CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761085Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 121493

MEETING MINUTES

Evolus, Inc.
Attention: Adelbert Stagg, PhD
Vice President, Regulatory
1027 Garden Street
Santa Barbara, CA 93101

Dear Dr. Stagg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for botulinum toxin Type A for injection.

We also refer to the meeting between representatives of your firm and the FDA on October 19, 2016. The purpose of the meeting was to discuss the development program for botulinum toxin Type A for injection and submission of a Biologic License Application (BLA) for the treatment of moderate to severe glabellar lines.

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 Belainesh Robnett, Regulatory Health Project Manager at (240) 402-4236.

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	October 19, 2016; 10:00 AM (ET)
Meeting Location:	White Oak Campus
Application Number:	IND 121493
Product Name:	botulinum toxin Type A
Proposed Indication:	treatment of moderate to severe glabellar lines
Sponsor Name:	Evolus, Inc.
Meeting Chair:	Kendall A. Marcus, MD
Meeting Recorder:	Belainesh Robnett

FDA ATTENDEES
Kendall A, Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jianyong Wang, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biopharmaceutics III (DB III)
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Luke Oh, PhD, Senior Staff Fellow, Division of Clinical Pharmacology III
Howard Anderson, PhD, Product Quality Team Leader, Division of Biotechnology Review and Research III (DBRR III)
Ennan Guan, MD, PhD, Product Quality Reviewer, DBRR III
Davinna Ligons, PhD, Product Quality Reviewer, DBRR III
Roy Blay, PhD, Good Clinical Practice Assessment Branch, Office of Scientific Investigations (OSI)
J. Paul Phillips, MS, Lead Regulatory Health Project Manager, DDDP
Belainesh Robnett, MS, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Chris Marmo, PhD, CEO, Evolus, Inc.
Rui Avelar, MD, CMO, Evolus, Inc.
John Gross, MD, CSO, Evolus, Inc.
Scott Cannizzaro, PhD, COO, Evolus, Inc.
Del Stagg, PhD, VP Regulatory, Evolus, Inc.

Sierra Webb, PhD, Regulatory Scientist, Evolus, Inc.
Song Wang, PhD, Statistical Science Director, Biostatistics, Pharmaceutical Product Development
Bongyong Lee, PhD, Executive Vice President, Daewoong Pharmaceutical
Seongsoo Park, Nabota Business Unit, Daewoong Pharmaceutical
Chung-Sei Kim, PhD, Research Fellow, Biological Research Center, Daewoong Pharmaceutical

1.0 BACKGROUND

The purpose of the meeting was to discuss the development program for botulinum toxin Type A for injection and submission of a Biologic License Application (BLA) for the treatment of moderate to severe glabellar lines.

Regulatory Correspondence History

We have had the following teleconferences with you:

- 03/11/2015 Pre-Phase 3
- 03/12/2014 Pre-IND

We have sent the following correspondences:

- 06/28/2016 Proprietary Name Denied
- 02/12/2016 Advice
- 12/22/2015 Proprietary Name Granted
- 07/14/2015 Advice
- 04/28/2015 Advice
- 12/19/2014 Special Protocol Agreement
- 10/16/2014 Special Protocol- No Agreement
- 09/08/2014 Study May Proceed

2.0 DISCUSSION

2.1. Regulatory

BLA Organization and Structure

Question 1:
The Proposed Table of Contents (TOC) for the BLA addresses each section of the BLA and is included as Appendix 1: Proposed BLA Table of Contents.

Does FDA agree that the documentation reflected in the proposed Table of Contents will be sufficient to accept the BLA for review to gain approval for this claim?

FDA Response:
The overall Table of Contents (TOC) appears reasonable.

However, we have the following comments below:

- 1.12.1. (Pre-IND Correspondence) – a single pdf file can be provided (instead of separate pdf files for each document) with proper bookmarks of all correspondence, table of contents and hyperlinks.
- For archival purposes, you should also submit a pdf file of any labeling document submitted in word. Also, when you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.
- Make sure the Risk Management Plan documents are placed in their proper sub-sections of m1.16.2.
- To submit PADER descriptive portion (only) in eCTD format, it should be provided as a single pdf file with bookmarks, table of contents and hyperlinks in the eCTD section, m5.3.6. Since each report is for a specific time period, ensure that the leaf title of the report includes the reporting period (e.g., PADER-04-21-15-thru-04-20-16), and it helps reviewers differentiate one report from another.

Question 2:
The application will be submitted in eCTD format in accordance with the FDA Data Standards Catalog v4.4 and will follow the eCTD TECHNICAL CONFORMANCE GUIDE v.1.0 (October 2015) and the guidance for industry Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (eCTD Guidance).

Does the Agency require the sponsor to submit a sample eCTD or Standardized Data Sample to the FDA?

FDA Response:
The sample eCTD and standardized data sample are not required. However, if you do not have experience with eCTD and standardized data submission, then the Agency can provide assistance in validating them.

Question 3:
The Sponsor proposes that, in accordance with the regulatory standard, only the individual case report forms (CRFs) for each subject who died within 30 days of the study drug administration or who discontinued study drug due to AEs be included. The sponsor agrees to provide any additional CRFs in response to the Agency's requests during the course of review of the BLA.

Does the Agency agree with the proposal to include only the individual case report forms (CRFs) for each subject who died within 30 days of the study drug administration or who discontinued study drug due to AEs?

FDA Response:
You propose to provide case report forms (CRFs) for all deaths and discontinuations due to adverse events which occurred in Phase 2 and 3 trials.

Provide CRFs for all serious adverse events, hypersensitivity reactions and possible spread of toxin (PSOT) events. If you plan to organize the CRFs by trial in Module 5 Section 5.3.5.1, then the CRFs for each trial should be placed in a CRF folder under the applicable trial with a file tag of "casereport-forms."

Provide electronic links to the following CRFs in the Integrated Summary of Safety (ISS) and Clinical Study Reports (CSR):

a) all deaths

b) all serious AEs

c) all subjects discontinued due to adverse events

d) all hypersensitivity reactions

e) all possible spread of toxin events

Other eCRFs should be readily available upon request.

You also propose to provide narratives for all deaths, serious adverse events, other significant adverse events and adverse events of special interest. Ensure that you include narratives for all pregnancies, possible spread of toxin (PSOT) events, hypersensitivity reactions, and adverse events leading to discontinuation which occurred in the Phase 2 and 3 trials. Other narratives should be available upon request.

You indicate that you plan to include narratives by trial in Module 5 Section 5.3.5.1. We recommend that you also provide electronic links to the narratives in the Integrated Summary of Safety (ISS), Section 5.3.5.3.

Question 4:
The Company proposes to follow the same process as under Question 3 above.

Does the Agency agree with the proposal to include the same data as described in question 3 in the 120-day safety update?

FDA Response:
Under section 505(i) of the act, the applicant should update the BLA application with "new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if applicable, any Medication Guide required under part 208 of this chapter." This update should provide a summary of information which was not submitted in the BLA including the following:

- A detailed description of any significant changes or findings in the safety profile.
- A tabulation of the incidence of deaths, discontinuations due to adverse events, serious adverse events, and common adverse events.
- Narrative summaries for subjects who died during a clinical trial, experienced a serious adverse event or who did not complete a trial because of an adverse event.

- A description of any information that suggests a substantial change in the incidence of common, but less serious adverse events.
- A summary of worldwide experience on the safety of this drug. Include an updated estimate of use for the drug marketed in other countries.

Also see our responses to Question #3.

Administrative Items

Question 1:
The Table of Contents (TOC) for the Clinical Study Reports (CSR) and an outline of data listing is provided in Appendix 5: CSR Table of Contents and Data Listing Outline.

Does the Agency agree with the proposed CSR format and data listings format as presented in Appendix 5 of the Briefing Book?

FDA Response:
The proposed Clinical Study Report (CSR) format and data listings format as presented in Appendix 5 appear reasonable. Also, see response to Question 3.

Refer to the guidance for industry, *E3 Structure and Content of Clinical Study Reports Questions and Answers (R1).*

For the data part in module 5, the SDTM folder should also include the define.xml and study data reviewer guide. The programs used to create the analysis datasets and primary and key secondary outcomes are required to submit in ADAM folder.

Question 2:
The format, dictionaries, and safety analysis is included as Appendix 6: List of Studies and Standards.

Does the Agency agree with the proposed format, dictionaries, and safety analysis as presented in Appendix 6 of the Briefing Book?

FDA Response:
Your approach is acceptable; however, the define.pdf file is required to be submitted along with define.xml v1.0.

Question 3:
Data will be provided in accordance with the *FDA Data Standards Catalog v4.4* (Data Standards Catalog) and the *Study Data Technical Conformance Guide v3.0* (March 31, 2016).

A Study Data Standards Plan, including a list of completed clinical studies along with the planned standards, formats, and terminologies and their versions is included as Appendix 6: List of Studies and Standards.

Does the Agency agree with the Company's proposal for the study data as presented in Appendix 6 of the Briefing Book?

FDA Response:
See response to Question 2.

For the analysis datasets, we have the following general comments:

- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.
- The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. For ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

Question 4:
In compliance with the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) Evolus, Inc. submitted a request for a Waiver from conducting Pediatric Studies for this product in relation to this indication in the original IND application (sn0000). Development of glabellar lines, as with facial wrinkles, is a typical component of the intrinsic aging process of the skin. When we are young (< 18 years of age) these lines or wrinkles are not permanently etched in the skin because of the elastic quality of youthful skin, and these lines are not present when not frowning. As we age, frown lines become permanent, more obvious and deeper over time, and can give a mistaken impression of being angry or hostile.

Since the indication, moderate to severe glabellar lines, does not occur in any of the pediatric patients, the benefit / risk ratio cannot justify the use of this product in any pediatric population. Further, all of the botulinum toxins approved for this indication state in the labels to not use the product in subjects under 18 years of age.

Does the Agency agree that the company has provided adequate documentation to grant a waiver from pediatric studies?

FDA Response:
Your proposal to request a full waiver from conducting pediatric studies with your product in the population <17 years for the indication of the treatment of moderate to severe glabellar lines appears reasonable.

A sponsor who is planning to submit a marketing application for a drug that is subject to Pediatric Research Equity Act (PREA) (includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration), is required to submit an initial pediatric study plan (iPSP) unless the drug has been granted orphan designation for the proposed indication at the time that the iPSP is required. You should submit an initial pediatric study plan as early as practicable but no later than 210 calendar days before you submit a marketing application. Your iPSP should include information to support your request for a waiver from conducting studies in the pediatric population. For additional advice regarding the content and format of the iPSP refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans.*

Meeting Discussion:
The sponsor asked if they would need to resubmit their request for a waiver of the PREA requirements. The Agency clarified that the sponsor would need to submit a copy of their agreed iPSP with their BLA submission. The agreed iPSP will document the waiver request and be sufficient for the Agency to review and determine whether or not to grant the waiver at the time of an action on the BLA.

2.2. Chemistry, Manufacturing and Controls (CMC)

Drug Substance (DS)

Question 1:
The Company is of the opinion that we have addressed the Agency observations from the letters dated, 09/08/2014 and 03/27/2015 and that the data supplied via amendments to the IND close out these observations (Reference ID 3261516 and 3722355, respectively). The observations and amendment with data to demonstrate conformance are presented below in Table 1.

Does the Agency agree that the Sponsor has addressed the Agency's observations for those items identified as being completed in the following company position?

FDA Response:
(b) (4)

(b) (4). The potency of the drug product in the vial must be accurately stated on the label.

The FDA has briefly reviewed the numerous reports referenced in Table 1 and the reports appear to address the previous FDA comments. However, the documents will not be fully reviewed until they are submitted in the BLA.

Meeting Discussion:
The sponsor indicated that (b) (4) (b) (4) the resulting drug product was 100 Units per vial, consistent with the product label. The Agency indicated that the proposed (b) (4) may be appropriate; however, a final decision will be made when all batch analysis results are reviewed.

Question 2:
As per the agency's guidance; we have established a two-tier call banking system A Master Cell Bank (MCB) and Working Cell Bank (WCB) from which the Drug Substance is produced. The MCB was established to maintain the WCB over the life of the product. The strategy and characterization of the Working Cell Bank in relation to the Master Cell Bank along with the implementation procedures is provided in a summary; Appendix 2: Strategy and Characterization of the Working Cell Bank.

Does the Agency agree with our process for establishing a two-tier cell banking system?

FDA Response:
Yes, we agree with your proposed strategy in the Appendix for the two-tier master and working cell bank system.

Question 3:
We have developed a Reference Standard for the Drug Substance (DS) and use that Reference Standard to determine the potency of the Drug Substance. Documentation on the Reference Standard was provided in IND 121,493 amendment sn0024.

Does the Agency agree with the process used to establish the DS Reference Standard and its use for determining the potency of the Drug Substance?

FDA Response:
The reference standard (RS) described in amendment SN 0024 appears to be adequately characterized and appropriate for the reference material. However, the amendment does not indicate if the RS was evaluated in the current US Phase 3 clinical trial. Ideally the original RS material is evaluated in the pivotal III trial or demonstrated to be physicochemically comparable to the Phase 3 material

Meeting Discussion:
The sponsor provided a brief overview of the reference standard used in the Phase 3 trial in the slides. The Agency indicated that the reference standard information will be reviewed when the BLA is submitted.

Question 4:
The Company proposes to use the mouse LD50 assay to define the specific activity of the DS as this assay is still the standard by which the DS specific activity is determined for all toxin products currently approved for marketing. We have not yet been able to develop an in vitro assay for reasons explained under Question 3 for drug product below.

Does the Agency agree with the strategy for use of the mouse LD50 assay to define the specific activity of the DS until an in vitro assay can be developed?

FDA Response:
Yes, we agree that the mouse LD50 method is appropriate for the determination of the potency.

Drug Product (DP)

Question 1:
The Company will have stability/shelf life data for the finished drug product (DP) out to 6 months from the "new" facility at the time of the BLA submission as part of a 3-year stability protocol. The stability protocol is consistent with previous FDA approved drug stability protocols. We commit to update the stability data during review of the BLA and include stability data in the quarterly and annual reports.

In addition to this stability study, we have an ongoing 3-year stability study on the DP manufactured in the "old" facility that is formulated with (b) (4) Human Serum Albumin and is vacuum dried (b) (4). Batches of this DP were used in the Phase 3 clinical studies and second Phase 2 repeat dose study (EV-006). This stability study has passed the 18 month timepoint and will be at the 24 month time point when the BLA is submitted. These data will be used to support the position that this formulation and manufacturing process results in a stable product meeting specifications.

FDA Response:
The approved drug product expiry will be based on the ICH Q5C guidance for industry, *Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* that recommends,

> "A minimum of 6 months data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested. For drug products with storage periods of less than 6 months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis. Product expiration dating should be based upon the actual data submitted in support of the application."

Stability updates can be submitted during the BLA review. It should be noted that the change of the drug product manufacturing site is considered a major process change and the comparability of the products made at the new and old sites should be evaluated and the results should be provided in the BLA.

Meeting Discussion:
The Agency indicated that the comparability studies for the product manufactured at the old and new facilities should include accelerated temperature, forced degradation and photo stress analysis. The sponsor indicated they plan to conduct the studies and they will include the results in the BLA. The Agency agreed with the sponsor's proposal to include the information in eCTD-Module 2 Sections 2.1.P.2.3 and Module 3 3.2.P.2.3.

Question 2:
The Company needs clarification on how the Agency will release individual batches of the product for distribution into the market after the BLA is approved. The Company proposes to submit test results and the CoA for each batch of this product manufactured outside the United States to the FDA for review and acceptance. In parallel, the Company will ship the batch to its US distribution center so we can release it for distribution upon FDA acceptance.

Will the Agency release drug product based on review of the test results and COA supplied by the Company?

FDA Response:
Yes. As per the requirement of 21 CFR 610.2(a) the FDA will release this drug product because it is not a specified biologic. Refer to the guidance for industry, *Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format - Lot Release Protocols*.
http://www.fda.gov/downloads/BiologicsBloodVaccines/Guidance Compliance Regulatory Information/Guidances/General/UCM179118.pdf

Question 3:
It is difficult to develop a cell-based potency release assay for the drug product. The two cell-based assays currently approved by regulatory agencies are protected by patents and the owners of the patents have declined to license the assays. The patents also make the development of alternate cell-based assays difficult because the scope and broadness of the patents include other obvious methods and assays. We commit to develop an alternate cell based assay. Until the cell based assay is developed, the Company should be able to enter the market using the LD50 assay similar to the other toxins.

For the BLA, will the Agency accept the proposed plan to use the LD50 potency assay for the drug product until we can complete the development of an alternate assay?

FDA Response:
Yes, we agree. However, a commitment should be provided in the BLA to develop a cell-based potency assay for drug product release and stability testing.

2.3. Nonclinical

Question 1:
Based on previous correspondence with the Agency, the Company is of the opinion that we have completed all required non-clinical pharmacology/toxicological assessments to support this BLA. (Reference FDA Study may Proceed Letter of September 8, 2014, ID 3621516).

Does the Agency agree that the Company has completed all non-clinical testing to support the BLA application?

FDA Response:
Yes, we agree.

Meeting Discussion:
The sponsor stated that they plan to use a new facility for production in the future. The sponsor proposed to conduct a single dose toxicity bridging study to compare the toxicity for products manufactured from the old and the new facilities. They also proposed to conduct a repeat dose toxicity study with the product manufactured from the new facility. The Agency commented that the proposal appears reasonable.

2.4. Clinical

Question 1:
Does the Agency agree that submission of data from the EV-001, EV-002, EVB-003, EV-004 and EV-006 studies and the Korean Phase 1/3 study provide adequate numbers of subjects, repeat treatments and duration of exposure to support regulatory decision-making for a claim to use DWP-450 (Botulinum toxin, Type A) Injection for the proposed indication?

FDA Response:
You plan to submit the data from the following trials in support of efficacy and safety of your product for the treatment of moderate to severe glabellar lines:

- **Trials EV-001** and **EV-002:** randomized, placebo controlled, single- dose Phase 3 trials of identical design with a 150 day follow-up which enrolled a total of 654 US subjects (Protocol EV-001 reviewed under SPA)
- **Trials EV-004** and **EV-006**: open-label, repeat- dose (up to 4 doses), Phase 2 trials with 365 day follow-up which enrolled a total of 922 US subjects.
- **Trial EVB-003**: randomized, placebo and active controlled, single-dose Phase 3 trial which enrolled 540 Canadian and EU subjects (Summary information not provided)
- **Korean Trial(s):** 2- arm active- controlled Phase 1 and Phase 3 trials which enrolled 288 Korean subjects (supportive data).

In your briefing document, you provided the number of subjects enrolled in single- dose trials EV-001, EV-002 and EVB-003 (1194 subjects**)** and repeat- dose trials EV-004 and EV-

006 (922 subjects); however, you have not provided information regarding the number of subjects who received 1, 2, 3, or 4 treatments. In your BLA submission, we request that you provide exposure in a tabular format by the number of treatments received as presented below.

	Numbers of Subjects				
Number of Treatments	Trial EV-001	Trial EV-002	Trial EVB-003	Trial EV-004	Trial EV-006
1					
2					
3					
4					
Totals					

Meeting Discussion:
The Agency concurred with the format and numbers of subjects provided.

Question 2:
Does the Agency agree that clinical design and approach based on the EV-001, EV-002, EVB-003, EV-004 and EV-006 studies could provide adequate information to support regulatory decision-making for a claim for use of DWP-450 (Botulinum toxin, Type A) Injection (understanding the Agency will not have insight into the data, this is a question regarding design)?

FDA Response:
The general trial designs and approach are reasonable; however, the adequacy of the data to support an approval of your product will be determined upon the review of your submission.

Question 3:
Following un-blinding Phase III studies (EV001 and EV002), it became apparent that the proportion of subjects in the placebo group who experienced a 2-point improvement was, as expected, very low at all-time points. In fact, for the primary endpoint, in EV001 83 out of the 84 and in EV002 77 out of 78 Placebo participants were non-responders under the twopoint or greater definition of composite response. In each of EV001 and EV002, at 9 of the 10 investigative sites, no placebo subject was a responder. The small number of placebo subjects in each site (the expected number of responders in the placebo group are less than 5 for most sites) renders the pre-specified test unsuitable for the analysis of the data. A posthoc decision was made to perform the efficacy analyses using an exact unconditional test along with its corresponding exact confidence intervals calculated by inversion of two onesided intervals. Calculations were performed using the unconditional procedure in StatExact 10 (Cytel software 2013) called “confidence interval for difference of proportions.” The results for the CMH test, as specified in the SAP finalized prior to un-blinding, will be provided for the purposes of transparency only. See Appendix 4: Updated SAP for EV001and EV002 for additional details.

Is the post-hoc decision to perform the efficacy analyses using of an exact unconditional test along with its corresponding exact confidence intervals acceptable to the Agency?

FDA Response:
As the number of subjects that achieved composite success at Day 30 in the placebo group in each trial is very small (i.e., only 1 subject in each trial), your proposal to conduct the efficacy analyses using an exact unconditional test along with its corresponding exact confidence intervals appears reasonable.

Question 4:
During the study, pictures of subjects were captured primarily for the purposes of safety. The sponsor plans to provide photos for the adverse events (AE) of ptosis since it may be of assistance for the Agency during the review process. The sponsor is not planning on providing other photos related to AE's at this time, but should it be necessary, access to the full library of photos is available.

Is the inclusion of subject photographs for only adverse events of ptosis acceptable to the Agency?

FDA Response:
You obtained photographs of the brow area of all subjects at all visits in the Phase 2 and Phase 3 trials. In addition to the submission of images to document the adverse event of ptosis, we request that you submit images obtained at Baseline and Day 30 (timepoint for the primary efficacy evaluation) for subjects enrolled in the pivotal Phase 3 trials (EV-001 and EV-002).

Question 5:
The sponsor is unaware of any standard the FDA may have in establishing a duration claim for a Botulinum toxin for the treatment of glabellar lines. As such, the sponsor plans to establish duration as the point in time when there is no longer a statistical difference between the treatment and placebo arms, using a 2 point or greater composite score. Both Phase III studies incorporated this analysis into the secondary end points and controlled for a type 1 error. Onset would be established as the point in time when there is a statistical difference between the treatment and placebo arm, using a 2 point or greater GLS improvement at maximum frown by investigator assessment.

Is the Company's approach for determining a duration claim acceptable to the Agency?

FDA Response:
While information about the onset and duration of treatment effect are important (for patients and clinicians), your plan to "establish duration as the point in time when there is no longer a statistical difference between the treatment and placebo arms, using a 2 point or greater composite score" may be difficult to interpret using post-hoc analyses that involve multiple tests over time. Furthermore, duration of treatment effect as assessed by the time until no longer a statistical difference between the treatment and placebo arms exist may not be as informative as reporting the proportion of subjects who remain success at a pre-specified

time point after achieving success. Finally, control of the Type I error rate is relevant only for pre-specified hypotheses, which is not the case for your analysis plan.

Meeting Discussion:
The sponsor sought guidance from the Agency regarding the assessment of duration of treatment effect. The Agency responded that after establishing treatment effect against placebo at the primary time point, comparison against placebo would not be meaningful for assessing the duration of treatment effect. Taking into account that subjects randomized to placebo during the maintenance period are expected to "lose their response" at a certain time point during the maintenance period, all that would be needed to maintain a statistically significant difference is a small proportion to remain a success. Duration of effect should not be when a small proportion of subjects remain a success, as this does not reflect the response for the majority of the subjects. For assessing duration of effect a comparison can be made against a threshold level which, along with formal testing, is determined at the design stage. In addition, a criterion for "loss of response" should be defined *a priori* and agreed upon with the Agency.

Question 6:
Proposed format for ISS/ISE – The ISS will combine all safety data from the Sponsor studies (EV001, EV-002, EVB-003, EV-004 and EV-006). The ISE will combine the US Phase III studies (EV-001 and EV-002) and will incorporate EU PIII (EVB-003) results as supportive analysis.

Does the Agency agree with the Company's proposal for the format of the ISS/ISE or would the Agency prefer to see the ISS/ISE in a different format?

FDA Response:
You have provided very limited information regarding the content and analyses you plan to present in the Integrated Summary of Efficacy (ISE). It should be noted 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 done for the ISE, such analyses are considered exploratory. Establishing an efficacy claim would be based on efficacy data from the individual Phase 3 trials along with a replication of study findings.

In addition, you provided limited information regarding the analyses, content or format of your proposed integrated summary of safety (ISS). Therefore, we have the following general comments intended to assist you in preparing an analysis of the safety of your product:

The integrated summary of safety is detailed, integrated analysis of all relevant data from clinical study reports and provides a comprehensive discussion of safety across the entire clinical program. In addition to the analysis of safety data included in the individual clinical study reports, the ISS should include separate analyses of the following pooled data:

1. Pool #1: Single dose, placebo- controlled, pivotal Phase 3 Trials **EV-001** and **EV-002**
2. Pool #2: Single dose, placebo- controlled, Phase 3 trials **EV001** and **EV-002** and **EVB-003**

3. Pool #3: Repeat-dose open- label, Phase 2 trials **EV-004** and **EV-006** to compare incidence of treatment emergent adverse events from repeated injections to single injections.

The pooled analyses should include the following:

- Adverse event tables ≥ 1% regardless of causality.
- Adverse reaction tables (adverse reactions defined as those AEs with possible or probable causality) ≥ 1%.
- Case report forms (CRFs) and narratives with corresponding electronic links as discussed above.
- Line listings for all abnormal safety findings (e.g. adverse events, vital signs etc.)
- 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.
- Shift tables for all vital signs
- An analysis of ECG data
- If the product is approved in any other jurisdiction, provide a worldwide safety update in addition to the 120 day safety update.
- A discussion of any differences in the safety monitoring among the pooled trials and a comparison of safety results from the individual trials and pooled data.
- Safety analyses in subgroups of subjects by sex, race, age group (>65 years versus < 65 years), and baseline severity as measured by the investigator using the GLS.
- Evaluation of uncommon, rare or unexpected events that may be possibly related to the study drug
- An analyses of treatment emergent adverse events (TEAEs) in the pooled datasets to include all TEAEs, treatment-related TEAEs, serious TEAEs, discontinuations due to TEAEs, and possible spread of toxin TEAEs.

We agree with your plan to recode all safety data in the Phase 2 and Phase 3 trials using the MedDRA dictionary (v 17.0) to facilitate the pooled analyses.

For additional information about the location of ISS and ISE in the CTD, refer to the guidance for industry, *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* at:
http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm136174.pdf

Meeting Discussion:
The sponsor inquired regarding the approach to the benefit-risk assessment. The Agency recommended that the sponsor discuss how their product compares to the benefits and risks of all the products indicated for the treatment of glabellar lines.

Question 7:
The Agency released Ipsen Biopharmaceutical and Merz Pharmaceutical, the Sponsors of the Dysport and Xeomin products, from the Risk Evaluation Mitigation Strategy (REMS) requirement as long as a Medication Guide was part of the approved labeling. The letters to Ipsen Biopharmaceutical and Merz Pharmaceutical were dated 05/22/2012 and 07/16/2012, respectively.

Will the Agency release the company from preparing a REMS as long as the Sponsor has a Medication Guide as part of the approved labeling?

FDA Response:
Based on our review of the brief summary of safety information contained in your meeting package, a REMS may not be required for the safe use of your product in the treatment of moderate to severe glabellar lines. However, our final determination regarding the need for REMS will be based on the overall risk benefit assessment for your product at the time of the BLA review.

Additional comments

1. At the time of BLA submission, submit the coding dictionary used for mapping investigator verbatim terms to preferred terms or identify where this will be located in the proposed submission. The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).
2. Include the full text version of any referenced articles.
3. Provide your rationale/discussion regarding the acceptability of your foreign data. The acceptance of the foreign clinical data depends on its ability to be extrapolated to the US population. Refer to the ICH guidance for industry, *E5 Ethnic factors in the Acceptability of Foreign Clinical Data*.
4. As part of our review of your original biologic, the Agency will conduct a comprehensive assessment of the benefits and risks of your drug product. The information needed to complete this analysis is described in the Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making Draft PDUFA V Implementation Plan which is available at: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm. In your BLA submission, you should consider/discuss why your product provides an advantage with regard to benefit/risk compared with other FDA approved products.

To facilitate review of the data, we recommend that your BLA submission include a summary of the trials in tabular form such as the following:

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No.of subjects enrolled	Study Population	No.of Centers & Countries
Controlled Studies to Support Efficacy and Safety							
Studies to Support Safety							
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							

3.0 ADMINISTRATIVE INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The sponsor stated they intend to submit a complete application and therefore, there are no agreements for late submission of application components.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

- A preliminary discussion on the need for a REMS was held and it was concluded that at this time there does not appear to be a need for a REMS.

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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP 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 PSP 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 PSP, including a PSP 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.

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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

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 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).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. 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.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

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

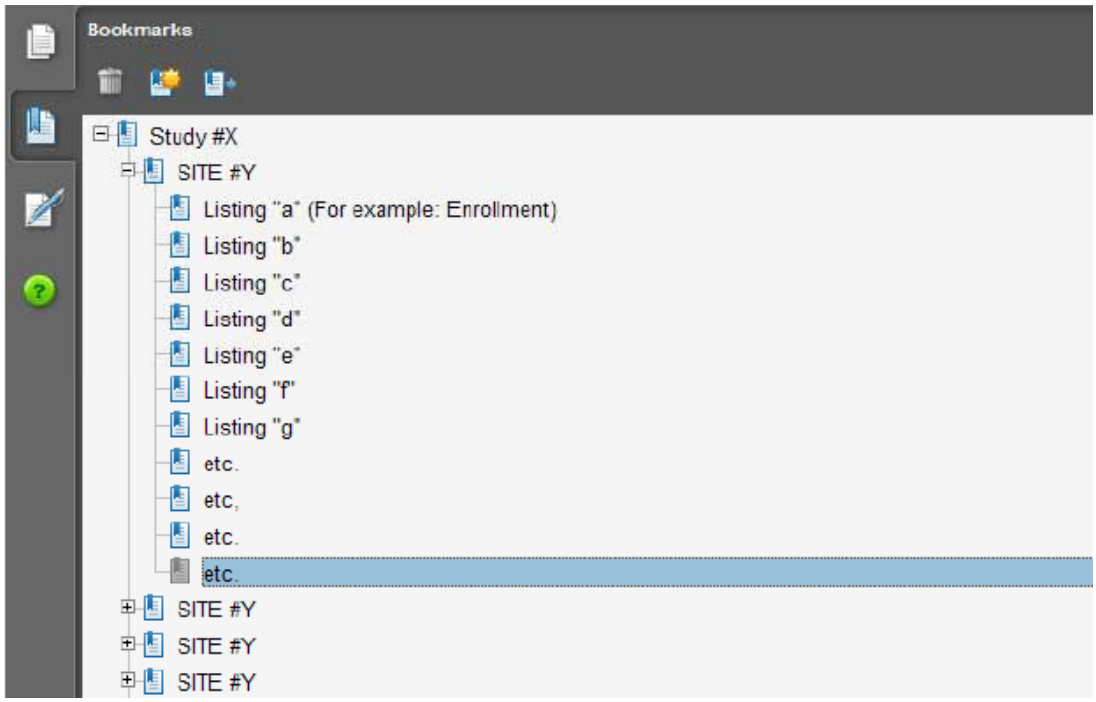
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571,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

4. 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).
5. 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

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
    a. 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
    b. Subject listing for treatment assignment (randomization)
    c. 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
    d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
    e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
    f. By subject listing, of AEs, SAEs, deaths and dates
    g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
    h. 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.
    i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
    j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. 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:

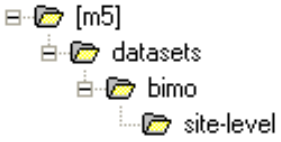
OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide 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

A. 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 Item[1]	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

B. 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

17 Pages have been Withheld In Full as B4(CCI/TS) Immediately Following this Page

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

/s/

KENDALL A MARCUS
10/27/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 121493

MEETING MINUTES

Evolus, Inc.
Attention: Del Stagg, PhD
Vice President, Regulatory
1027 Garden Street
Santa Barbara, CA 93101

Dear Dr. Stagg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for botulinum toxin type A for injection.

We also refer to the teleconference between representatives of your firm and the FDA on March 11, 2015. The purpose of the meeting was to discuss the development program for botulinum toxin type A 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 Belainesh Robnett, Regulatory Project Manager at (240) 402-4236.

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-Phase 3 Meeting

Meeting Date and Time: March 11, 2015; 10:00am
Meeting Format: Teleconference

Application Number: IND 121493
Product Name: botulinum toxin type A for injection
Proposed Indication: Treatment of moderate to severe glabellar lines
Sponsor Name: Evolus, Inc.

Meeting Chair: Kendall Marcus, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES
Kendall Marcus, MD, Director, DDDP
David Kettl, Acting Deputy Director, DDDP
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Roxy Harbowyj, MD, Clinical Reviewer, DDDP
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Belainesh Robnett, MS, Regulatory Health Project Manager, DDDP
Dawn Williams, BSN, Regulatory Health Project Manager, DDDP
Maria-Teresa Gutierrez-Lugo, PhD, Product Quality Team Leader, DTP
Paul Kirwan, PhD, Product Quality Reviewer, DTP
Mohamed Alosh, Biostatistics Team Leader, DB III
Matt Guerra, PhD, Biostatistics Reviewer, DB III
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP III

SPONSOR ATTENDEES
Chris Marmo, PhD, CEO
Rui Avlar, MD, CMO
John Gross, MD, CSO
Scott Cannizzaro, PhD, CFO
Gregg Peterson, Sr. Director, Clinical Operations
Fran Reid, RAC, Associate Director, Regulatory
(b) (4) (Consultant)
Del Stagg, PhD, VP Regulatory

TELECONFERENCE OBJECTIVES:
To discuss the development program for botulinum toxin type A for injection

Regulatory Correspondence History

We have had the following teleconference with you:
- March 12, 2014 Pre-IND

We have sent the following correspondences:
- December 19, 2014 Special Protocol Agreement
- October 16, 2014 Special Protocol- No Agreement
- September 8, 2014 Study May Proceed

Chemistry, Manufacturing and Controls (CMC)

Question 1:
Does the Agency concur the product now meets specifications per ICH Q5A?

Response:
Your question is unclear. We do not understand whether your question is related to drug substance or drug product specifications. Additionally, the ICH guideline to which you are referring covers viral safety issues of biotechnology products derived from cell lines of human or animal origin.

Based on the background information you provided, it appears that you are requesting feedback on the approach used to address the (b) (4)% overage of your drug product. To support reduction of overage from (b) (4)% to (b) (4)%, you changed the drug product (DP) manufacturing process (b) (4) (b) (4) to vacuum drying and provided process validation, release and stability results for the process validation batches. You also indicate that the phase 3 clinical supplies were manufactured using the vacuum drying process. Overall, your strategy to reduce DP overage is reasonable. However, prior to beginning phase 3 clinical trials, you should demonstrate analytical comparability between drug product manufactured (b) (4) (b) (4) (pre-change DP) and drug product manufactured by the vacuum dried process (post-change DP). Comparability of the pre-change and post-change DP is necessary to justify the relevance of the clinical and non-clinical data generated using the pre-change DP. For additional guidance on comparability, please refer to ICH Q5E.

Meeting Discussion:
The sponsor clarified the relationship between their product and the NABOTA product.

The sponsor will provide additional documentation regarding the products that they use in the different clinical studies.

The sponsor requested guidance on items that should be delineated in this report. The Agency clarified that the drug substance quality attributes should be presented in a side by side format for the drug product manufactured by the 2 different manufacturing processes.

Question 2:
Does the Agency concur with the validated LD_{50} Assay for product release?

Response:
No, we do not concur. In order to establish that your LD50 assay is acceptable for product release, you should address the following:

a. As there is no international or national reference standard for botulinium toxin A, a qualified, in-house reference material should be established and the potency of your product lots should be reported as in-house units (ICH Q6B).

b. The in-house primary reference material should be prepared from lot(s) that are representative of production and clinical materials. This is typically a well characterized drug product (or drug substance) lot of your own product (ICH Q6B). (b) (4) (b) (4) (b) (4). For in-house reference material, the license holder has the responsibility to have control of the quality of the qualified reference material.

c. Release potency testing of DWP-450 drug product intended to be used in the phase 3 clinical studies should be determined using your qualified in-house reference material. This is important because your product is labeled and administered based on potency units.

The design of the LD50 assay, including the numbers of animals used per dilution, the total number of dilutions points, and the Probit regression analysis of parallelism, appears acceptable.

Question 3a:
Does the Agency concur with the timing for this data to be submitted to the BLA?

Response:
We interpret your question as the timing for amending your IND 121493 with the characterization data referred to above. The proposed March 2015 timeframe is acceptable. The characterization data will be reviewed upon submission.

Question 3b:
Does the Agency concur with the analysis and identity of the single (b) (4) impurity?

Response:
The extent of characterization of the (b) (4) impurity is acceptable at this stage of development.

Question 4:

Does the Agency concur with the timing for this data to be submitted with BLA?

Response:
We interpret your question as the timing for amending your IND 121493 with the force degradation stability data. Your proposal of amending your IND with this data prior to submission of a BLA is acceptable.

Question 5:
Does the Agency concur with the timing for the additional specification to be established and submitted with BLA?

Response:
Yes, we concur with the timing for establishing additional specifications for control of drug substance.

With respect to your current IND 121493, the proposed acceptance criteria for release and stability testing of drug substance are acceptable at this stage of development.

Question 6a:
Does the Agency concur with our proposed total protein specification?

Response:
Yes, we concur. The proposed total protein specification is acceptable at this stage of development.

Question 6b:
Does the Agency concur with our proposal to not include the abnormal toxicity test?

Response:
No, we do not concur with your proposal of omitting the abnormal toxicity test or the general safety test because this test is a regulatory requirement for naturally derived products as per 21 CFR 610.11. To comply with this regulatory requirement, please address the following:

a) Implement the general safety test or abnormal toxicity test in lieu of the general safety test, for DP release and include the general safety test in DP specification. A modified abnormal toxicity test or general safety test is conducted on a group of animals by injecting a mixture of a monospecific neutralizing antitoxin A antibody and your drug product.

b) Demonstrate the specificity of type A antibody used in the general safety test or abnormal toxicity test.

Monospecific antibodies for botulinum toxin type A are commercially available.

Question 7:
Does the Agency concur with our proposed cell bank system and timing to be submitted with BLA?

Response:
We cannot comment on the adequacy of the cell bank system until we review your data. Your proposal to submit data supporting a two-tier cell bank system at the time of BLA submission is acceptable.

Question 8:
Does the Agency concur with this plan for updating the drug substance stability testing program?

Response:
Yes, we concur with your plan for updating the drug substance stability testing program to include accelerated stability studies.

Question 9a:
Does the Agency concur that the validations of the building, equipment and manufacturing process of finished product manufactured in the new facility is adequate to support the use of the new facility to manufacture commercial product?

Response:
We cannot answer your question until we review the data supporting the transfer of drug substance manufacturing to the new manufacturing site. Additionally, a new manufacturing site for drug substance would require an inspection.

Meeting Discussion:
The sponsor clarified that only the drug product will be transferred and when this happens, they will consult the Agency.

Question 9b:
Does the FDA concur with us that completion of the above listed studies would meet all non-clinical testing requirements in support of the new facility manufactured toxin clinical use and regulatory requirements?

Response:
Yes, we concur.

Question 9c:
Based on the current Validation Schedule for the new manufacturing facility, the stability studies for product manufactured in the new facility will start in October 2015. Can Evolus submit the BLA with 3 months of long-term and accelerated stability data for product manufactured in the new facility and supplement the BLA with additional stability data during the review period without impacting the review cycle?

Response:
We generally expect a minimum of 6 months of long term stability data at the time of BLA submission. Additionally, please be aware that the shelf life of your product will be established based upon the actual data submitted in support of the application (see ICH Q5C).

Meeting Discussion:
The Agency requested that 6 months of stability data be submitted with the BLA submission. If 3 months of stability data are provided followed by an additional 6 months, only 9 months of shelf life will be supported.

Pharmacology/Toxicology

Question 10:
Does the Agency concur that no further non-clinical studies are needed for drug product manufactured via the vacuum drying process (b) (4)?

Response:
Yes, we concur.

Clinical

Question 11:
Does the Agency agree that the addition of a new Phase 2 Open Label study to collect safety data in 475 subjects conducted in the United States will fulfill the safety data requirements for ICH E1A?

Response:
You propose a new Phase 2 trial (EV-006) that is an open label, single dose trial to evaluate the safety of DWP-450 in 475 adult subjects for the treatment of moderate to severe glabellar lines (assessed by the investigator and subject). Subjects will be followed on day 7, 14 and 30 days after a single dose injection. Safety evaluation will include review of systems, directed questionnaire and physical exam (blood pressure, heart rate, respiratory rate, testing cranial nerves, extra-ocular movement and muscular weakness). However, you proposed not to conduct cardiac safety assessment (e.g. EKG) as well as laboratory assessment.

Drug products for the temporary improvement of upper facial lines have the potential for chronic intermittent use; therefore, you should establish the long-term safety of the drug product in the proposed population at the proposed dose. Long-term controlled trial data are preferred over open-label extension safety data because of the difficulty in interpreting adverse events data in the absence of a concurrent control.

The ICH guidance for industry E1A (The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions) provides advice regarding the number of subjects exposed and duration of treatment needed to inform the safety database. However, because upper facial lines are aesthetic indications and the risk-benefit assessment for this indication differs from that for indications such as blepharospasm, cervical dystonia, migraine, or spasticity, the minimum number of subjects described in ICH E1A may not be sufficient to allow assessment of the risk versus the benefit for the indications of upper facial lines, conditions with minimal morbidity. The size of the safety database may vary depending on the formulation and anatomic location to be treated, as well as the need to assess the safety outcomes of multiple dose use.

We acknowledge that the trial EV-004 [<300 subjects; open label, multiple dose (up to 4 treatments), with f/u for 365 days) is ongoing; data from this trial has not been submitted for review. For safety assessments of repeat dosing, it appears that your currently proposed number of subjects with multiple exposures and a minimum of twelve month follow-up is insufficient. You are referred to previously communicated review comments from September 8, 2014.

Therefore, we recommend that the study design of your proposed Phase 2 trial (EV-006) should be modified to include adequate assessment of safety of multiple doses of DWP-450 in the target population. You should also address the potential for immunogenicity of botulinum toxin and evaluate the effect of immunogenicity on the efficacy and safety. Safety monitoring should also include periodic EKG and laboratory assessments.

While the number of additional subjects you propose for trial EV- 006 may be sufficient to achieve compliance with the E 1 A guidelines, the adequacy of the safety database will be a review issue.

Meeting Discussion:
There was general discussion regarding size and consistency of the population recommended for safety analyses. The sponsor agreed to revise their protocol EV-006 to include the study population defined by investigator and subject severity scale, and to provide sufficient multiple doses (more than 2) safety data. The sponsor noted that they would include cardiac safety monitoring (ECGs) and periodic laboratory assessment including immunogenicity.

Question 12:
Does the Agency agree with following design regarding the EV006 open label study?

Response:
Please refer to Agency comments on Question 11 above. Please also refer to FDA Draft Guidance for Industry Upper Facial Lines: Developing Botulinum Toxin Drug Products which is located at the following link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM407983.pdf

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

3. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You

should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

4. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.

5. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP 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 PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP 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

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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 CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

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/s/

KENDALL A MARCUS
03/27/2015