

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761146Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110077

MEETING MINUTES

Auxilium Pharmaceuticals, LLC
c/o Endo Pharmaceuticals, Inc.
Attention: Erin Abdallah
Associate Director, Regulatory Affairs
1400 Atwater Drive
Malvern, PA 19355

Dear Ms. Abdallah:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for collagenase clostridium histolyticum, for injection.

We also refer to the meeting between representatives of your firm and the FDA on January 30, 2019. The purpose of the meeting was to discuss the development program for collagenase clostridium histolyticum, for injection.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cristina Attinello, Senior Regulatory Project Manager at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures:
Meeting Minutes
Sponsor-Provided Response Document



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-sBLA

Meeting Date and Time: January 30, 2019, 8:30 – 9:30 am
Meeting Location: WO22, Room 1311

Application Number: IND 110077
Product Name: collagenase clostridium histolyticum, for injection
Proposed Indication: for the treatment of moderate to severe edematous fibrosclerotic panniculopathy (EFP)/cellulite in adult female patients

Sponsor Name: Auxilium Pharmaceuticals, LLC

Meeting Chair: Kendall Marcus, MD
Meeting Recorder: Cristina Attinello, MPH

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Denise Cook, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DPC) III
Liping (Cindy) Pan, PhD, Clinical Pharmacology Reviewer, DCP III
Xianghong (Emily) Jing, PhD, Product Quality Team Leader, OPQ
Brian Roelofs, PhD, Product Quality/CMC Reviewer, OPQ
Kathleen Fritsch, PhD, Biometrics Reviewer, DB III
Rebecca Hager, PhD, Biometrics Reviewer, DB III
Lindsey Crist, PharmD, Risk Management Analyst, DRISK
Teresa McMillan, PharmD, Safety Evaluator, DMEPA
James Schlick, MBA, RPh, Safety Evaluator, DMEPA
Cristina Attinello, MPH, Senior Regulatory Project Manager, DDDP

SPONSOR ATTENDEES

Erin Abdallah, Endo Pharmaceuticals
Davina Cupo, Endo Pharmaceuticals
Matthew Davis, Endo Pharmaceuticals
(b) (4)
Rosalie Filling, Endo Pharmaceuticals

Timothy Halton, Endo Pharmaceuticals
Genzhou Liu, Endo Pharmaceuticals
William McIntyre, Endo Pharmaceuticals
Michael McLane, Endo Pharmaceuticals
Rosanne Middleton, Endo Pharmaceuticals
Harris Rotman, Endo Pharmaceuticals
Saji Vajayan, Endo Pharmaceuticals

1.0 BACKGROUND

Purpose of Meeting:

The purpose of this meeting is to discuss the development program for collagenase clostridium histolyticum, for injection

Regulatory Correspondence History:

We have had the following meetings/teleconferences with you:

- March 26, 2018: Written Response Only (Guidance)
- June 28, 2017: Guidance Meeting
- February 8, 2017: End of Phase 2 Meeting
- December 14, 2015: Guidance Teleconference
- December 17, 2014: Guidance Teleconference

We have sent the following correspondences:

- December 3, 2018: Advice Letter
- July 23, 2018: Advice Letter
- April 23, 2018: Advice Letter
- March 22, 2018: Advice Letter
- January 11, 2018: Special Protocol No Agreement Letter
- November 17, 2017: Advice Letter
- November 8, 2017: Special Protocol Request Denied Letter
- October 24, 2017: Written Response Only Meeting Minutes
- August 14, 2017: PSP Initial Agreement Letter
- July 21, 2017: Advice/Information Request
- July 3, 2017: PSP Written Response
- December 8, 2016: Advice/Information Request Letter
- November 22, 2016: Information Request
- August 18, 2016: Advice Letter
- June 30, 2016: Advice Letter
- December 15, 2015: Written Response Only Meeting Minutes
- May 7, 2014: Advice/Information Request Letter
- January 27, 2012: Study May Proceed Letter

- May 12, 2011: Written Response Only Meeting Minutes
- May 12, 2011: Written Response Only Meeting Minutes

2.0 DISCUSSION

2.1. Regulatory

Question 15:

Does the Division agree with the Sponsor's proposal to file an original BLA for CCH for the treatment of EFP, commonly known as cellulite?

FDA Response to Question 15:

No. Submit an Efficacy Supplement to your existing application, BLA 125338 for Xiaflex.

Meeting Discussion:

The sponsor sought clarification on the Agency's position regarding the request for an efficacy supplement in lieu of a separate BLA. The Agency stated that the formulations of CCH are the same and an efficacy supplement continues to be strongly recommended. The sponsor provided the following clarifications regarding their rationale for a separate BLA submission:

- Anticipated differences in REMS requirements, labeling, methods of use, etc.;
- Different patient populations (males vs. females) and indications (medical vs. aesthetic);
- Minor differences in present formulation (e.g. excipients) and potential future formulation changes, additional indications sought, vial size, dilution/reconstitution, etc.; and
- Business reasons.

The Agency continues to recommend submission of an efficacy supplement to the existing BLA.

Question 17:

Does the Division anticipate that this BLA would be presented to an Advisory Committee prior to any action being taken?

FDA Response to Question 17:

The Agency will determine the need for an Advisory Committee upon receipt of your application. Soon after the filing period ends, you will be informed of our determination.

2.2. Chemistry, Manufacturing and Controls

Question 2:

Does the Division agree that the amount of stability data described would be sufficient to allow for a substantial review?

FDA Response to Question 2:

With regards to the amount of stability data described, we refer you to ICHQ5C concerning the stability testing of biotechnological/biological products. Final determination of the shelf life will be a review matter upon submission of your BLA efficacy supplement.

To support the determination of final product shelf life with stability data from pre-change representative clinical lots, you will need to submit comparative analytical and stability data, including comparative forced degradation study results, in your submission for review.

2.3. Nonclinical

Question 1:

As agreed between Endo and the DDDP at the End of Phase 2 meeting (Food and Drug Administration [FDA] Minutes dated February 22, 2017), the existing nonclinical pharmacology and toxicology data available under BLA 125338 are sufficient to support registration of CCH for EFP. As such, Endo intends to cross refer to BLA 125338 for all nonclinical pharmacology and toxicology studies and summary documents.

Does the Division agree?

FDA Response to Question 1:

See Agency response to Question 15. The existing nonclinical pharmacology and toxicology data currently available under BLA 125338 for Xiaflex are sufficient to support an efficacy supplement for the EFP indication.

2.4. Clinical Pharmacology

Question 3:

Does the Agency agree that the Phase 1 PK studies, EN3835-102 and EN3835-104, provide the basis for a complete clinical pharmacology package to register CCH at the dose of 0.84 mg for use in up to 2 treatment areas (0.84 mg per treatment area)?

FDA Response to Question 3:

The proposed Clinical Pharmacology package for registration of the proposed dose regiment of 0.84 mg/treatment area up to 2 treatment areas appears reasonable to support filing of the application. Adequacy of the data will be a review issue.

Question 4:

Does the Division agree with the use of validated methods under standard operating procedures (SOPs) SM3-272 and SM3-273 for analysis of study samples from of PK study EN3835-103?

FDA Response to Question 4:

We acknowledge that you have validated bioanalytical methods for the quantitation of your products according to your internal SOPs. We also acknowledge that the bioanalytical methods described in your SOPs (SM3-272 and SM3-273 documents) appear to be in compliance with the

current FDA Bioanalytical Method Validation Guidance (2018) with the exception of Section III.B.6 (Accuracy, Precision, and Recovery). We have noted that frozen-thawed calibration standards and quality control samples (QCs) were used for your accuracy and precision runs for the PK study EN3835-103; while, freshly prepared calibrators and QCs are recommended in the current guidance. In your BLA provide a justification to address this issue. We recommend that you submit your Bioanalytical Method Tabulated Summary according to the current Bioanalytical Method Validation Guidance (2018) in your future BAL submission. The bioanalytical method validation reports will be reviewed in detail at the time of your BLA submission.

Question 14:

Does the Division agree with the proposed approach for presenting immunogenicity data in the BLA?

FDA Response to Question 14:

Your proposal on presenting immunogenicity data in the BLA appears reasonable. In addition, we recommend that you evaluate the impact of immunogenicity (e.g. ADA, NAb, ADA titer levels) on CCH efficacy across Phase 2 and 3 studies and address this in your BLA submission.

2.5. Clinical/Biostatistics

Question 5:

Does the Division agree with the content and placement of the patient-reported outcomes (PRO) dossier?

FDA Response to Question 5:

Per guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*¹, if PRO information is provided electronically, it should be placed in section 5.3.5.3 of the electronic common technical document. This would also be applicable for other COA information (e.g., clinician-reported outcome assessments).

Please refer to previous communications surrounding the concerns regarding the additional COA instruments (i.e., Subject Global Aesthetic Improvement Scale (S-GAIS), Investigator Global Aesthetic Improvement Scale (I-GAIS), Patient-Reported Cellulite Impact Scale (PR-CIS), Subject Self-Rating Scale (SSRS), and Satisfaction with Cellulite Treatment Assessment (SCTA).

Question 6:

Does the Division agree that the proposed safety database is sufficient to allow for review of CCH for the EFP/cellulite indication?

FDA Response to Question 6:

You state that the safety data base of the application will include safety data from more than 900 subjects with EFP, including more than 500 subjects followed for 6 months and 189 subjects

¹ <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm193282.pdf>

followed for at least 12 months. The data base also includes 163 subjects who have had repeat exposure.

This safety data base is reasonable to allow for review of CCH for the proposed indication.

Question 7:

Does the Agency agree with the inclusion of digital images in the BLA submission (ie, electronic photographs) from the EN3835-205 sub-study as an appendix to the clinical study report (CSR)? Does the Agency have advice on formatting of the files in order to facilitate electronic submission?

FDA Response to Question 7:

You propose the addition of these photographs to the BLA to add value in the assessment of the known adverse event of bruising. This is a reasonable proposal.

From a technical standpoint (not content related), including digital images as appendices to CSR and tagged as “image”, is acceptable. However, please see additional comments below:

- Please refer to section 16. Appendices located <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073113.pdf> for more information.
- Please note that per FDA guidelines located at <https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/electronic submissions/ucm347471.pdf>, only the following image formats are accepted to be placed under module 5:
 - .bmp
 - .gif
 - .jpg or .jpeg
 - .png

Question 8:

Does the Division agree that the proposal as outlined in Section 1.3.4 meets the requirements of the 4-month safety update submission?

FDA Response to Question 8:

You propose to include in your application safety data for the treatment of EFP of the buttock area for both Phase 3 trials (EN3835-302 and EN3835-303) and the open-label trial (EN3835-304). In addition, you propose to include any serious adverse events (SAEs) from the ongoing “thigh development program”. You propose that the safety data from the open-label trial will be integrated into Pool 3 (all EN3835-treated 0.84 mg/area trials) of the ISS and associated Summary of Clinical Safety text will be updated accordingly at the time of the 4-month safety update. It is not clear from this proposal how much long-term safety data will be available for review at the time of the sBLA submission (see response to Question 12). We would recommend that at the time of the sBLA submission that at a minimum, 6 months of long term safety data from the open label trial (304) be included.

Question 9:

Does the Division agree with the inclusion of site level Bioresearch Monitoring (BIMO) data in the BLA for the 4 key studies (EN3835-201, EN3835-302, EN3835-303, and EN3835-304)?

FDA Response to Question 9:

Yes, we agree with the proposal to include site level BIMO data in the BLA for the 4 key studies mentioned above.

Question 10:

Does the Division agree with the proposal for submission of case report forms (CRFs) and patient narratives in the BLA?

FDA Response to Question 10:

The CRFs for each trial should be placed in a CRF folder under the applicable trial with a file tag of "case-report-forms."

1. Provide electronic links for the following:
 - a) all serious AEs
 - b) all severe AEs
 - c) all subjects discontinued regardless of reason
 - d) all deaths
2. CRF should be referenced under the trial in which it belongs and tagged as
 - a) "case report forms" in that trial's stf.xml file.
3. CRFs that are not submitted should be readily available upon request.

Yes, we agree with the proposal for submission of patient narratives in the BLA.

Question 11:

Does the Division agree with the proposal to include an Integrated Summary of Efficacy (ISE) and ISS in Module 5.3.5.3 referring to Modules 2.7.3 and 2.7.4 for the text portion of each integrated document and Module 5.3.5.3 to include tables, appendices, and datasets only?

FDA Response to Question 11:

If you believe Modules 2.7.3 and 2.7.4 would be sufficiently detailed to serve as the summary portion of the ISE and ISS, then your proposal to provide the text portion of the ISS and ISE in Modules 2.7.3 and 2.7.4 and the tables, appendices, and datasets in Module 5.3.5.3 in accordance with the guidance for industry, *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document* appears reasonable.

Question 12:

Does the Division agree with the data pools that will be utilized in the proposed integrated safety analyses?

FDA Response to Question 12:

Pool 1 data for the ISS will composed the 2 placebo-controlled double-blind Phase 3 trials (EN3835-302 and EN3835-303). This is reasonable. In addition, for this pool, provide raw incidence rates (at $\geq 1\%$) by treatment group.

Pool 2 will add the double-blind Phase 2 trial EN3835-201. The Phase 2 safety data should only include the subjects who received treatment in the buttocks. You should also include subjects from trial AUX-CC-831 who received 0.84 mg in the buttocks.

Pool 3 will include all the EN3835-treated 0.84 mg/area trials and will also include an updated 4-month safety update with available data from the Phase 3b open-label safety trial (EN3835-304). The pool should only include those treated in the buttock area. The Phase 3 trials (302 & 303) end at Day 71 and the open-label trial (304) begins 6 months after the end of the Phase 3 trials. Clarify where the local/systemic safety data during those 6 months between the end of the Phase 3 trials (302 and 303) and the beginning of the open label trial (304) will be included in the sBLA submission.

In addition, for your pooled analyses, provide:

- a. Line listings for all abnormal safety findings (e.g., adverse events, vital signs, etc.);
- b. Shift tables for all laboratory values. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate; and
- c. Shift tables for all vital signs. Provide the normal range of values for all parameters.

Provide safety data for any serious adverse events from the thigh trials separately.

Meeting Discussion:

The sponsor provided a written response document containing clarification to Questions 8 and 12; see appended document. No further discussion was required by the Agency or sponsor.

Question 13:

Does the Division agree with the pools that will be utilized in the proposed integrated efficacy analyses?

FDA Response to Question 13:

Pool 1 which pools data from the two double-blind Phase 3 studies (EN3835-302, EN3835-303) appears reasonable. You propose to also perform integrated efficacy analyses on Pool 2 which pools data from the double-blind Phase 2 study (EN3835-201) with data from the two Phase 3 studies (EN3835-302, EN3835-303). As EN3835-201 allowed for treatment of either the thigh or the buttock and the treatment effect appeared to differ by region, pooling efficacy results from both regions for the ISE does not appear to be appropriate.

While pooled analyses of the Phase 3 studies can be a component of the ISE, the ISE should include discussions regarding the strength of evidence across all studies, including discussion of any difference in outcomes across studies.

We note that the objective of the ISE is to support the analysis results obtained from the individual trials and not to establish a new efficacy claim based on pooling data from the individual trials. Therefore, while analyses based on pooled data may be performed for the ISE, such analyses are considered exploratory. Establishing an efficacy claim will be based on efficacy data from the individual Phase 3 trials to provide replication of study findings.

Question 16:

Does the Division agree with the overall contents of the planned BLA?

FDA Response to Question 16:

See responses to Questions 8 and 12.

Question 18:

Does the Agency agree with the assessment to support the conclusion that a REMS program would not be required?

FDA Response to Question 18:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Question 19:

Does the Division agree that no human factors studies would be required?

FDA Response to Question 19:

Based on the information that you have provided at this time, it is unlikely you will need to submit the results of a human factors (HF) validation study to the Agency. However, further consideration may be needed if a REMS is needed for this product.

Question 20:

Does the Division agree that a unique and separate USPI and trade name is appropriate for CCH for the treatment of cellulite?

FDA Response to Question 20:

The acceptability of a dual trade name will be a review issue. We recommend you submit a request for a proposed proprietary name review as soon as possible along with your justification for a dual trade name. If you require information on submitting a request for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022, (<https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf>)

Question 21:

Does the Division agree that the proposed labeling documents and artwork are acceptable in order to review the application?

FDA Response to Question 21:

At this time, this is a review issue.

Additional Comment:

Table 6 of the meeting package states that trials EN3835-302 and EN3835-303 enrolled 378 and 377 subjects respectively, while the protocols stated that it was planned to enroll approximately 420 subjects in each trial. Clarify this discrepancy.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U>

[CM360507.pdf](#). In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This

information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

Introduction:

Endo has received FDA's Preliminary Comments dated January 23, 2019 for the pre-submission meeting scheduled for January 30, 2019. Endo acknowledges the Division's responses to Questions 2-4, 6-7, 9-11, 13-14, and 16-21, and are not requesting any further input or discussion.

Endo is providing written responses to the remaining questions below and has indicated when appropriate if additional discussion is required.

FDA's Preliminary Response is written in **bold** followed by Endo's Response in *italics*.

FDA Response to Question 15:

No. Submit an Efficacy Supplement to your existing application, BLA 125338 for Xiaflex.

Endo response:

Endo does not agree with FDA's assessment to submit the application as an efficacy supplement and would like to better understand the Division's rationale for this response.

FDA Response to Question 1:

See Agency response to Question 15. The existing nonclinical pharmacology and toxicology data currently available under BLA 125338 for Xiaflex are sufficient to support an efficacy supplement for the EFP indication.

Endo response:

Endo would like to better understand the Agency's response to this question in light of our intent to submit a separate BLA. See response to Question 15.

FDA Response to Question 5:

Per guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*¹, if PRO information is provided electronically, it should be placed in section 5.3.5.3 of the electronic common technical document. This would also be applicable for other COA information (e.g., clinician-reported outcome assessments).

Please refer to previous communications surrounding the concerns regarding the additional COA instruments (i.e., Subject Global Aesthetic Improvement Scale (S-GAIS), Investigator Global Aesthetic Improvement Scale (I-GAIS), Patient-Reported Cellulite Impact Scale (PR-CIS), Subject Self-Rating Scale (SSRS), and Satisfaction with Cellulite Treatment Assessment (SCTA).

Endo response:

Endo agrees with the placement of the PRO dossier in section 5.3.5.3 and acknowledges the Division's previous communications surrounding the concerns regarding the additional COA instruments. Endo has completed content validity studies of the S-GAIS, SSRS and PR-CIS and is currently conducting a stand-alone test-retest study on these instruments. Quantitative

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measurement properties and ability to detect change as well as clinically meaningful changes are being further assessed for the S-GAIS, SSRS and PR-CIS as part of a secondary analysis of clinical trial data. In summary, results supporting the additional instruments will be documented and submitted to the Agency in the PRO dossier. No further discussion needed.

FDA Response to Question 8:

You propose to include in your application safety data for the treatment of EFP of the buttock area for both Phase 3 trials (EN3835-302 and EN3835-303) and the open-label trial (EN3835- 304). In addition, you propose to include any serious adverse events (SAEs) from the ongoing “thigh development program”. You propose that the safety data from the open-label trial will be integrated into Pool 3 (all EN3835-treated 0.84 mg/area trials) of the ISS and associated Summary of Clinical Safety text will be updated accordingly at the time of the 4-month safety update. It is not clear from this proposal how much long-term safety data will be available for review at the time of the sBLA submission (see response to Question 12). We would recommend that at the time of the sBLA submission that at a minimum, 6 months of long term safety data from the open label trial (304) be included.

Endo response:

Endo acknowledges the Division’s responses to Questions 8 and 12. We will submit 6 months long term safety data from the open label 304 rollover study at the time of the submission.

In addition, Endo would like to clarify the 304 study design. Study 304 is a 5-year long term rollover study that begins immediately following subject completion in the pivotal phase 3 studies (302/303). Study 304 Day 1 begins immediately after completion of Day 71 in the pivotal studies (302/303). Safety events that occur after the completion of the pivotal phase 3 studies are collected for all consented subjects. The first 6 months of the 304 study consist of site and subject blinded observation/assessment to evaluate response durability seen from the phase 3 pivotal studies and to collect safety data. After completion of the 6-month visit (Day 180) and unblinding of the phase 3 pivotal studies, all subjects and sites are unblinded and those who received placebo in the pivotal studies are discontinued. After the last subject enrolled completes the Day 180 visit, an interim data cut occurs. The CSR for 304 will provide 6 months of durability and long term safety data in the application at the time of submission. If this explanation suffices, no further discussion is needed.

FDA Response to Question 12:

Pool 1 data for the ISS will composed the 2 placebo-controlled double-blind Phase 3 trials (EN3835-302 and EN3835-303). This is reasonable. In addition, for this pool, provide raw incidence rates (at $\geq 1\%$) by treatment group.

Pool 2 will add the double-blind Phase 2 trial EN3835-201. The Phase 2 safety data should only include the subjects who received treatment in the buttocks. You should also include subjects from trial AUX-CC-831 who received 0.84 mg in the buttocks.

Pool 3 will include all the EN3835-treated 0.84 mg/area trials and will also include an updated 4-month safety update with available data from the Phase 3b open-label safety

trial (EN3835-304). The pool should only include those treated in the buttock area. The Phase 3 trials (302 & 303) end at Day 71 and the open-label trial (304) begins 6 months after the end of the Phase 3 trials. Clarify where the local/systemic safety data during those 6 months between the end of the Phase 3 trials (302 and 303) and the beginning of the open label trial (304) will be included in the sBLA submission.

In addition, for your pooled analyses, provide:

- a. Line listings for all abnormal safety findings (e.g., adverse events, vital signs, etc.);
- b. Shift tables for all laboratory values. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate; and
- c. Shift tables for all vital signs. Provide the normal range of values for all parameters.

Provide safety data for any serious adverse events from the thigh trials separately.

Endo response:

Endo agrees with the Agency's recommendation and will include raw incidence rates (at $\geq 1\%$) by treatment group for Pool 1. Pool 2 will include subjects from AUX-CC-831. Endo agrees that the integrated safety analysis should be differentiated between buttock and thigh for all studies.

Endo would like to reiterate the design of study 304. All consented subjects immediately rollover from the pivotal phase 3 studies (302/303) into study 304 (See Response to Question 8). The local/systemic safety data collected from the 304 study will be submitted in a CSR at the time of submission.

In addition, pooled analyses will be provided as recommended in lines a-c above and the SAEs from the thigh program will not be integrated into these pools. If this explanation suffices, no further discussion is needed.

FDA additional comment:

Table 6 of the meeting package states that trials EN3835-302 and EN3835-303 enrolled 378 and 377 subjects respectively, while the protocols stated that it was planned to enroll approximately 420 subjects in each trial. Clarify this discrepancy

Endo response:

Table 6 inadvertently included the number of subjects who completed studies 302/303 as opposed to the number of subjects enrolled. The correct numbers of subjects enrolled are below and therefore we believe this resolves the discrepancy.

- EN3835-302=423 enrolled subjects
- EN3835-303=422 enrolled subjects

*Endo Pharmaceuticals
Confidential*

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KENDALL A MARCUS
02/06/2019 08:09:23 PM



IND 110077

MEETING MINUTES

Auxilium Pharmaceuticals, LLC
c/o Endo Pharmaceuticals Inc.
Attention: Tara Chapman, PharmD
Senior Director, Regulatory Affairs
1400 Atwater Drive
Malvern, PA 19355

Dear Dr. Chapman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for collagenase clostridium histolyticum, for injection.

We also refer to the teleconference between representatives of your firm and the FDA on February 8, 2017. The purpose of the meeting was to discuss the development program for collagenase clostridium histolyticum, for injection.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cristina Attinello, Senior Regulatory Project Manager at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD, FAAD
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: February 8, 2017 at 11 AM
Meeting Location: WO 22, Rm. 1313

Application Number: IND 110077
Product Name: collagenase clostridium histolyticum, for injection
Proposed Indication: for the treatment of edematous fibrosclerotic panniculopathy (EFP) in adult patients

Sponsor Name: Auxilium Pharmaceuticals, LLC

Meeting Chair: Jill Lindstrom, MD
Meeting Recorder: Cristina Attinello, MPH

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III
Jill Lindstrom, MD, Deputy Director, DDDP
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Denise Cook, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III
Carin Kim, PhD, Biostatistics Reviewer, DB III
Rebecca Hager, PhD, Biostatistics Reviewer, DB III
Hae-Young Ahn, PhD, Deputy Director, DCP 3
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, DCP3
Luke Oh, PhD, Clinical Pharmacology Reviewer, DCP 3
Selena Daniels, PharmD, MS, Clinical Outcome Assessment Reviewer, COA Staff
Brian Roelofs, PhD, Chemistry Reviewer, OBP
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Cristina Attinello, MPH, Senior Regulatory Health Project Manager, DDDP
Cecilia Robinson, MPH, Regulatory Health Project Manager, DDDP
Angela Brown, MPH, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Tara Chapman, PharmD, Senior Director, Regulatory Affairs
Jeff Davidson, PhD, Vice President, Biometrics

Matthew Davis, MD, RPh, Senior Vice President, Research and Development Branded Pharmaceuticals

Frank Diana, PhD, Vice President, Pharmaceutical Development

Glen Frick, MD, PhD, Vice President, Clinical Development and Operations

Genzhou Liu, PhD, Director, Biostatistics

William McIntyre, PhD, Senior Vice President, Regulatory Affairs

Mike McLane, PhD, Director, Clinical Development

Rosanne Middleton, Manager, Regulatory Affairs

Tony Priestley, PhD, Senior Director, Pharmacology

Harris Rotman, PhD, Vice President, Regulatory Affairs

1.0 BACKGROUND

Purpose of Teleconference:

The primary purpose of this teleconference is to discuss the development program for collagenase clostridium histolyticum

Regulatory Correspondence History:

We have had the following teleconference with you:

- December 14, 2015: Guidance Teleconference
- December 17, 2014: Guidance Teleconference

We have sent the following correspondences:

- December 8, 2016: Advice/Information Request Letter
- November 22, 2016: Information Request
- August 18, 2016: Advice Letter
- June 30, 2016: Advice Letter
- December 15, 2015: Written Response Only Meeting Minutes
- May 7, 2014: Advice/Information Request Letter
- January 27, 2012: Study May Proceed Letter
- May 12, 2011: Written Response Only Meeting Minutes

2.0 DISCUSSION

2.1. Nonclinical/Pharmacokinetics

Question 1:

Based on the available nonclinical data relating to EN3835, does the Agency agree that no additional pharmacology/toxicology work is required to support the filing and approval for EFP?

FDA Response to Question 1:

We agree that the available nonclinical data support submission of a BLA for EN3835 for EFP.

2.2. Chemistry, Manufacturing and Controls (CMC)

No CMC questions were provided in the meeting package; however, we have the following comment:

The CMC information (section 9) was inappropriately included in your End of Phase 2 Type B meeting package (12/16/2016). Pursuant to 21 CFR 312.31(a)(1), “New toxicology, chemistry, or other technical information” should be reported as an IND information amendment. Submit this information at least 30 days prior to the initiation of your Phase 3 study and follow all of the directives in 21 CFR 312.31(b).

2.3. Clinical/Clinical Pharmacology/Biostatistics

Introductory Comments

In this submission, you presented your Phase 2a trial (AUX-CC-831) results in 150 female subjects, where the trial utilized several different scales. Your results included the mean score change from baseline in the Cellulite Severity Scale (CSS) at Day 73 as well as the mean score change from baseline for the subject Cellulite Severity Item (CSI). It was based on this Phase 2a study that you selected the high-dose (0.84 mg) to pursue in your Phase 3 trials.

For your Phase 2b trial (EN3835-201) results, you presented composite response [i.e., ≥ 2 -point improvement on both the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) and the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)] rates of 10.6% and 1.6% for EN3835 and placebo, respectively. You proposed to use such estimates to calculate your sample size for your Phase 3 trials. However, it should be noted that your composite response results by region (buttocks vs. thigh) showed substantial difference where the treatment effects for the buttock and thigh were 13% and 4%, respectively. Given the difference in treatment effect by region, it is not clear whether you plan to use such information in designing your future development program.

As your Phase 2a study utilized several different scales that might have limited regulatory utility (per our Advice Letter dated 5/7/2014), and as you only presented bullet-point, high-level results for your Phase 2b trial that used the CR-PCSS and the PR-PCSS, the following information will be helpful to make better judgment regarding the treatment effects of EN3835:

- Shift tables for efficacy agreement in CR-PCSS score and in PR-PCSS score, at baseline and at Day 73 (e.g. 5x5 table that will show agreements along the diagonal and disagreements along the non-diagonals)
- Shift table of clinician CR-PCSS score at baseline (rows) and at Day 73 (columns)
- Shift table of subject PR-PCSS score at baseline (rows) and at Day 73 (columns)

In the absence of having detailed analyses in assessing the agreement between the investigator and subject assessment scales, it might be difficult to make a meaningful interpretation of your results and whether they would provide reliable estimates of treatment effect to power your future Phase 3 trials. Consequently, it would be difficult for the Agency to concur with the design of your planned Phase 3 trials.

Meeting Discussion:

In advance of the meeting, the sponsor provided a response document that included areas of clarification. The document is appended to these minutes.

There was extensive discussion concerning study design and assessment of efficacy and safety by region. The sponsor clarified that they propose to combine efficacy results from individually treated regions (either buttock or thigh for a given subject). In response, the Agency noted that treatment effect in the clinical trial would be driven by the proportion of subjects treated in each region as the response rate varied by region. The Agency advised the sponsor to consider a study design that reflects the prevalence of cellulite in the general patient population. In addition, as treatment may be used for both regions, information about safety and efficacy of concurrent treatment of both areas would be helpful for interpretation of study findings, even though one prespecified region would be assessed for efficacy.

With regard to dosing, the sponsor clarified that the volume would be fixed; however, the number of injections and number of treatment cycles might vary depending on the patient response. The Agency noted that as the number of treatment cycles may vary by severity and the patient's background factors, the sponsor should consider such factors when estimating the treatment effect.

Question 2:

Does the Agency agree that the available pharmacokinetic data, showing no systemic exposure, is sufficient and no additional pharmacokinetic data is needed for the Phase 3 studies, the filing and approval for EFP?

FDA Response to Question 2:

We acknowledge that you plan to conduct a PK study at 1.68 mg EN3835 for which we have a comment in response to Question 3. If Study EN3835-103 evaluates two dose levels (1.68 mg and 0.84 mg), we would agree that you do not need to collect PK data in the Phase 3 studies evaluating 0.84 mg EN3835.

Question 3:

Does the Agency concur with Study EN3835-103 to profile pharmacokinetics (PK) after a concomitant subcutaneous dose of 1.68 mg into 2 quadrants (0.84 mg/quadrant)?

FDA Response to Question 3:

We agree with your plan to evaluate the systemic exposure of EN3835 for a dose higher than that planned for the Phase 3 studies. However, we recommend that you add an additional treatment arm for 0.84 mg EN3835 to further characterize the PK of EN3835 because 0.84 mg appears to be the potentially therapeutic dose for EN3835. The results will enhance the overall PK data package. We may have additional comments when we review your study protocol in a future IND submission. Also, see our response to Question 2.

Question 4:

Endo believes that if no systemic exposure is observed after concomitant dosing of 2 quadrants no additional data will be required to be collected for concomitant dosing of 2 quadrants. Does the Agency concur?

FDA Response to Question 4:

As the nature of the question is not immediately clear to us, we will provide comment based on our interpretation of this question. We interpret that your question applies to the condition when results of Study EN3835-103 show no systemic exposure at the dose of 1.68 mg, and your proposal is not to collect additional PK data in the two pivotal phase studies. See our response to Questions 2 and 3.

Meeting Discussion:

The Agency agreed that if data from Study EN3835-103 shows no systemic exposure, no additional PK data for the dose of 0.84 mg will be needed. However, if any systemic exposure is detected, the Agency recommends inclusion of PK assessment in a subset of subjects in the Phase 3 studies.

Question 5:

Endo believes that the Clinical-Reported Photometric Cellulite Severity Scale (CR-PCSS) and Patient-Reported Photometric Cellulite Severity Scale (PR-PCSS) are reliable and valid clinician-reported and patient-reported instruments (clinician-reported outcome [CRO] and patient-reported outcome [PRO], respectively) that will be used to assess improvement in cellulite in pivotal studies. Does the Agency concur?

FDA Response to Question 5:

In principle, the content validity for the CR-PCSS and PR-PCSS appears to be reasonably established. There are some concerns surrounding the reliability of the proposed instruments; however, they are not critical and could probably be improved upon with appropriate training and standardization.

The following comments are not regulatory requirements, but offered in the spirit of improving measurement and, therefore, maximizing the opportunity for your study to successfully demonstrate efficacy.

CR-PCSS

1. There is concern that the buttock photographs used in the 'Mild' and 'Moderate' categories are problematic based on the expert input. Three out of the five clinicians (60%) reported that the photos in the 'Moderate' and 'Mild' categories are very similar (page 23 of the Study EVA-18167-00 qualitative summary report ("*Cognitive Interviews with Clinicians to Confirm the Content Validity of the CR-PCSS*").
2. See response to Question 9 in regards to the reliability of the CR-PCSS via live assessment.

PR-PCSS

3. Clarify whether all patients reported that the descriptors appropriately matched the cellulite severity for the PR-PCSS thigh scale. The qualitative summary report indicates only two patients reported that the descriptors were appropriate:
'Participants were also questioned on whether they felt the descriptors match the cellulite severity; descriptors were appropriate as more dimples meant greater thigh cellulite severity (n=2).' (page 13 of the Study EVA-18167-00 qualitative summary report ("Cognitive Interviews with Patients to Confirm the Content Validity of the PR-PCSS"))
4. For the buttock ratings, the 'Moderate' category showed the lowest level of agreement, while for the thigh ratings, the 'Mild' category showed the lowest level of agreement across the two visits. Because your target population are subjects with moderate to severe cellulite and the primary endpoint is a ≥ 2 -category change, these low level of agreements in these categories are concerning as they may minimize the opportunity for your study to successfully demonstrate efficacy. Subject training in these scales will be important.
5. Provide patient interview transcripts, if available.

Question 6:

Does the Agency agree that a composite primary efficacy endpoint,

Composite 2-level CR-PCSS response and 2-level PR-PCSS response at day 71 (ie, the proportion of subjects who had at least a 2-level improvement in both the CR-PCSS and the PR-PCSS),

is appropriate for pivotal studies of EN3835 for improvement of cellulite?

FDA Response to Question 6:

Provided that there is good agreement between the CR-PCSS and the PR-PCSS, a composite primary endpoint composed of both the CR-PCSS and the PR-PCSS with at least a 2-level improvement in both scales, would be an appropriate primary efficacy endpoint for this aesthetic indication. See Introductory Comments and response to Question 5.

Question 7:

The Sponsor's Phase 2 study results show statistically significant improvements in number of 1-point responders in PR-PCSS of EN3835-treated subjects (72.3%) and Subject Global Aesthetic Improvement Scale (S-GAIS) responders with score of 1 or greater in EN3835-treated subjects (73.1%) compared to placebo treated subjects (51.6% and 43.7%, respectively). The Sponsor believes these are appropriate key secondary endpoints that would potentially be supportive (b) (4), if they achieve statistical significance in Phase 3 studies. Does the Agency agree?

FDA Response to Question 7:

In general, we view global ratings (i.e., I-GAIS, S-GAIS) as exploratory measures that can be used as anchors for determining what constitutes a clinically meaningful change in another measure.

In the absence of an objective measure of efficacy, a one-point change in PR-PCSS should be anchored to a two-point change in S-GAIS.

In the absence of agreement between the two scales (PR-PCSS and the CR-PCSS), it would be difficult to concur that an improvement in one scale, of one point, would be clinically meaningful. It should be noted that a one grade improvement in one scale, if associated with improvement of at least one grade with the other scale, could be clinically meaningful and may support the finding of the primary endpoint (the composite of the two scales).

(b) (4)

The synopses specified that the details regarding the hierarchical order of the endpoints would be specified in the SAP. Note that the SAP should be submitted as part of the protocol.

The Agency advised that to preserve the integrity of the Phase 3 trials, protocols should include important details relevant to the study design, conduct and analysis methods, which should be prespecified prior to the initiation of the trials. The Agency recommended that the SAPs be submitted along with the protocols for Agency comment.

Question 8:

The Sponsor's Phase 2 study results show 72.3% of EN3835-treated subjects were responders with a 1-level improvement in cellulite severity (PR-PCSS) compared to 51.6% in placebo-treated subjects and 10.6% were composite responders with a 2-level improvement compared to 1.6% in placebo-treated subjects. The Sponsor believes these are appropriate, meaningful, and approvable rates of response, if demonstrated in Phase 3 studies. Does the Agency concur?

FDA Response to Question 8:

See response to Question 7.

Meeting Discussion:

The Agency stated that this will be a review issue.

Question 9:

Does that Agency agree that the test-retest reliability study of the CR-PCSS conducted using digital images of cellulite supports the use of the CR-PCSS utilizing live assessments?

FDA Response to Question 9:

No. You have not provided data to support that the two modes of assessment for CR-PCSS (i.e., digital images and live assessment) would be equivalent. Because your primary efficacy endpoint is based on the use of the CR-PCSS via live assessment, and due to some of the issues observed from your test-retest reliability results (see below), we recommend you perform similar analyses using the live assessment CR-PCSS data collected in your Phase 2b trial to confirm the reliability of the CR-PCSS and other measurement properties where feasible. This does not preclude you from using the CR-PCSS in your planned trials; however you will be taking a risk

proceeding to Phase 3 without fully evaluating the measurement properties of the CR-PCSS via live assessment.

Although the test-retest reliability estimates for the CR-PCSS via digital assessment fall in the acceptable range, the data should be interpreted cautiously as your study has limitations as noted in your final report. Below are our specific comments on the results from your CR-PCSS test-retest reliability study.

1. The photographs tested did not seem to cover the full spectrum of cellulite severity. The images selected for the study were rated by the clinicians as predominantly falling in the 'Almost None,' 'Mild,' and 'Moderate' categories, with 'Almost None' being the most frequently represented category, and considerably fewer images in the 'None' and 'Severe' categories. Your target population is subjects with moderate to severe cellulite; however, there was minimal representation of severe subjects, which limits interpretation of reliability in this subgroup. This would be more of a concern if digital assessment was being used for the primary endpoint.
2. There were notable differences in cellulite severity ratings between Assessment 1 and 2 evaluations among the clinicians. It would be expected that the ratings would not change so much as the clinicians were viewing the same images at both time points, which obviated any change in disease state or cellulite severity. However, +1-category changes were demonstrated between ratings from Assessments 1 and 2 for both the buttock (14% to 39%) and thigh (12% to 42%) photographs, as well as -1-category changes (buttock: 3 to 16%; thigh: 3 to 19%) (Tables 3.3 and 4.3 in *Test-Retest of the CR-PCSS Study Report*).
3. There was minimal agreement on the cellulite severity ratings between all five clinicians and panel consensus ratings. All five clinicians collectively agreed with the panel consensus ratings in approximately one-third or less of the images for both thigh and buttocks, separately. Further there was notable variability of agreement between clinicians for both buttock (Assessment 1: 53-72%; Assessment 2: 56-73%) and thigh (Assessment 1: 39-65%; Assessment 2: 39-70%) images (Tables 7.1-7.2 and 8.1-8.2 in *Test-Retest of the CR-PCSS Study Report*).

Because of these noted issues, ensuring appropriate training and a standardized approach to assessment and administration (e.g., lighting conditions, photographs, etc.) will be critical to maximize the opportunity for your study to successfully demonstrate efficacy regardless of the mode of assessment (refer to response to Question 5).

Meeting Discussion:

The sponsor confirmed that clinicians would be assessing the same subjects and quadrant area with the same CR-PCSS score at the following timepoints:

- Screening and Day 1 Visits of Study EN3835-201
- Screening Visits at Study EN3835-201 and Study EN3835-202

The Agency agreed that the sponsor's approach to evaluate test-retest reliability appeared reasonable.

Question 10:

Does the Agency agree with the proposed immunogenicity profiling with assessments (ie, antibody titers) in the pivotal studies at beginning (pre-treatment) and end of study?

FDA Response to Question 10:

We do not agree. We recommend that you analyze all immunogenicity samples collected on Days 1 (pre-treatment), 22, 43, and 71 (end of study) for the assessment of immunogenicity potential of EN3835 in subjects with EFP. Because subjects with EFP will receive repeated SC injection in the proposed Phase 3 studies, the immunogenicity profile, including the time course of anti-drug antibody (ADA) formation and the extent of neutralizing activity of ADA, can be different from those observed in the clinical studies for the approved indications. We note that the population of specialized immune cells in target tissue of EFP (subcutaneous fat) could be different from the immune cells in the target tissues in Dupuytren's contracture and Peyronie's disease. The proposed SC injection can also trigger immunological cascade, which may be different from immune response to intralesional injection in Dupuytren's contracture and Peyronie's disease, possibly leading to different dynamic course of immunogenicity. In addition, we may have additional comments when we receive the full protocol of your proposed Phase 3 studies.

Meeting Discussion:

The Agency agreed with the proposal (see appended document from sponsor), with the caveat that we may request analysis of additional samples if there are safety signals from the studies. The sponsor indicated that they will retain all collected samples for such analysis, should it be needed.

Question 11:

Does the Agency agree that the planned safety database is sufficient for registration of EN3835 for this indication?

FDA Response to Question 11:

You plan to enroll 900 subjects in the two planned Phase 3 trials, with 450 subjects to be treated with EN3835. This is a reasonable number of subjects to evaluate safety of your drug product in the placebo controlled portion of your Phase 3 trials. Your drug product for the treatment of EFP has the potential for chronic intermittent use, therefore you should establish the long term safety of your product in the population. You will need to determine the duration of effect of your drug product in order to assess the long term safety of your drug product with repeat exposures.

Question 12:

Does the Agency agree with the number of subjects and planned timings of assessments proposed to assess safety after re-exposure?

FDA Response to Question 12:

You plan to follow 300 subjects for 6 months and 100 subjects for 12 months, yet you only plan to re-expose 50 to 70 of the total subjects in your Phase 2b trial to EN3835. Evaluating the safety of your drug product after multiple exposures would be an important safety issue to consider in the evaluation of your drug product for EFP. To adequately do this, you will have to

ascertain the duration of effect and then design a study to evaluate repeat exposures. We cannot ascertain, at this time, the duration of time that would be needed to gather this data.

Question 13:

Does the Agency agree with the proposed definition of durability and obtaining durability in study EN3835-202 as described?

FDA Response to Question 13:

Your definition of durability (from the open label Phase 2 trial) was the time duration from first improvement in PR-PCSS and/or CR-PCSS until the time at which the PR-PCSS and CR-PCSS ratings are equal to or worse than the baseline ratings for that quadrant. We don't agree with this definition. We would prefer that the time point of durability should begin at the efficacy evaluation time point and it should end when the subject fails to be a success.

Meeting Discussion:

There was extensive discussion regarding safety informational needs. The sponsor inquired whether their proposal was fileable. The Agency responded that the proposal appeared fileable, but emphasized the importance of understanding duration of effect of their product, and potential informational needs related to retreatment that may extend from that.

Question 14:

Does the Agency agree with the proposed final assessment of 28 days post last treatment in the Phase 3 pivotal studies?

FDA Response to Question 14:

The briefing package states that the most common TEAEs in the Phase 2 trials were at the injection site and consisted of injection site bruising, injection site pain, injection site pruritus, injection site nodule, swelling, induration, erythema, and discoloration. The most common AEs were injection site bruising and pain. These AEs tended to resolve before the next visit and the median duration was 11-15 days for injection site bruising and 4-5 days for injection site pain. Thus, a 28-day follow-up post last injection seems reasonable.

Question 15:

Does the Agency agree with the sample size and power estimation for each of our Phase 3 clinical trials?

FDA Response to Question 15:

Whether the study is powered sufficiently for your Phase 3 trials will depend on having reliable estimates of treatment effect for the endpoint recommended by us. Given the lack of information concerning the agreement in the clinician and subject scales, it would be difficult to comment on the adequacy of powering your Phase 3 trials. See Introductory Comments.

Question 16:

Does the Agency agree with the proposed procedures to replace missing data?

FDA Response to Question 16:

For handling of missing data, you proposed that subjects without any post-injection evaluation for either CR-PCSS or PR-PCSS will be considered as non-responders, and also stated that the last observation carried forward (LOCF) will be used to handling missing data at Day 71. Because the scientific justification for LOCF is limited, you should provide a rationale for why LOCF is appropriate in this situation or propose an alternate method that has a reasonable justification.

Question 17:

Does the Agency agree with the pivotal trials enrollment of adult women only?

FDA Response to Question 17:

Provide your rationale for excluding men from your Phase 3 trials. Include this in the IND with the submission of your Phase 3 protocol.

Additional Comments-Clinical Outcome Assessments

Comments regarding Photography User Manual:

1. Clarify whether subjects and clinicians are forced to complete a response for each treatment quadrant in the electronic applications (e.g., PCSS, S-GAIS, I-GAIS) before advancing to the next screen.
2. Clarify whether there is a “finish” button/screen to indicate the end of the subjects’ and/or clinicians’ assessment in the electronic applications (e.g., PCSS, S-GAIS, I-GAIS) or if the site is able to see the individual’s last response when closing out the application.
3. We recommend you have a back-up plan (e.g., paper, web-based) implemented in the case there are any malfunctions with the electronic applications. Additionally, we suggest you perform usability testing of the applications prior to the start of the trial to orient the subjects and clinicians.

Comments regarding CR-PCSS User Manual:

4. Lighting conditions for the live assessments should be standardized across all sites.
5. The user manual should be updated with training and qualification for the pivotal trials.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized

format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

Site number

Principal investigator

Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)

Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:

Number of subjects screened at each site

Number of subjects randomized at each site

Number of subjects treated who prematurely discontinued for each site by site

Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:

Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

Subject listing for treatment assignment (randomization)

Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued

Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol

By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)

By subject listing, of AEs, SAEs, deaths and dates

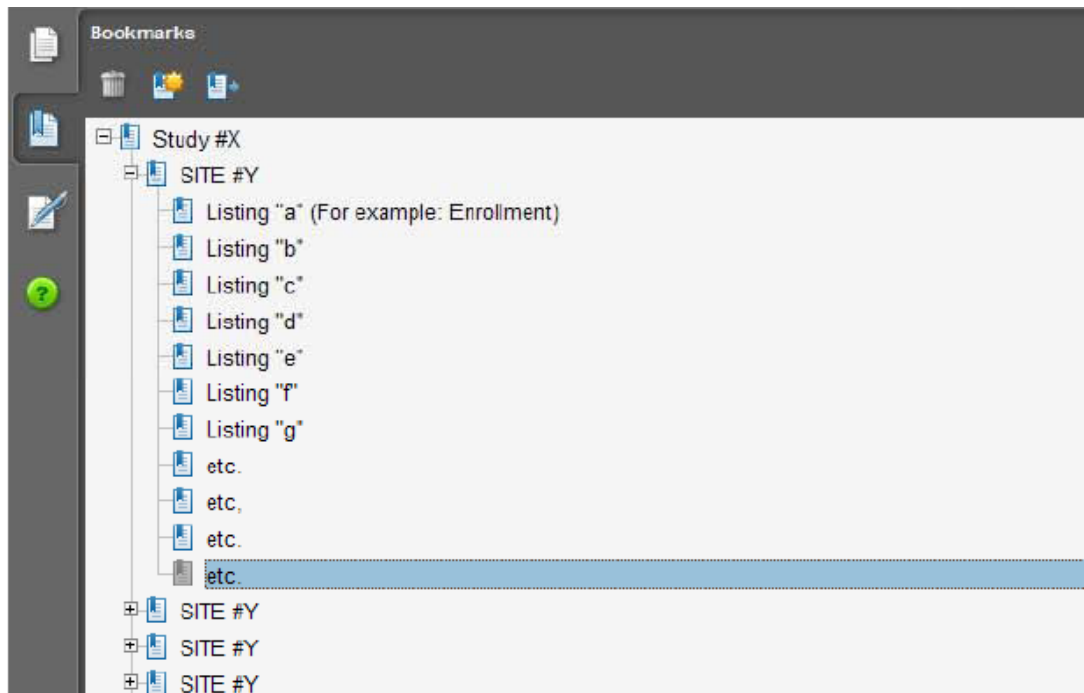
By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.

By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

In response to the Meeting Preliminary Comments provided by FDA on February 6, 2017, Endo has the following clarifications. Only those questions that Endo requires clarification or comment on are listed. Endo's clarifications are listed under the FDA comment in bold, italics font.

Chemistry, Manufacturing and Controls (CMC)

Endo Clarification:

Endo acknowledges the FDA comment and will provide the information as an IND information amendment at least 30 days prior to the initiation of our Phase 3 studies.

Clinical/Biometrics

FDA Introductory Comments:

For your Phase 2b trial (EN3835-201) results, you presented composite response [i.e., ≥ 2 -point improvement on both the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) and the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)] rates of 10.6% and 1.6% for EN3835 and placebo, respectively. You proposed to use such estimates to calculate your sample size for your Phase 3 trials. However, it should be noted that your composite response results by region (buttocks vs. thigh) showed substantial difference where the treatment effects for the buttock and thigh were 13% and 4%, respectively. Given the difference in treatment effect by region, it is not clear whether you plan to use such information in designing your future development program.

As your Phase 2a study utilized several different scales that might have limited regulatory utility (per our Advice Letter dated 5/7/2014), and as you only presented bullet-point, high-level results for your Phase 2b trial that used the CR-PCSS and the PR-PCSS, the following information will be helpful to make better judgment regarding the treatment effects of EN3835:

- Shift tables for efficacy agreement in CR-PCSS score and in PR-PCSS score, at baseline and at Day 73 (e.g. 5x5 table that will show agreements along the diagonal and disagreements along the non-diagonals)
- Shift table of clinician CR-PCSS score at baseline (rows) and at Day 73 (columns)
- Shift table of subject PR-PCSS score at baseline (rows) and at Day 73 (columns)

In the absence of having detailed analyses in assessing the agreement between the investigator and subject assessment scales, it might be difficult to make a meaningful interpretation of your results and whether they would provide reliable estimates of treatment effect to power your future Phase 3 trials. Consequently, it would be difficult for the Agency to concur with the design of your planned Phase 3 trials.

Endo Clarification:

The Sponsor envisions that a therapy that treats EFP will be used in the predominant areas in which EFP is located i.e., the buttocks and the posterolateral thighs. The Sponsor plans to select and administer EN3835 in both regions in our Phase 3 clinical trials and combine the efficacy results from both regions into a single primary endpoint analyses of changes of the

EFP severity of the treated area. The Phase 3 studies will not be powered to observe significant differences of the primary endpoint by region (i.e., buttock or thigh). However we plan to stratify the randomization by region to prevent an imbalance between treatment groups. Does the Division concur with this proposal?

Endo proposes the following tables to be prepared by treatment and region as requested in bullets #1 – 3 above:

Proposed Table 1: Day 1 agreement between PR-PCSS and CR-PCSS

		CR-PCSS				
		0	1	2	3	4
PR-PCSS	0					
	1					
	2					
	3					
	4					

Proposed Table 2: Day 71 agreement between PR-PCSS and CR-PCSS

		CR-PCSS				
		0	1	2	3	4
PR-PCSS	0					
	1					
	2					
	3					
	4					

Proposed Table 3: Change from baseline to day 71. Comparison between PR-PCSS and CR-PCSS

		CR-PCSS					
		-4	-3	-2	-1	0	+1
PR-PCSS	-4						
	-3						
	-2						
	-1						
	0						
	+1						

Proposed Table 4: Shift table of clinician CR-PCSS score at baseline (rows) and at Day 71 (columns)

		CR-PCSS Day 71				
		0	1	2	3	4
CR-PCSS Day 1	0					
	1					
	2					
	3					
	4					

Proposed Table 5: Shift table of clinician PR-PCSS score at baseline (rows) and at Day 71 (columns)

		PR-PCSS Day 71				
		0	1	2	3	4
PR-PCSS Day 1	0					
	1					
	2					
	3					
	4					

Can the Division confirm the proposed tables are acceptable per the request in bullets #1 - #3 above?

Endo intends to respond to your request for the agreed to shift tables by the end of this week (February 10, 2017). In addition, the Phase 3 trials are scheduled to begin in June 2017. Can the Agency provide a tentative response timeline for the questions that required additional information before definitive responses could be provided? Endo has made note of these questions in this clarification document.

Question 2: Does the Agency agree that the available pharmacokinetic data, showing no systemic exposure, is sufficient and no additional pharmacokinetic data is needed for the Phase 3 studies, the filing and approval for EFP?

FDA Response:

We acknowledge that you plan to conduct a PK study at 1.68 mg EN3835 for which we have a comment in response to Question 3. If Study EN3835-103 evaluates two dose levels (1.68 mg and 0.84 mg), we would agree that you do not need to collect PK data in the Phase 3 studies evaluating 0.84 mg EN3835.

Endo Clarification:

See Endo Clarification Question 3.

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Question 3: Does the Agency concur with Study EN3835-103 to profile pharmacokinetics (PK) after a concomitant subcutaneous dose of 1.68 mg into 2 quadrants (0.84 mg/quadrant)?

FDA Response:

We agree with your plan to evaluate the systemic exposure of EN3835 for a dose higher than that planned for the Phase 3 studies. However, we recommend that you add an additional treatment arm for 0.84 mg EN3835 to further characterize the PK of EN3835 because 0.84 mg appears to be the potentially therapeutic dose for EN3835. The results will enhance the overall PK data package. We may have additional comments when we review your study protocol in a future IND submission. Also, see our response to Question 2.

Endo Clarification:

FDA are proposing that both 0.84 mg and 1.68 mg dose levels be assessed for systemic exposure in Study EN3835-103. Endo would like to take this opportunity to clarify that the 0.84 mg dose level was subject to a full pharmacokinetic assessment in 11 female subjects as part of the EN3835-102 study. EN3835 was administered to EN3835-102 study subjects in precisely the same manner as is being proposed in the protocol for Study EN3835-103 and in no instances were measurable plasma exposures to EN3835 detected at any of the sampling time points (intensive for 24 hours followed by 2, 7 and 21 days). Our intention in Study EN3835-103 was not to replicate the 0.84 mg dose level but, rather, to extend the assessment only to the higher 1.68 mg dose. If, as expected, no systemic exposure is detected at the 1.68 mg dose, does the Agency agree that the aggregate data from studies EN3835-102 and -103 would be sufficient and that no additional PK would be required in the planned Phase 3 studies?

Question 4: Endo believes that if no systemic exposure is observed after concomitant dosing of 2 quadrants no additional data will be required to be collected for concomitant dosing of 2 quadrants. Does the Agency concur?

FDA Response:

As the nature of the question is not immediately clear to us, we will provide comment based on our interpretation of this question. We interpret that your question applies to the condition when results of Study EN3835-103 show no systemic exposure at the dose of 1.68 mg, and your proposal is not to collect additional PK data in the two pivotal phase studies. See our response to Questions 2 and 3.

Endo Clarification:

Endo confirms your interpretation is correct. No additional clarification is necessary.

Question 5: Endo believes that the Clinical-Reported Photometric Cellulite Severity Scale (CR-PCSS) and Patient-Reported Photometric Cellulite Severity Scale (PR-PCSS) are reliable and valid clinician-reported and patient-reported instruments (clinician-reported outcome [CRO] and patient-reported outcome [PRO], respectively) that will be used to assess improvement in cellulite in pivotal studies. Does the Agency concur?

FDA Response:

In principle, the content validity for the CR-PCSS and PR-PCSS appears to be reasonably established. There are some concerns surrounding the reliability of the proposed instruments; however, they are not critical and could probably be improved upon with appropriate training and standardization.

The following comments are not regulatory requirements, but offered in the spirit of improving measurement and, therefore, maximizing the opportunity for your study to successfully demonstrate efficacy.

CR-PCSS

1. There is concern that the buttock photographs used in the 'Mild' and 'Moderate' categories are problematic based on the expert input. Three out of the five clinicians (60%) reported that the photos in the 'Moderate' and 'Mild' categories are very similar (page 23 of the Study EVA-18167-00 qualitative summary report ("*Cognitive Interviews with Clinicians to Confirm the Content Validity of the CR-PCSS*").
2. See response to Question 9 in regards to the reliability of the CR-PCSS via live assessment.

PR-PCSS

3. Clarify whether all patients reported that the descriptors appropriately matched the cellulite severity for the PR-PCSS thigh scale. The qualitative summary report indicates only two patients reported that the descriptors were appropriate: '*Participants were also questioned on whether they felt the descriptors match the cellulite severity; descriptors were appropriate as more dimples meant greater thigh cellulite severity (n=2).*' (page 13 of the Study EVA-18167-00 qualitative summary report ("*Cognitive Interviews with Patients to Confirm the Content Validity of the PR-PCSS*").
4. For the buttock ratings, the 'Moderate' category showed the lowest level of agreement, while for the thigh ratings, the 'Mild' category showed the lowest level of agreement across the two visits. Because your target population are subjects with moderate to severe cellulite and the primary endpoint is a >2-category change, these low level of agreements in these categories are concerning as they may minimize the opportunity for your study to successfully demonstrate efficacy. Subject training in these scales will be important.
5. Provide patient interview transcripts, if available.

Endo Clarification:

Endo acknowledges the Division's suggestions and plans to respond to them in the submission proposed under the introductory comments (to be submitted by February 10, 2017). In addition, the patient interview transcripts will also be provided at that time.

Question 6: Does the Agency agree that a composite primary efficacy endpoint,

Composite 2-level CR-PCSS response and 2-level PR-PCSS response at day 71 (i.e., the proportion of subjects who had at least a 2-level improvement in both the CR-PCSS and the PR-PCSS),

is appropriate for pivotal studies of EN3835 for improvement of cellulite?

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FDA Response:

Provided that there is good agreement between the CR-PCSS and the PR-PCSS, a composite primary endpoint composed of both the CR-PCSS and the PR-PCSS with at least a 2-level improvement in both scales, would be an appropriate primary efficacy endpoint for this aesthetic indication. See Introductory Comments and response to Question 5.

Endo Clarification:

Endo requests that following the planned February 10, 2017 submission that the Division confirm that the proposed composite primary endpoint is acceptable. Does the Division agree to confirm following submission of the additional information?

Question 7: The Sponsor's Phase 2 study results show statistically significant improvements in number of 1-point responders in PR-PCSS of EN3835-treated subjects (72.3%) and Subject Global Aesthetic Improvement Scale (S-GAIS) responders with score of 1 or greater in EN3835-treated subjects (73.1%) compared to placebo treated subjects (51.6% and 43.7%, respectively). The Sponsor believes these are appropriate key secondary endpoints that would potentially be supportive (b) (4), if they achieve statistical significance in Phase 3 studies. Does the Agency agree?

FDA Response:

In general, we view global ratings (i.e., I-GAIS, S-GAIS) as exploratory measures that can be used as anchors for determining what constitutes a clinically meaningful change in another measure. In the absence of an objective measure of efficacy, a one-point change in PR-PCSS should be anchored to a two-point change in S-GAIS.

In the absence of agreement between the two scales (PR-PCSS and the CR-PCSS), it would be difficult to concur that an improvement in one scale, of one point, would be clinically meaningful. It should be noted that a one grade improvement in one scale, if associated with improvement of at least one grade with the other scale, could be clinically meaningful and may support the finding of the primary endpoint (the composite of the two scales).

(b) (4)

The synopses specified that the details regarding the hierarchical order of the endpoints would be specified in the SAP. Note that the SAP should be submitted as part of the protocol.

Endo Clarification:

Endo acknowledges the Division's response and proposes to provide the analysis of the primary endpoints and key secondary endpoints in detail in the context of the protocol. A complete SAP will be prepared and submitted at a later date before database lock. Does the Division concur?

Question 8: The Sponsor's Phase 2 study results show 72.3% of EN3835-treated subjects were responders with a 1-level improvement in cellulite severity (PR-PCSS) compared to 51.6% in placebo-treated subjects and 10.6% were composite responders with a 2-level improvement compared to 1.6% in placebo-treated subjects. The Sponsor believes these are appropriate,

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meaningful, and approvable rates of response, if demonstrated in Phase 3 studies. Does the Agency concur?

FDA Response:

See response to Question 7.

Endo Clarification:

The Sponsor's Phase 2 study responder analyses of 2-level composite responders (subjects with both a 2-level improvement in CR-PCSS and PR-PCSS) showed 10.6% of EN3835-treated subjects were composite responders compared to 1.6% in placebo-treated subjects. The Sponsor believes these are appropriate, meaningful, and approvable rates of response if demonstrated in Phase 3 studies. Does the agency concur?

The Sponsor's Phase 2 study results showed 72.3% of EN3835-treated subjects were responders with a 1-level improvement in cellulite severity PR-PCSS compared to 51.6% in placebo-treated subjects. Assuming the Sponsor can provide sufficient evidence of anchoring for a 1-level improvement in cellulite severity as assessed by the PR-PCSS, the Sponsor believes these are appropriate, meaningful, and approvable rates of response if demonstrated in Phase 3 studies. Does the agency concur?

Question 9: Does that Agency agree that the test-retest reliability study of the CR-PCSS conducted using digital images of cellulite supports the use of the CR-PCSS utilizing live assessments?

FDA Response:

No. You have not provided data to support that the two modes of assessment for CR-PCSS (i.e., digital images and live assessment) would be equivalent. Because your primary efficacy endpoint is based on the use of the CR-PCSS via live assessment, and due to some of the issues observed from your test-retest reliability results (see below), we recommend you perform similar analyses using the live assessment CR-PCSS data collected in your Phase 2b trial to confirm the reliability of the CR-PCSS and other measurement properties where feasible. This does not preclude you from using the CR-PCSS in your planned trials; however you will be taking a risk proceeding to Phase 3 without fully evaluating the measurement properties of the CR-PCSS via live assessment.

Although the test-retest reliability estimates for the CR-PCSS via digital assessment fall in the acceptable range, the data should be interpreted cautiously as your study has limitations as noted in your final report. Below are our specific comments on the results from your CR-PCSS test-retest reliability study.

1. The photographs tested did not seem to cover the full spectrum of cellulite severity. The images selected for the study were rated by the clinicians as predominantly falling in the 'Almost None,' 'Mild,' and 'Moderate' categories, with 'Almost None' being the most frequently represented category, and considerably fewer images in the 'None' and 'Severe' categories. Your target population is subjects with moderate to severe cellulite; however, there was minimal representation of severe subjects, which limits interpretation of reliability in this subgroup. This would be more of a concern if digital assessment was being used for the primary endpoint.

2. There were notable differences in cellulite severity ratings between Assessment 1 and 2 evaluations among the clinicians. It would be expected that the ratings would not change so much as the clinicians were viewing the same images at both time points, which obviated any change in disease state or cellulite severity. However, +1-category changes were demonstrated between ratings from Assessments 1 and 2 for both the buttock (14% to 39%) and thigh (12% to 42%) photographs, as well as -1-category changes (buttock: 3 to 16%; thigh: 3 to 19%) (Tables 3.3 and 4.3 in Test-Retest of the CR-PCSS Study Report).
3. There was minimal agreement on the cellulite severity ratings between all five clinicians and panel consensus ratings. All five clinicians collectively agreed with the panel consensus ratings in approximately one-third or less of the images for both thigh and buttocks, separately. Further there was notable variability of agreement between clinicians for both buttock (Assessment 1: 53-72%; Assessment 2: 56-73%) and thigh (Assessment 1: 39-65%; Assessment 2: 39-70%) images (Tables 7.1-7.2 and 8.1-8.2 in Test-Retest of the CR-PCSS Study Report).

Because of these noted issues, ensuring appropriate training and a standardized approach to assessment and administration (e.g., lighting conditions, photographs, etc.) will be critical to maximize the opportunity for your study to successfully demonstrate efficacy regardless of the mode of assessment (refer to response to Question 5).

Endo Clarification:

To clarify the following comment above, "...we recommend you perform similar analyses using the live assessment CR-PCSS data collected in your Phase 2b trial to confirm the reliability of the CR-PCSS and other measurement properties where feasible." Endo will use the live assessment responses from the CR-PCSS that were collected at screening during the EN3835-201 study and compare them with the live assessment responses from the CR-PCSS collected at screening for the EN3835-202 study for those untreated quadrants in the EN3835-201 study. Shift tables will be prepared along with the correlation coefficient. The goal is to demonstrate reliability of the scale when the same clinician views the same subjects whose cellulite is not expected to have changed in severity from the first study to the second. Does the Division agree with this approach and that if successful confirms the test-retest reliability of the CR-PCSS.

Additionally, Endo acknowledges the comments in item numbers 1-3 and commits to ensuring appropriate training and a standardized approach to assessment and administration.

Question 10: Does the Agency agree with the proposed immunogenicity profiling with assessments (i.e., antibody titers) in the pivotal studies at beginning (pre-treatment) and end of study?

FDA Response:

We do not agree. We recommend that you analyze all immunogenicity samples collected on Days 1 (pre-treatment), 22, 43, and 71 (end of study) for the assessment of immunogenicity potential of EN3835 in subjects with EFP. Because subjects with EFP will receive repeated SC injection in the proposed Phase 3 studies, the immunogenicity profile, including the time course of anti-drug antibody (ADA) formation and the extent of neutralizing activity of ADA, can be different from those observed in the clinical studies for the approved indications. We note that

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the population of specialized immune cells in target tissue of EFP (subcutaneous fat) could be different from the immune cells in the target tissues in Dupuytren's contracture and Peyronie's disease. The proposed SC injection can also trigger immunological cascade, which may be different from immune response to intralesional injection in Dupuytren's contracture and Peyronie's disease, possibly leading to different dynamic course of immunogenicity. In addition, we may have additional comments when we receive the full protocol of your proposed Phase 3 studies.

Endo Clarification:

Endo agrees 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 study. In addition, a subset of plasma samples from seropositive subjects will be assayed for neutralizing antibody activity using the approach adopted in prior studies with EN3835.

Question 11: Does the Agency agree that the planned safety database is sufficient for registration of EN3835 for this indication?

FDA Response:

You plan to enroll 900 subjects in the two planned Phase 3 trials, with 450 subjects to be treated with EN3835. This is a reasonable number of subjects to evaluate safety of your drug product in the placebo controlled portion of your Phase 3 trials. Your drug product for the treatment of EFP has the potential for chronic intermittent use, therefore you should establish the long term safety of your product in the population. You will need to determine the duration of effect of your drug product in order to assess the long term safety of your drug product with repeat exposures.

Endo Clarification Questions 11, 12, and 13:

The Sponsor agrees that currently the durability of drug effect is unknown but as noted on page 49 of the submitted Briefing Book, durability information will be gathered in the on-going Study EN3835-202. This information could be supplemented and enriched by obtaining data from an open-label extension study post-submission study (Phase 4) which could be initiated prior to registration submission filing but would not be complete at time of filing or during the review cycle of the application. The plan would not include completed durability data to be submitted at the time of registration filing or during the review cycle of the application (would be post-approval). Does the Division agree with this proposal?

For clarification to the comment (Written Response, line 335) that the timepoint of durability should begin at the efficacy evaluation timepoint and it should end when the subject fails to be a success; the Sponsor is agreement with initiation at an assessment evaluation timepoint i.e. Day 21, 43 or 71 and ends when that subject fails to be a success. Success based on the primary endpoint of composite responders will not allow an accurate reflection of durability due to the low number of 2-point responders (n=20 of 187 enrolled subjects). Therefore an efficacy endpoint that reflects drug activity i.e., 1-level improvement composite responders should allow sufficient numbers of subjects to be followed for a more accurate assessment of durability; with duration ending when the PR-PCSS and CR-PCSS rating return to baseline. Does the Division agree with this proposal?

The Sponsor agrees that there is a likelihood of intermittent use for the treatment of EFP. To gain safety information of re-exposure, on-going Study EN3835-202 is enrolling subjects

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previously treated with EN3835 in Study EN3835-201 are being offered additional treatments. Currently there are 114 subjects enrolled that were previously treated with EN3835 which may potentially result in 114 re-exposed subjects. In addition, currently there are 134 subjects enrolled who were placebo-treated subjects from EN3835-202; these subjects will be offered two sequential courses of treatments i.e., two areas to be treated. Together this study may afford safety on greater than 200 re-exposed subjects. The Sponsor offered safety from 50-75 re-exposed subjects as the confidence level is very high that those number are obtainable but likely there will be greater than 150 re-exposed subjects, assuming dropouts and/or withdrawals, at time of filing. Does the Division agree with the proposed re-exposure numbers with this clarification?

From the Written Response, the Sponsor's understanding is that 900 subjects exposed at the proposed therapeutic dose (0.84 mg) would be sufficient for single exposure safety and 300 subjects followed for 6 months and 100 for 1-year safety would be sufficient for registration filing. Can the Division please confirm this understanding is correct?

Question 12: Does the Agency agree with the number of subjects and planned timings of assessments proposed to assess safety after re-exposure?

FDA Response:

You plan to follow 300 subjects for 6 months and 100 subjects for 12 months, yet you only plan to re-expose 50 to 70 of the total subjects in your Phase 2b trial to EN3835. Evaluating the safety of your drug product after multiple exposures would be an important safety issue to consider in the evaluation of your drug product for EFP. To adequately do this, you will have to ascertain the duration of effect and then design a study to evaluate repeat exposures. We cannot ascertain, at this time, the duration of time that would be needed to gather this data.

Endo Clarification:

See Question 11.

Question 13: Does the Agency agree with the proposed definition of durability and obtaining durability in study EN3835-202 as described?

FDA Response:

Your definition of durability (from the open label Phase 2 trial) was the time duration from first improvement in PR-PCSS and/or CR-PCSS until the time at which the PR-PCSS and CR-PCSS ratings are equal to or worse than the baseline ratings for that quadrant. We don't agree with this definition. We would prefer that the time point of durability should begin at the efficacy evaluation time point and it should end when the subject fails to be a success.

Endo Clarification:

See Question 11.

Question 15: Does the Agency agree with the sample size and power estimation for each of our Phase 3 clinical trials?

FDA Response:

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Whether the study is powered sufficiently for your Phase 3 trials will depend on having reliable estimates of treatment effect for the endpoint recommended by us. Given the lack of information concerning the agreement in the clinician and subject scales, it would be difficult to comment on the adequacy of powering your Phase 3 trials. See Introductory Comments.

Endo Clarification:

Endo requests that following the planned February 10, 2017 submission that the Division confirm that the proposed sample size and power estimation is acceptable. Does the Division agree to confirm following submission of the additional information?

Question 16: Does the Agency agree with the proposed procedures to replace missing data?

FDA Response:

For handling of missing data, you proposed that subjects without any post-injection evaluation for either CR-PCSS or PR-PCSS will be considered as non-responders, and also stated that the last observation carried forward (LOCF) will be used to handling missing data at Day 71. Because the scientific justification for LOCF is limited, you should provide a rationale for why LOCF is appropriate in this situation or propose an alternate method that has a reasonable justification.

Endo Clarification:

All prior studies of EN3835 have used LOCF to replace missing values. The completed studies (for Peyronie's disease and study EN3835-201) have demonstrated that improvement occurs over time, therefore the LOCF method is considered to be conservative.

Several sensitivity analyses including multiple imputation procedures will be conducted based upon the design of the trials, and the SAPs for the phase III studies will elaborate on these methods.

Does the Division agree with this approach?

Question 17: Does the Agency agree with the pivotal trials enrollment of adult women only?

FDA Response:

Provide your rationale for excluding men from your Phase 3 trials. Include this in the IND with the submission of your Phase 3 protocol.

Endo Clarification:

Endo acknowledges the responses and will provide the rationale in the IND with the submission of the Phase 3 protocols.

Additional Comments-Clinical Outcome Assessments

Endo Clarifications are provided below. Please confirm the Division has no additional clarifications based on the information provided.

Comments regarding Photography User Manual:

1. Clarify whether subjects and clinicians are forced to complete a response for each treatment quadrant in the electronic applications (e.g., PCSS, S-GAIS, I-GAIS) before advancing to the next screen.

Endo Clarification:

The (b) (4) applications built for PCSS, S-GAIS, and I-GAIS for our trials allow viewing of the image but the responses are entered directly into an ePRO/EDC system. In the (b) (4) application once a digital image is viewed in the PCSS applications it cannot be recalled for viewing. The electronic data capture (EDC) system has separate logins and passwords for the subject and the investigator that are not shared to prevent unblinding or biasing of ratings and/or responses. Once a response is submitted into the EDC system it cannot be recalled or changed by subject or investigator.

The responses to S-GAIS and I-GAIS are recorded on a source document by subject/investigator and then entered into EDC by site personnel.

2. Clarify whether there is a “finish” button/screen to indicate the end of the subjects’ and/or clinicians’ assessment in the electronic applications (e.g., PCSS, S-GAIS, I-GAIS) or if the site is able to see the individual’s last response when closing out the application.

Endo Clarification:

Responses are not entered into the (b) (4) application, rather they are entered directly into an ePRO/EDC system. The patient and investigator have individual logins and passwords to the EDC system to reduce the opportunity of unblinding or biasing of responses.

After the subject enters their rating into the ePRO/EDC, the subject hits a 'Next' button that takes them to a Thank you screen that states 'You have completed all the assessments for today. It is now safe to logout and close this browser window'; after which the subject logs out of the EDC system.

3. We recommend you have a back-up plan (e.g., paper, web-based) implemented in the case there are any malfunctions with the electronic applications. Additionally, we suggest you perform usability testing of the applications prior to the start of the trial to orient the subjects and clinicians.

Endo Clarification:

The Sponsor will take your guidance under advisement. The investigators and subjects undergo training and usability testing of the application prior to use in the trial.

Comments regarding CR-PCSS User Manual:

4. Lighting conditions for the live assessments should be standardized across all sites.

Endo Clarification:

The Sponsor will take your guidance under advisement.

5. The user manual should be updated with training and qualification for the pivotal trials.

Endo Clarification:

The Sponsor will take your guidance under advisement.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JILL A LINDSTROM
02/22/2017