)
Nervous system disorders	Syncope	n (%)	3 (0.9)	0 (0.0)

Source: BLA 761146, SDN 28 dated April 21, 2020
Abbreviations: CCH = Collagenase clostridium histolyticum

15.3.3. Safety Findings From Phase 1 Trials

Brief Review of Safety From Open-label, Pharmacokinetics Trials

The Applicant conducted four single-dose (single treatment visit), open-label, pharmacokinetics (PK) and safety trials. None of the subjects in these trials (who had no quantifiable level at baseline) had a quantifiable level of plasma AUX-I or AUX-II postdose. A subgroup of subjects in each trial developed anti-AUX-I and/or anti-AUX-II antibodies. The trial designs, PK and

immunogenicity findings are discussed in greater detail in Section 6 Clinical Pharmacology of this review and Appendix 15.6. For all trials, investigators recorded adverse events (AEs) and vital signs at every visit. For Trials 102, 103 and 104, safety monitoring included a laboratory assessment (hematology, biochemistry and urinalysis) at screening and end of treatment. For Trial 830, safety monitoring included a laboratory assessment at screening, Day 2, Day 30, Day 60 and Day 90. The following are brief descriptions of the trials and key pertinent safety findings.

Trial EN3835-102 (102)

In Trial 102, 11 female subjects with a median age of 52 years (range 36-66 years) and moderate to severe cellulite of the buttock or thigh (PR-PCSS and CR-PCSS ratings of 3 or 4) received a single dose of 0.84 mg of CCH into 1 treatment area. Subjects were evaluated until Day 22 post injection. There were no deaths, serious adverse events (SAEs) or TEAEs that led to discontinuation. All subjects experienced at least one TEAE. The most common TEAEs were: injection site bruising (10 subjects, 91%), injection site pain (9 subjects, 82%) and injection site swelling (3 subjects, 27%). All TEAEs were mild in severity. The most common adverse reactions (ARs) were: injection site bruising (10 subjects, 91%), pain (9 subjects, 82%), and swelling (3 subjects, 27%). One subject (9%) also reported injection site hemorrhage. There were no clinically meaningful changes in the laboratory parameters or vital signs.

Trial EN3835-104 (104)

In Trial 104, 18 female subjects with a median age of 44 years (range 28 to 67 years) and mild to severe cellulite of the buttocks or thigh (PR-PCSS and CR-PCSS ratings of 2, 3 or 4) received a single dose of 0.84 mg into 2 treatment areas (total dose: 1.68 mg). Subjects were evaluated until Day 22 post injection. There were no deaths, SAEs or TEAEs that led to discontinuation. All subjects experienced at least one TEAE. The most common TEAEs were: injection site bruising (18 subjects, 100%), injection site pain (15 subjects, 83%), injection site edema (10 subjects [56%]), and injection site pruritus (2 subjects [11%]). All TEAEs were mild to moderate in severity. The most common ARs were: injection site bruising (18 subjects, 100%), injection site pain (15 subjects, 83%), injection site edema (10 subjects [56%]), and injection site pruritus (2 subjects [11%]). In addition, one subject (b) (6) experienced mild paranesthesia for 24 hours in association with injection site edema and bruising; one subject (b) (6) experienced mild transient facial flushing assessed as related to injection site pain. There were no clinically meaningful changes in the laboratory parameters or vital signs.

Trial EN3835-103 (103)

In Trial 103, 12 female subjects with a median age of 52 years (range 31 to 67 years) and mild to severe cellulite of the buttocks or thigh (PR-PCSS and CR-PCSS ratings of 2, 3 or 4) received a single dose of 0.84 mg into 4 treatment areas (total dose: 3.36 mg). Subjects were evaluated until Day 22 post injection. There were no deaths, SAEs or TEAEs that led to discontinuation. One subject had a quantifiable level of plasma AUX-I at baseline and postdose. All subjects experienced at least one TEAE (138). The most common TEAEs were: injection site bruising (12 subjects, 100%), injection site pain (12 subjects, 100%), injection site edema (4 subjects [33%]),

and injection site swelling (2 subjects [17%]). All TEAEs were mild to moderate in severity. The most common ARs were injection site bruising (12 subjects, 100%), injection site pain (12 subjects, 100%), injection site edema (4 subjects [33%]), and injection site swelling (2 subjects [17%]). There were no clinically meaningful changes in the laboratory parameters or vital signs. However, one subject had an elevated pulse on Day 2 which resolved on Day 3.

AUX-CC-830 (830)

In Trial 830, 99 female subjects with a median age of 44 years (range 21 to 60 years) and moderate to severe cellulite of the buttock or thigh (Hexsel severity score ≥7) received a single dose of CCH (0.0029 mg, 0.0145 mg, 0.0435 mg, 0.116 mg, 0.232 mg, or 0.464 mg in a total volume of 1 or 5 mL) into one treatment area. Subjects had prespecified range of Fitzpatrick Skin Types. Subjects were evaluated until Day 90 post injection. There were no deaths, SAEs, or TEAEs leading to discontinuation. All subjects in cohorts who received a dose of ≥0.0435 mg experienced at least one TEAE. The most common TEAEs and ARs were injection site hemorrhage (ecchymosis), injection site pain, injection site erythema, injection site discomfort, and injection site edema. There were no substantial differences in the types or frequencies of TEAEs based on dose or volume. All TEAEs and AR were mild to moderate in severity. There were no clinically meaningful changes in the laboratory parameters or vital signs. However, one subject (b) (6) had an elevated alanine aminotransferase value (102 IU/L) on Day 90; one subject had an elevated aspartate aminotransferase value (136 IU/L) on Day 93; one subject had a low hematocrit and hemoglobin values (0.298 and 98 g/L, respectively) on Day 7. Five subjects had a low diastolic blood pressure (42 to 50 mm Hg) and some timepoint and 2 subjects had a low systolic blood pressure (67 to 87 mm Hg) at some timepoint. Two of these subjects (b) (6) had associated TEAEs (presyncope and orthostatic hypotension, respectively) at 60 minutes post-injection which resolved within one day.

15.4. Additional Scales and Efficacy Results

15.4.1. Patient-Reported Outcome Scales

Figure 10. Subject Global Aesthetic Improvement Scale (S-GAIS)

Rating	Response Option	Description
+3	Very much improved	My treated cellulite looks very much better.
+2	Much improved	My treated cellulite looks much better, but additional treatment would slightly improve the result.
+1	Improved	My treated cellulite looks better, but additional treatment is necessary.
0	No change	My treated cellulite looks essentially the same as it did originally.
−1	Worse	My treated cellulite looks worse than it did originally.
−2	Much worse	My treated cellulite looks much worse than it did originally.
−3	Very much worse	My treated cellulite looks very much worse than it did originally.

Source: Applicant's Table 5 on page of 74 of Protocol EN3835-302 Amendment 3

Figure 11. 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

Source: Applicant's Table 8 on page of 76 of Protocol EN3835-302 Amendment 3

Figure 12. Patient-Reported Cellulite Impact Scale (PR-CIS)

Please select the rating that best represents your answer on a scale of 0 to 10 with 0 representing "Not at all" and 10 representing "Extremely" while viewing digital images of your buttocks. Please answer each question.

1. Thinking about the areas selected for treatment, how happy are you with the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

2. Thinking about the areas selected for treatment, how bothered are you by the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

3. Thinking about the areas selected for treatment, how self-conscious are you about the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

4. Thinking about the areas selected for treatment, how embarrassed are you about the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

5. Thinking about the areas selected for treatment, how much older do you look because of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

6. Thinking about the areas selected for treatment, how overweight or out of shape do you look because of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

Source: Applicant's Appendix D of Protocol EN3835-302 Amendment 3

For the SSRS assessment in Figure 13, the protocols specify that on Day 1 (baseline), subjects will be instructed to answer: "Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time?"

On Day 71, subjects will be instructed to answer: "Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time whether or not in your judgment it is due entirely to treatment with EN3835?"

Figure 13. Subject Self-Rating Scale (SSRS)

Rating	Response Option
6	Extremely satisfied
5	Satisfied
4	Slightly satisfied
3	Neither satisfied nor dissatisfied
2	Slightly dissatisfied
1	Dissatisfied
0	Extremely dissatisfied

Source: Applicant's Table 7 on page of 75 of Protocol EN3835-302 Amendment 3

15.4.2. Additional Efficacy Results

Table 46. Crosstabulation of Baseline Disease Characteristics of Each Buttock in ITT Population in Trials EN3835-302 and EN3835-303

	EN3835-302						EN3835-303					
	CCH (N=210)			Placebo (N=213)			CCH (N=214)			Placebo (N=206)		
CR-PCSS		***Left***			***Left***			***Left***			***Left***	
Right	3	4	Total	3	4	Total	3	4	Total	3	4	Total
3	110	18	128	113	16	129	112	24	136	114	17	131
4	9	73	82	15	69	84	10	68	78	14	61	75
Total	119	91	210	128	85	213	122	92	214	128	78	206
PR-PCSS		***Left***			***Left***			***Left***			***Left***	
Right	3	4	Total	3	4	Total	3	4	Total	3	4	Total
3	66	27	93	64	28	92	72	29	101	61	22	83
4	14	103	117	10	111	121	15	98	113	15	108	123
Total	80	130	210	74	139	213	87	127	214	76	130	206

Source: Reviewer's analysis
Abbreviations: CCH = Collagenase clostridium histolyticum, CR-PCSS = Clinician-Reported Photonumeric Cellulite Severity Scale, PR-PCSS = Patient-Reported Photonumeric Cellulite Severity Scale

Table 47. Target Buttock Assignment in ITT Population in Trials EN3835-302 and EN3835-303

	EN3835-302		EN3835-303	
ITT Population	**CCH N=210**	**Placebo N=213**	**CCH N=214**	**Placebo N=206**
Target Side				
Left	103 (49%)	106 (50%)	106 (50%)	99 (48%)
Right	107 (51%)	107 (50%)	108 (50%)	107 (52%)

Source: Reviewer's analysis
Abbreviations: CCH = Collagenase clostridium histolyticum, ITT = intention-to-treat

Table 48. Mean Change From Baseline to Day 71 for Each PR-CIS Question in ITT Population in Trials EN3835-302 and EN3835-303

	EN3835-302		EN3835-303	
Mean Change from Baseline	**CCH N=210**	**Placebo N=213**	**CCH N=214**	**Placebo N=206**
Q1 (happy)	3.2	1.3	2.8	1.4
Q2 (bothered)	-1.7	-1.1	-1.7	-1.2
Q3 (self-conscious)	-1.6	-0.9	-1.7	-1.1
Q4 (embarrassed)	-1.7	-1.1	-2.0	-1.1
Q5 (older)	-1.4	-0.8	-1.7	-0.9
Q6 (overweight)	-1.2	-0.7	-1.6	-0.9

Source: Reviewer's analysis. Standard errors were all approximately 0.15-0.28

Table 49. S-GAIS Results at Day 71 in ITT Population in Trials EN3835-302 and EN3835-303

	EN3835-302		EN3835-303	
S-GAIS at Day 71	**CCH N=210**	**Placebo N=213**	**CCH N=214**	**Placebo N=206**
+3 – very much improved	12 (6%)	3 (1%)	10 (5%)	0
+2 – much improved	37 (18%)	10 (5%)	28 (13%)	9 (4%)
+1 – improved	86 (41%)	69 (32%)	88 (41%)	37 (18%)
0 – no change	64 (30%)	123 (58%)	82 (38%)	145 (70%)
-1 – worse	10 (5%)	5 (2%)	5 (2%)	14 (7%)
-2 – much worse	0	2 (1%)	0	0
-3 – very much worse	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)

Source: Reviewer's analysis

Table 50. Cross Tabulation of PR-PCSS Results for the Target Buttock at Baseline and Day 71 in ITT Population in Trials EN3835-302 and EN3835-303

	EN3835-302						EN3835-303					
	PR-PCSS at Day 71						PR-PCSS at Day 71					
Baseline	**0**	**1**	**2**	**3**	**4**	**Total**	**0**	**1**	**2**	**3**	**4**	**Total**
CCH												
3	0	15	28	42	3	88	2	14	38	33	4	91
4	0	10	26	35	51	122	1	5	23	41	53	123
Total	0	25	54	77	54	210	3	19	61	74	57	214
Placebo												
3	0	3	19	51	10	83	0	2	22	56	5	85
4	2	2	19	32	75	130	0	0	10	27	84	121
Total	2	5	38	83	85	213	0	2	32	83	89	206

Source: Reviewer's analysis. Missing data imputed with baseline observation.
Abbreviations: CCH = Collagenase clostridium histolyticum, PR-PCSS = Patient-Reported Photonumeric Cellulite Severity Scale

Table 51. Cross Tabulation of CR-PCSS Results for the Target Buttock at Baseline and Day 71 in ITT Population in Trials EN3835-302 and EN3835-303

	EN3835-302						EN3835-303					
	CR-PCSS at Day 71						CR-PCSS at Day 71					
Baseline	**0**	**1**	**2**	**3**	**4**	**Total**	**0**	**1**	**2**	**3**	**4**	**Total**
CCH												
3	0	22	42	53	10	127	1	16	55	57	1	130
4	0	3	10	30	40	83	0	0	15	34	35	84
Total	0	25	52	83	50	210	1	16	70	91	36	214
Placebo												
3	2	5	28	82	10	127	0	2	29	93	8	132
4	0	1	4	22	59	86	0	0	1	20	53	74
Total	2	6	32	104	69	213	0	2	30	113	61	206

Source: Reviewer's analysis. Missing data imputed with baseline observation.
Abbreviations: CCH = Collagenase clostridium histolyticum, CR-PCSS = Clinician-Reported Photonumeric Cellulite Severity Scale

Table 52. Crosstabulation of Change From Baseline in CR-PCSS and PR-PCSS Scores at Day 71 in Pooled Trials EN3835-302 and EN3835-303 by Treatment Arm (Observed Cases; Target Buttock)

	CCH Subjects (N=390)							Placebo Subjects (N=383)						
Change in	Change in PR-PCSS							Change in PR-PCSS						
CR-PCSS	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**Total**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**Total**
-4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-3	0	1	2	0	1	0	4	0	0	0	1	2	0	3
-2	0	6	19	26	13	0	64	0	1	4	4	2	1	12
-1	0	8	38	71	50	1	168	0	1	13	37	47	2	100
0	1	2	19	50	66	5	143	2	0	16	55	165	12	250
1	0	0	1	1	8	1	11	0	0	1	4	13	0	18
Total	1	17	79	148	138	7	390	2	2	34	101	229	15	383

Source: Reviewer's analysis.
Abbreviations: CCH = Collagenase clostridium histolyticum, CR-PCSS = Clinician-Reported Photonumeric Cellulite Severity Scale, PR-PCSS = Patient-Reported Photonumeric Cellulite Severity Scale

Table 53. Primary Endpoint Results by Site –Trial EN3835-302

Site ID	**Total n (CCH, Placebo)**	**Composite Trt Difference (CCH, Placebo)**	**Clinician Trt Difference (CCH, Placebo)**	**Patient Trt Difference (CCH, Placebo)**
1321	40 (20, 20)	5% (5%, 0)	5% (5%, 0)	20% (25%, 5%)
1356	40 (20, 20)	5% (5%, 0)	5% (5%, 0)	0 (20%, 20%)
1370	31 (15, 16)	0 (0, 0)	53% (53%, 0)	1% (13%, 13%)
1342	30 (15, 15)	7% (13, 7%)	13% (20%, 7%)	7% (33%, 27%)
1344	30 (15, 15)	7% (7%, 0)	7% (7%, 0)	27% (33%, 7%)
1350	26 (13, 13)	0 (8%, 8%)	8% (23%, 15%)	-15% (8%, 23%)
1352	25 (12, 13)	8% (8%, 0)	1% (8%, 8%)	1% (8%, 8%)
1358	21 (10, 11)	0 (0, 0)	10% (10%, 0)	22% (40%, 18%)
1327	17 (9, 8)	0 (0, 0)	-1% (11%, 13%)	11% (11%, 0)
1366	15 (7, 8)	0 (0, 0)	0 (0, 0)	0 (0, 0)

Source: Reviewer's analysis. Only includes sites with ≥15 subjects total.
Abbreviations: CCH = Collagenase clostridium histolyticum, TRT = treatment

Table 54. Primary Endpoint Results by Site –Trial EN3835-302

Site ID	Total n (CCH, Placebo)	Composite Trt Difference (CCH, Placebo)	Clinician Trt Difference (CCH, Placebo)	Patient Trt Difference (CCH, Placebo)
1320	40 (20, 20)	0 (0, 0)	5% (5%, 0)	20% (0.25%, 5%)
1329	38 (19, 19)	0 (0, 0)	5% (11%, 5%)	5% (5%, 0)
1343	38 (19, 19)	0 (0, 0)	5% (5%, 0)	16% (21%, 5%)
1299	37 (19, 18)	11% (11%, 0)	16% (16%, 0)	10% (26%, 17%)
1363	32 (16, 16)	0 (0, 0)	6% (6%, 0)	13% (19%, 6%)
1373	29 (15, 14)	0 (0, 0)	6% (13%, 0.07%)	13% (20%, 7%)
1359	25 (12, 13)	8% (8%, 0)	17% (17%, 0)	18% (33%, 15%)
1349	23 (12, 11)	25% (25%, 0)	25% (25%, 0)	33% (33%, 0)
1323	22 (11, 11)	9% (9%, 0)	27% (27%, 0)	27% (27%, 0)
1353	17 (8, 9)	0 (0, 0)	13% (13%, 0)	0 (0, 0)
1369	17 (9, 8)	0 (0, 0)	22% (22%, 0)	0 (0, 0)

Source: Reviewer's analysis. Only includes sites with ≥15 subjects total.
Abbreviations: CCH = Collagenase clostridium histolyticum, TRT = treatment

15.5. Nonclinical Pharmacology/Toxicology

Revisions to the Applicant's proposed wording for the nonclinical and related sections of the label are provided below. Reviewer proposed deletions are annotated as ~~double strikeout~~ text and reviewer proposed additions are annotated as double underlined text.

Section 13.2 (Animal Toxicology and/or Pharmacology) should be deleted for this labeling since there is no systemic exposure under clinical maximal use conditions.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Qwo is a combination of bacterial collagenases indicated for the treatment of moderate to severe cellulite in the buttocks of adult women (1).

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

(b) (4) There are no available data on collagenase clostridium histolyticum use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Following subcutaneous injection, the systemic concentrations for Qwo were below the bioanalytical assay limit of quantification *[see Clinical Pharmacology (12.3)]*. In animal reproduction studies,

intravenous administration of collagenase clostridium histolyticum to pregnant rats during organogenesis at doses up to 0.13 mg/rat revealed no evidence of harm to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

~~Data~~

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Collagenases are proteinases that hydrolyze collagen in its native triple helical conformation under physiological conditions~~,~~ (b) (4) . The exact mechanism for the treatment of moderate to severe cellulite is unknown.

(b) (4)

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Long-term animal studies to evaluate the carcinogenic potential of collagenase clostridium histolyticum have not been conducted.

(b) (4)

Purified collagenase clostridium histolyticum was not mutagenic in *Salmonella typhimurium* (AMES test) and was not clastogenic in both an in vivo mouse micronucleus assay and an in vitro chromosomal aberration assay in human lymphocytes.

(b) (4)

Collagenase clostridium histolyticum did not impair fertility and early embryonic development when administered intravenously (b) (4) to rats at doses up to 0.13 mg/rat (b) (4)

(b) (4)

(b) (4)

15.6. Clinical Pharmacology Appendices

Qwo cellulite clinical development program included 11 clinical trials in support of the proposed indication. All trials were conducted in adult women with cellulite.

- Four Phase 1 trials
  - Trial AUX-CC-830: an open-label, dose escalation trial (buttock or thigh)
  - Trial EN3835-102: an open-label, single-dose trial (buttock or posterolateral thigh)
  - Trial EN3835-103: an open-label single-dose trial (buttocks and thighs)
  - Trial EN3835-104: an open-label, single-dose trial (buttock-buttock, thigh-thigh, or buttock-thigh)
- Three Phase 2 trials
  - Trial AUX-CC-831: a randomized, double-blind, placebo-controlled dose ranging trial
  - Trial EN3835-201: a randomized, double-blind, placebo-controlled repeat-dose trial
  - Trial EN3835-205: An open-label, repeat-dose, 2 treatment areas trial

- Two Phase 3 efficacy and safety trials
  - Trial EN3835-302: a pivotal trial
  - Trial EN3835-303: a pivotal trial
- Two long-term extension trials
  - Trial EN3835-202: Trial EN3835-201 extension with retreatment option, open-label trial
  - Trial EN3835-304: Trials EN3835-302/-303 extension with retreatment option, open-label trial

The biopharmaceutics program is summarized below.

Drug Substance and Drug Products

CCH comprises a mixture of 2 collagenases, Clostridial type I collagenase (AUX-I) and Clostridial type II collagenase (AUX-II) in an approximate 1:1 mass ratio. These collagenases are isolated and purified from the fermentation of the bacterium *Clostridium histolyticum*. The CCH drug product manufacturing process consists of (b) (4) (b) (4) (b) (4) The Applicant has conducted analytical comparability evaluations to support manufacturing process.

Two CCH drug product formulations have been developed and used in clinical trials (Table 55). The drug product used in the cellulite Phase 3 trials is the same as the to-be-marketed drug product.

Table 55. CCH Drug Product Formulations Used in Clinical Trials

Phase	Clinical Trial	Drug Product Formulation
Phase 1	AUX-CC-830	(b) (4) mg/mL CCH, (b) (4) sucrose, and (b) (4) Tris/HCl pH (b) (4)*
	END3835-102	
Phase 2	AUX-CC-831	
	END3835-201	
	END3835-202	
Phase 1	END3835-103	(b) (4) CCH, (b) (4) sucrose, (b) (4) mannitol, and (b) (4) Tris/HCl pH 8 (b) (4)**
	END3835-104	
Phase 2	END3835-205	
Phase 3	END3835-302	
	END3835-303	
	END3835-304	

(Source of data: Review's summary based on Module 2.7.2, Table 1)
*Approved Xiaflex formulation
**Proposed to-be-marketed drug product formulation/product
Abbreviations: CCH = Collagenase clostridium histolyticum

15.6.1. Summary of Bioanalytical Method Validation and Performance

15.6.1.1. PK Assays: Bioanalytical Methods for Determination of AUX-I and AUX-II Concentrations in human Plasma

The Applicant developed and validated two separate ELISA assays for measurement of AUX-I and AUX-II concentrations in human plasma samples obtained from four Phase 1 trials. The method is applicable for the quantitation of AUX-I within a nominal range of 5 to 40 ng/mL with LLOQ of 5 ng/mL, and for the quantitation of AUX-II within a nominal range of 25 to 500 ng/mL with LLOQ of 25 ng/mL. In the assays, polyclonal anti-AUX-I or anti-AUX-II antibodies are precoasted onto a microplate. Samples are pipetted into the wells and anti-AUX-I or anti-AUX-II biotin is added. The minimum dilution for validation samples and test samples is 1:50. Any AUX-I or AUX-II present in the samples are bound at the same time by anti-AUX-I or anti-AUX-II biotin and the immobilized anti-AUX-I or anti-AUX-II antibodies. After a washing step, poly-streptavidin-peroxidase is added which binds to the anti-AUX-I or anti-AUX-II biotin. After a further washing step, peroxidase bound in the complex is visualized by TMB (3,3',5,5' tetramethyl benzidine) substrate solution. After stopping the enzymatic reaction with sulfuric acid, the intensity of the resulting color is determined at 450 nm. The color intensity is proportional to the concentration of AUX-I or AUX-II in the sample. The validation parameters and performance of the ELISA are summarized in Table 56 and Table 57, respectively.

Table 56. Summary of Validation Parameters for AUX-I

Validation Parameter		Description/Validated Value			
Analyte		AUX-I			
Matrix		Human Plasma (Li-heparinated)			
Method SOP Number		SOP SM3-272B			
Assay Method		ELISA			
Assay Volume Required per Assay		10 µL (for duplicate determination)			
Minimum Required Dilution (MRD)		1:50 in dilution buffer			
Regression Type		4-PL curve			
Quantitation Range		5.00 – 40.0 ng/mL			
Inter-assay Precision and Accuracy for Validation Samples		*Set a*		*Set b*	
		Precision (%)	*Accuracy (%)*	*Precision (%)*	*Accuracy (%)*
8 valid runs	VS 1 (5.00 ng/mL) VS 2 (12.5 ng/mL) VS 3 (17.5 ng/mL) VS 4 (32.5 ng/mL) VS 5 (40.0 ng/mL)	6.9 3.1 4.9 6.1 6.2	103.8 96.4 103.1 101.4 102.5	5.9 4.5 4.7 4.8 6.1	104.0 95.9 104.4 100.5 103.0
Intra-assay Precision and Accuracy for Validation Samples		*Precision (%)*		*Accuracy (%)*	
6 duplicates in 1 run	VS 1 (5.00 ng/mL) VS 2 (12.5 ng/mL) VS 3 (17.5 ng/mL) VS 4 (32.5 ng/mL) VS 5 (40.0 ng/mL)	1.1 2.7 2.5 0.9 0.8		101.5 99.5 105.8 97.9 100.7	
Dilution Linearity		Up to 1:8000 in human plasma (before MRD of 1:50 in dilution buffer)			
High Dose Hook Effect		No high dose hook effect up to 40'000 ng/mL			
Selectivity / Specificity					
Background determination in 20 individual human plasma samples		All 20 samples analyzed as BLQ (< 5.00 ng/mL)			
Spike recovery with 6.25 ng/mL AUX-I in 10 individual human plasma samples		Recovery ranged from 86.1% to 102.9%; 10 of 10 within 70% - 130%			
Spike recovery with 32.5 ng/mL AUX-I in 10 individual human plasma samples		Recovery ranged from 55.8% to 113.6%; 9 of 10 within 70% - 130%			
Stability					
F/T Stability		Up to 3 cycles at -80 °C / ice-bath			
Short-term Stability in human plasma		Up to 3 hours in an ice-bath (2°C) and up to 2 hours at 5°C			
Short-term stability in diluted human plasma (1:50 dilution in dilution buffer)		Up to 1 hour in an ice-bath (2°C) and at 5°C			

BLQ=Below the limit of quantification
Source: Validation Summary, Validation Report VAA41767CH-EB-03
Source of data: 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 5

Table 57. Summary of Validation Parameters for AUX-II

Validation Parameter		*Description / Validated Value*			
Analyte		AUX-II			
Matrix		Human Plasma (Li-heparinated)			
Method SOP Number		SOP SM3-273B			
Assay Method		ELISA			
Assay Volume Required per Assay		10 µL (for duplicate determination)			
Minimum Required Dilution (MRD)		1:50 in dilution buffer			
Regression Type		4-PL curve			
Quantitation Range		25.0 – 500 ng/mL			
Inter-assay Precision and Accuracy for Validation Samples		*Set a*		*Set b*	
		Precision (%)	*Accuracy (%)*	*Precision (%)*	*Accuracy (%)*
8 valid runs	VS 1 (25.0 ng/mL) VS 2 (75.0 ng/mL) VS 3 (250 ng/mL) VS 4 (375 ng/mL) VS 5 (500 ng/mL)	4.2 3.3 3.0 3.9 4.2	124.6 110.4 105.4 101.0 102.7	3.7 4.2 2.7 3.4 5.2	121.8 109.8 105.9 102.1 103.8
Intra-assay Precision and Accuracy for Validation Samples		*Precision (%)*		*Accuracy (%)*	
6 duplicates in 1 run	VS 1 (25.0 ng/mL) VS 2 (75.0 ng/mL) VS 3 (250 ng/mL) VS 4 (375 ng/mL) VS 5 (500 ng/mL)	5.0 1.2 1.2 0.7 0.7		122.6 111.5 106.8 103.1 103.9	
Dilution Linearity		Up to 1:1600 in human plasma (before MRD of 1:50 in dilution buffer)			
High Dose Hook Effect		No high dose hook effect up to 50'000 ng/mL			
Selectivity/Specificity					
Background determination in 20 individual human plasma samples		All 20 samples analyzed as BLQ (< 25.0 ng/mL)			
Spike recovery with 31.0 ng/mL AUX-II in 10 individual human plasma samples		Recovery ranged from 98.1% to 142.9%; 8 of 10 within 70% - 130%			
Spike recovery with 375 ng/mL AUX-II in 10 individual human plasma samples		Recovery ranged from 91.8% to 114.3%; 10 of 10 within 70% - 130%			
Stability					
F/T Stability		Up to 3 cycles at -80 °C/ice-bath			
Short-term Stability in human plasma		Up to 3 hours in an ice-bath (2°C) and Up to 2 hours at 5°C			
Short-term stability in diluted human plasma (1:50 dilution in dilution buffer)		Up to 1 hour in an ice-bath (2°C) and at 5°C			

Source: Validation Summary, Validation Report VAA41768CH-EB-01.
Source of data: 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 6

15.6.1.2. Immunogenicity Assays: Bioanalytical Methods for Testing Anti-Drug Antibodies and Neutralizing Anti-Drug Antibodies

The Applicant developed ELISA bridging assays for assessment of antidrug antibodies (ADAs) for AUX-I and AUX-II and ADA titer determination in CCH clinical trials. The main steps of the

screening/confirm assay are summarized as follows: human serum samples are diluted 1:10 in dilution buffer and added to the wells of a microtiter plate (MTP) precoated with free AUX-I or AUX-II, allowing the capture of anti-AUX-I or anti-AUX-II antibodies present in the sera. Biotinylated AUX-I or AUX-II is added to the plate and is bound to anti-AUX-I antibodies or anti-AUX-II antibodies. Strepatividin-horse radish peroxidase (HRP) conjugate is in turn added to the plate and is bound to biotin. Finally, incubation with TMB substrate results in color development, which is terminated by addition of a sulfuric acid stop solution. The optical density (OD) of each well is measured at a wavelength of 450 nm using a MTP reader. After confirmation of reactive samples for presence of anti-AUX-I/II antibodies (in the confirmatory assay), the screening assay format will be used for titer determination. For titer determination, anti-AUX-I/II antibody positive samples are determined from 2-fold dilutions. The validation parameters and performance of ELISA assays for the qualitative measurement of anti-AUX-I and anti-AUX-II antibodies in human serum are summarized in Table 58 and Table 59, respectively.

Enzymatic assays were developed and validated during drug development for measurement of neutralizing antibodies (NAbs) to AUX-I/II in human serum by two different vendors (b) (4) (b) (4) The methods developed (b) (4) (b) (4) and used for determination of NAbs in the 2 pivotal Phase 3 trials are summarized below: serum samples are pipetted to the wells of a black assay plate. AUX-I/II is diluted to the desired concentration with 1X Reaction Buffer and added to the wells. After 30 to 40 minutes incubation, the reconstituted Collagen Substrate is added to each well and the incubation is continued for 25 to 35 minutes. The plate is read well using a fluorescence reader (excitation wavelength: 495 nm, emission wavelength: 515 nm). The measured fluorescence (in cps) is proportional to the proteolytic activity of AUX-I/II and inversely proportional to the concentration of neutralizing anti-AUX-I/II antibodies in the samples. The validation parameter for detection of anti-AUX-I and anti-AUX-II NAbs in human serum are summarized in Table 60 and Table 61, respectively.

Table 58. Summary of Validation Parameters for Anti-AUX-I Antibody

Analyte	**Anti-AUX-I Antibodies**			
Matrix	Human serum			
Method SOP number Assay method **Sample volume** **Minimum required dilution**	SM3-406 ELISA Screening assay: 30 µL (manual) or 50 µL (automated) Confirmatory assay: 60 µL (manual) or 100 µL (automated) Titer assay: 30 µL (manual) or 35 µL (automated) 1:10 in dilution buffer			
Validation parameters	**Result**			
Correction Factor (rCP)	1.1212 (multiplication)			
Specificity Cut Point (iCP)	17.4%			
Acceptance Criteria (uninhibited) NC (OD) LPC (OD) MPC (OD) HPC (OD)	Lower limit 0.0528 ≥ rCP 0.9890 1.4955		Upper limit 0.2113 not used not used not used	
Screening Sensitivity	50% Consistency 0.188 ng/mL		99% Consistency 0.363 ng/mL	
Confirmatory Sensitivity	50% Consistency 0.183 ng/mL			
Precision	NC	LPC	MPC	HPC
Inter-Assay Precision (%CV)	22.3%	12.1%	10.3%	9.6%
Intra-Assay Precision (%CV)	2.7%	1.3%	2.7%	2.7%
Titer Precision %CV Titer correction factor (tCP)	tCP (5% false positive rate) 23.1% Not Used		tCP (0.1% false positive rate) 17.2% 1.3141 (multiplication)	
Selectivity LPC (0.363 ng/mL)	10/10 serum lots met selectivity criteria			
Recovery LPC (0.363 ng/mL)	10/10 serum lots met recovery criteria			
AUX-I Drug Tolerance LPC (0.363 ng/mL)	50 ng/mL of AUX-I drug			
Hemolysis NC (0 ng/mL) LPC (0.363 ng/mL)	1% Hemolysis Negative (no impact) Reactive (no impact)		5% Hemolysis Negative (no impact) Reactive (no impact)	
Stability F/T cycles	up to 10 cycles from either -20°C or -80°C			
Bench-top Storage at -20°C and -80°C	43 hours at RT Validated in this study for up to 19 days at either -20°C or -80°C and previously validated for up to 26 months at -80°C[a]			
Automation	Stress test and precision criteria met			

[a] Validation Report VAA33061-02
%CV=Percent coefficient of variation; HPC= high positive control; LPC= low positive control; MPC=medium positive control; NC=normal control; OD=optical density; RT=room temperature
Source: Validation report VCA23720-01 Validation Summary Table

Source of data: Method Validation Report VCA23720-01, Validation Summary page 11

Table 59. Summary of Validation Parameters for Anti-AUX-II Antibody

Analyte	**Anti-AUX-II Antibodies**			
Matrix	Human serum			
Method SOP number **Assay method** **Sample volume** **Minimum required dilution**	SM3-407 ELISA Screening assay: 30 µL (manual) or 50 µL (automated) Confirmatory assay: 60 µL (manual) or 100 µL (automated) Titer assay: 30 µL (manual) or 35 µL (automated) 1:10 in dilution buffer			
Validation parameters	**Result**			
Correction Factor (rCP)	1.1822 (multiplication)			
Specificity Cut Point (iCP)	14.2%			
Acceptance Criteria (uninhibited) NC (OD) LPC (OD) MPC (OD) HPC (OD)	Lower limit 0.0543 ≥ rCP 0.5772 1.6502		Upper limit 0.2171 not used not used not used	
Screening Sensitivity	50% Consistency 1.49 ng/mL		99% Consistency 5.37 ng/mL	
Confirmatory Sensitivity	50% Consistency 0.892 ng/mL			
Precision	NC	LPC	MPC	HPC
Inter-Assay Precision (%CV)	15.2%	9.1%	9.5%	7.0%
Intra-Assay Precision (%CV)	5.5%	3.1%	6.3%	4.0%
Titer Precision %CV Titer correction factor (tCP)	rCP (5% false positive rate) 47.7% Not used		tCP (0.1% false positive rate) 43.1% 1.3832 (multiplication)	
Selectivity LPC (5.37 ng/mL)	10/10 passed serum lots met selectivity criteria			
Recovery LPC (5.37 ng/mL)	9/10 passed serum lots met recovery criteria			
AUX-II Drug Tolerance LPC (5.37 ng/mL)	10 ng/mL of AUX-II drug			
Hemolysis NC (0 ng/mL) LPC (5.37 ng/mL)	1% Hemolysis Negative (no impact) Reactive (no impact)		5% Hemolysis Negative (no impact) Reactive (no impact)	
Stability F/T cycles	up to 10 cycles from either -20°C or -80°C			
Bench-top	44 hours at RT			
Storage at -20°C and -80°C	Validated in this study for up to 19 days at either -20°C or -80°C and previously validated for up to 26 months at -80°C[a]			
Automation	Stress test and precision criteria met			

[a] Validation Report VAA33062-02

Source: Validation Report VCA23720-02

Source of data: Method Validation Report VCA23720-02, Validation Summary page 11

Table 60. Validation of an Enzymatic Assay for Neutralizing Anti-AUX-I Antibody

Analyte	**Anti-AUX-I NAbs**	
Matrix	Human serum	
Method SOP number	SM3-409	
Assay method	ELISA	
Assay volume	10 µL sample/well	
Validation parameters	**Result**	
Correction Factor (rCP)	Healthy	Disease
	-4292.5 (Addition)	0.8304 (multiplication)
Acceptance Criteria	Lower limit	Upper limit
NC (OD)	18754.7	75018.9
LPC (OD)	not used	≤ rCP
Screening Sensitivity 50% Consistency 99% Consistency	Healthy 5.57 A.U/mL 11.0 A.U/mL	Disease 6.72 A.U/mL 12.7 A.U/mL
Precision	NC	LPC
Inter-Assay Precision (%CV)	3.4	6.5
Intra-Assay Precision (%CV)	1.2	3.6
Selectivity LPC (11 A.U./mL)	10/10 serum lots met selectivity criteria	
Recovery LPC (11 A.U./mL)	9/10 serum lots met recovery criteria	
AUX-I Drug Tolerance LPC (11 A.U./mL)	5000 ng/mL of Aux-I drug	
Hemolysis	1% Hemolysis	5% Hemolysis
NC (0 A.U./mL)	Negative (no impact)	Negative (no impact)
LPC (11 A.U./mL)	Reactive (no impact)	Reactive (no impact)
Stability		
F/T cycles	up to 8 cycles from either -20°C or -80°C	
Bench-top	42 hours at RT	
Storage	16 days at either -20°C or -80°C	

Source: Report VCA23842-01

Source of data: Integrated Summary of Immunogenicity, Table 17

Table 61. Validation of an Enzymatic Assay for Neutralizing Anti-AUX-II Antibody

Analyte	**Anti-AUX-II NAbs**	
Matrix	Human serum	
Method SOP number	SM3-410	
Assay method	Enzymatic assay	
Assay volume	2 x 10 µL	
Validation parameters	**Result**	
Correction Factor (rCP)	Healthy	Disease
	-4781.3	-5374.2
Acceptance Criteria (uninhibited) NC LPC	Lower limit 18682.1 not used	Upper limit 74728.4 ≤ rCP
Screening Sensitivity 50% Consistency 99% Consistency	Healthy	Disease
	1.95 A.U./mL	2.25 A.U./mL
	4.05 A.U./mL	4.66 A.U./mL
Precision	NC	LPC
Inter-Assay Precision (%CV)	5.1%	5.5%
Intra-Assay Precision (%CV)	1.0%	3.5%
Selectivity LPC (4.08 A.U./mL)[a]	10/10 passed serum lots met selectivity criteria	
Recovery LPC (4.08 A.U./mL)[a]	10/10 passed serum lots met recovery criteria	
AUX-II Drug Tolerance LPC (4.08 A.U./mL)[a]	5000 ng/mL of Aux-II drug	
Hemolysis NC (0 ng/mL) LPC (4.08 A.U./mL)[a]	1% Hemolysis Negative (no impact) Reactive (no impact)	5% Hemolysis Negative (no impact) Reactive (no impact)
Stability F/T cycles Bench-top Storage	up to 8 cycles from either -20°C or -80°C 42 hours at RT 16 days at either -20°C or -80°C	

[a] In error, a 99% screening sensitivity concentration of 4.08 A.U./mL instead of 4.05 A.U./mL was used as the concentration for the new low positive control level. This difference in concentration was deemed to be negligible and the validation assessments performed at 4.08 A.U./mL were not regarded as needing to be reassessed and this deviation is not considered to have had an impact on the integrity of the validation.
Source: Report VCA23842-02

Source of data: Integrated Summary of Immunogenicity, Table 18

15.6.2. Clinical Pharmacology Trials

15.6.2.1. Trial AUX-CC-830: Single Ascending Dose Trial in Adult Women With Cellulite

Trial design: Trial AUX-CC-830 was a Phase 1b, open-label, dose-escalation and PK trial of the safety, effectiveness, and PK of CCH in adult women with cellulite. The trial objectives were to

assess increasing doses ranging from 0.0029 mg to 0.464 mg using increasing concentrations from ranging 0.0029 mg/mL to 0.464 mg/mL and injectate volumes of either 0.1 mL or 0.5 mL per injection (10 SC injections for total volumes of 1 mL or 5 mL) in the treatment of adult women with cellulite. A total of 99 subjects were enrolled in this trial (Table 62).

Reviewer's comment: The approved formulation of Xiaflex for treatment of Peyronie's disease was used.

Table 62. Trial Drug Assignment by Cohort

Cohort	Subjects per Cohort	Dose CCH/Target Area[a]	Volume/Target Area[a]	Concentration
1	9	0.0029 mg	1 mL	0.0029 mg/mL
2a	9	0.0145 mg	5 mL	0.0029 mg/mL
2b	9	0.0145 mg	1 mL	0.0145 mg/mL
3a	9	0.0435 mg	5 mL	0.0087 mg/mL
3b	9	0.0435 mg	1 mL	0.0435 mg/mL
4a	9	0.116 mg	5 mL	0.0232 mg/mL
4b	9	0.116 mg	1 mL	0.116 mg/mL
5a	9	0.232 mg	5 mL	0.0464 mg/mL
5b	9	0.232 mg	1 mL	0.232 mg/mL
6a	9	0.464 mg	5 mL	0.0928 mg/mL
6b	9	0.464 mg	1 mL	0.464 mg/mL

[a] Administered as a total of 10 single injections of 0.1 mL for the 1 mL volume administered or as a total of 10 single injects of 0.5 mL for the 5 mL volume administered at the target injection sites across the 8 cm × 10 cm target cellulite area.

PK sampling: Blood samples were collected for the determination of AUX-I/II plasma concentrations at predose, 5, 10, 20, 30 minutes, and 1, 2, 4, 8, 12, and 24 hours postdose.

Results: There were no quantifiable plasma concentrations for AUX-I and AUX-II at any time point through 24 post injection for 93 of 99 subjects participated. The concentrations for 6 subjects were considered "not evaluable" due to possible assay interference and were not included in the AUX-I and/or AUX-II PK analysis.

15.6.2.2. Trial EN3835-102: Single Dose Trial in Adult Women With Cellulite

Trial design: Trial EN3835-102 was a Phase 1, open-label PK trial. Eleven adult female subjects with moderate to severe cellulite were subcutaneously injected with a single dose of CCH 0.84 mg per treatment area (left or right buttock, left or right posterolateral thigh) on Day 1.

Reviewer's comment: The approved formulation of Xiaflex for treatment of Peyronie's disease was used.

PK sampling: blood samples were collected for the determination of AUX-I/II plasma concentrations at predose, 5, 10, 20, 30 minutes, and 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours postdose.

Results: No quantifiable levels for plasma AUX-I or AUX-II concentrations were observed for any subjects following injection of CCH 0.84 mg.

15.6.2.3. Trial EN3835-103: Single Dose Trial in Adult Women With Cellulite

Trial design: Trial EN3835-103 was a Phase 1, open-label PK trial. Twelve adult women with cellulite were subcutaneously injected with a single dose of CCH 3.36 mg as 12 injections per quadrant in 4 quadrants concurrently (0.84 mg per quadrant) on Day 1.

Reviewer's comment: The drug product lot and formulation used in Trial EN3835-103 were the same as these used in the 2 pivotal Phase 3 trials. The to-be-marketed formation was used in the Phase 3 trials and Trial EN3835-103.

PK sampling: Blood samples were collected for the determination of AUX-I/II plasma concentrations at predose, 5, 10, 20, 30 minutes, and 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours postdose.

Results: No quantifiable levels for plasma AUX-I or AUX-II concentrations were observed for any subjects following injection of CCH 3.36 mg.

15.6.2.4. Trial EN3835-104: Single Dose Trial In Adult Women With Cellulite

Trial design: Trial EN3835-104 was a Phase 1, open-label, single-dose PK trial. Eighteen adult women with cellulite were subcutaneously injected with a single dose of CCH 1.68 mg in 2 treatment areas (bilateral buttocks, bilateral thighs, or unilateral buttock and thigh) for a total of 24 injections on Day 1

Reviewer's comment: The to-be-marketed formation was used in this trial.

PK sampling: Blood samples were collected for the determination of AUX-I/II plasma concentrations at predose, 5, 10, 20, 30 minutes, and 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours postdose.

Results: No quantifiable levels for plasma AUX-I or AUX-II concentrations were observed for 17 of 18 subjects following injection of CCH 1.68 mg given as 24 injections of CCH in 2 treatment areas. The concentration-time profiles for 1 subject were considered "not evaluable" due to possible assay interference in the AUX-I and/or AUX-II PK analysis.

15.7. Product Quality Appendices

N/A

15.8. Additional Clinical Outcome Assessment Analyses

The Applicant proposed three patient-reported outcome (PRO) instruments for use in secondary endpoint evaluation: Subject Self-Rating Scale (SSRS), Patient-Reported Cellulite Impact Scale (PR-CIS), and Subject Global Assessment of Aesthetic Improvement Scale (S-GAIS). The review team evaluated the qualitative and quantitative evidence submitted by the Applicant to determine if each instrument was fit-for-purpose in the target population.

See Section 9.1 for a discussion of the SSRS.

In regard to the PR-CIS, on face, there are some items (i.e., asking patients about how much older they look, how overweight they look) that may be misleading if taken out of context. The drug is specifically for the treatment of cellulite in adult women, not for helping patients to look younger or less overweight. During the cognitive interviews, some subjects indicated that PR-CIS item 5 (looking older due to cellulite) and item 6 (looking overweight) were irrelevant. Furthermore, some subjects associated looking old as in their overall look (not specific to their cellulite). Based on the qualitative evidence provided, the evidence to support the content relevance of the PR-CIS was not adequate. In regard to the evidence for the other measurement properties of the PR-CIS, it is key to note that testing the measurement properties (reliability, construct validity, and ability to detect change) for any clinical outcome assessment, while important, will not replace or rectify problems with content validity. Therefore, while the PR-CIS showed some adequate measurement properties, the content validity of the instrument was not sufficiently established. In reviewing the interpretation of the PR-CIS item scores, the change from baseline to Day 71 showed small effects of change for most of the items. And while the "happiness" item had a slightly higher magnitude of change, the concept overlaps with satisfaction which is already reflective in the SSRS instrument. Overall, the evidence to support the PR-CIS was not sufficient to consider this instrument fit-for-purpose in this target population.

In regard to the S-GAIS, the Applicant was advised that the Agency views the S-GAIS as an exploratory measure that can be used as an anchor for determining what constitutes a clinically meaningful within-patient change in other trial endpoints. This particular scale is susceptible to recall error due to the recall period (three weeks) and will not be able to allow change from baseline analyses. Furthermore, the S-GAIS is not granular enough to measure the concept of interest. And while the S-GAIS showed some adequate measurement properties, it does not replace of rectify the concerns regarding the content relevance. Based on these points, the S-GAIS (b) (4) can be used as an anchor for determining what constitutes a clinically meaningful within-patient change in the PR-PCSS and CR-PCSS.

Labeling for PR-PCSS and CR-PCSS:

Based on the submitted data from the Applicant, the PR-PCSS and the CR-PCSS are relevant concepts. Further, the psychometric data supports that both instruments are well-defined and reliable. As such, both instruments appear to be adequate to support the proposed labeling claims.

Additionally, it was previously communicated to the Applicant that each of instruments need to be anchored to a 2-point change on the GAIS to give them greater confidence in the change needed on the instruments. Based on a 2-level change in S-GAIS ('much improved"), the PR-PCSS meaningful change threshold is 1.45 points. Based on a 2-level improvement in I-GAIS ("much improved"), CR-PCSS meaningful-change threshold is 1.45 points.

Table 63. Meaningful Change Thresholds for PR-PCSS by S-GAIS Group – Target Buttock in Trials EN3835-302 and EN3835-303 Pooled Treatment of CCH and Placebo

	N	Day 1 Mean (SD)	Day 71 Mean (SD)	Change Mean (SD)	% Change from Baseline	Effect Size	
S-GAIS at Day 71							262.9 (<0.0001)
+3 Very much improved	25	3.40 (0.50)	1.36 (0.76)	-2.04 (0.84)	60.0%	-4.08	
+2 Much improved	84	3.50 (0.50)	2.05 (0.81)	-1.45 (0.81)	41.4%	-2.89	
+1 Improved	279	3.57 (0.50)	2.63 (0.77)	-0.94 (0.76)	26.3%	-1.89	
0 No change	322	3.61 (0.49)	3.38 (0.73)	-0.23 (0.68)	6.4%	-0.46	
-1, -2, -3 Worsen groups	40	3.75 (0.44)	3.60 (0.59)	-0.15 (0.48)	4.0%	-0.34	

Abbreviations: PR-PCSS=Patient Reported Photonumeric Cellulite Severity Scale; SD=standard deviation; S-GAIS= Subject Global Aesthetic Improvement Scale.
[1] Kruskal-Wallis one-way ANOVA model; ANOVA model includes S-GAIS group as the independent variable or the SSCTA group as the independent variable and the PR-PCSS change scores as the dependent variable
Source: Study EN3000-011 - PRO-Dossier Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) Table 11.1

Table 64. Meaningful Change Thresholds for CR-PCSS by I-GAIS Group – Target Buttock in Trials EN3835-302 and EN3835-303 Pooled Treatment of CCH and Placebo

	N	Day 1 Mean (SD)	Day 71 Mean (SD)	Change Mean (SD)	% Change from Baseline	Effect Size	H-valuel (p-value)
I-GAIS at Day 71							322.8 (<0.0001)
+3 Very much improved	14	3.07 (0.27)	0.93 (0.47)	-2.14 (0.53)	69.7%	-8.02	
+2 Much improved	96	3.31 (0.47)	1.86 (0.73)	-1.45 (0.69)	43.8%	-3.11	
+1 Improved	249	3.36 (0.48)	2.61 (0.69)	-0.75 (0.58)	22.3%	-1.55	
0 No change	377	3.43 (0.50)	3.30 (0.63)	-0.13 (0.53)	3.8%	-0.26	
-1, -2, -3 Worsen groups	13	3.46 (0.52)	3.62 (0.65)	0.15 (0.55)	4.3%	0.30	

Abbreviations: I-GAIS=Investigator Global Aesthetic Improvement Scale; SD=Standard deviation

[1] Kruskal-Wallis one-way ANOVA model; ANOVA model includes I-GAIS group as the independent variable and the CR-PCSS change scores as the dependent variable

Source: Study EN3000-012 - ClinRO Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) Table 11.1

(b) (4)

After review of the content validity evidence for the S-GAIS, PR-CIS, and SSRS that was provided by the Applicant, the PR-CIS and S-GAIS were determined to be not fit-for-purpose, (b) (4) (b) (4) (b) (4) while the SSRS showed adequate measurement properties to support the edited label claim.

Table 65. Frequency Distribution for SSRS – Day 71 in Trials EN3835-302 and EN3835-303

Visit SSRS rating	Statistic [2]	Study Drug CCH 0.84 mg/buttock (N=424)	Study Drug Placebo (N=419)
Day 71			
Extremely Satisfied (6)	n (%)	19 (5.1)	5 (1.3)
Satisfied (5)	n (%)	80 (21.6)	27 (7.1)
Slightly Satisfied (4)	n (%)	93 (25.1)	47 (12.3)
Neither Satisfied nor Dissatisfied (3)	n (%)	56 (15.1)	76 (19.9)
Slightly Dissatisfied (2)	n (%)	31 (8.4)	49 (12.9)
Dissatisfied (1)	n (%)	61 (16.5)	85 (22.3)
Extremely Dissatisfied (0)	n (%)	30 (8.1)	92 (24.1)
Not Done	n	54	38
	Mean	3.2	2.0
	SD	1.74	1.65

[1] ITT Population includes the randomized subjects who received at least 1 injection of trial drug (0.84mg CCH/buttock or placebo).
[2] Percentages are based on the number of evaluable subjects at each time point for each column.
Missing SSRS ratings at any time point are not imputed and therefore excluded in the summary.
Datasets (extraction): ADSSRS (03JUN2019)
Source: Integrated Summary of Efficacy-Tables Table 14.1.2.11

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