CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212489Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104380

MEETING PRELIMINARY COMMENTS

Neurocrine Biosciences, Inc.
Attention: Kika Teudt, MS
Director, Regulatory Affairs
12780 El Camino Real
San Diego, CA 92130

Dear Ms. Teudt:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BIA 9-1067 (Opicapone).

We also refer to your May 15, 2018, correspondence, received May 15, 2018, requesting a meeting to discuss the available data to support an NDA submission.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, please contact me at stacy.metz@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}
Stacy Metz, PharmD
Senior Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	PreNDA
Meeting Date and Time:	September 11, 2018; 1:00-2:00 PM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 104380
Product Name:	Opicapone (BIA 9-1067; OPC)
Indication:	Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "OFF" episodes.
Sponsor/Applicant Name:	Neurocrine Biosciences, Inc. (NBI)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 11, 2018; 1:00-2:00 PM EST; White Oak Building 22, Conference Room: 1315 between Neurocrine Biosciences, Inc. and the Division of Neurology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

A Type B End-of-Phase 2 (EOP 2) meeting between NBI and the Division of Neurology Products was held on January 18, 2018. The purpose of the meeting was to obtain the Division's comments on the sufficiency of the OPC development program data package to support an NDA.

The purpose of this Type B Pre-NDA meeting is to discuss the proposed opicapone (OPC, BIA 9-1067) NDA content, associated analysis plans, and format.

The Pre-NDA meeting objectives are to obtain Division comments on:

- The proposed statistical analysis plans (SAP) for the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS).
- The human OPC metabolite characterization data.
- The proposed stability data package.
- The proposal to solicit an environmental assessment claim of categorical exclusion.
- The proposed content and format of the OPC NDA that will constitutes the applicant's marketing application.

2.0 DISCUSSION

2.1. Integrated Summary of Effectiveness

Question 1:

Does the Division agree with the proposed pooling strategy for the ISE?

FDA Response to Question 1:
We agree that efficacy results from randomized, blinded and controlled trials should be analyzed separately from the efficacy information from open-label studies. The statistical analyses in an ISE are exploratory, and the appropriateness of these analyses will be a matter of review.

Question 2:

Does the Division agree with the proposed efficacy analysis methods for the ISE?

FDA Response to Question 2:
Please see our response to Question 1.

Question 3:

Does the Division agree with the efficacy subgroups planned for inclusion in the ISE?

FDA Response to Question 3:
Please see our response to Question 1. The ISE needs to include analyses of efficacy for all required subgroup specified under 21 CFR 314.50(d)(5)(v). If there are enough Parkinson patients who had neurosurgical intervention (including implanted deep brain stimulators [DBS]) or used amantadine during the studies, conduct a subgroup analysis of efficacy in these patients.

Question 4:

Does the Division agree that the ISE can be split across Module 2 and Module 5, with the narrative portion located in the Summary of Clinical Efficacy (SCE) Module 2.7.3, and the ISE appendices of tables, figures, and datasets located in Module 5.3.5.3?

FDA Response to Question 4:

Yes, provided the SCE document provides sufficient room for full presentation and appropriate discussion of all efficacy findings within the space limitations of the SCE. The text portion of the ISE should contain functioning hyperlinks to the information referenced in the appendices, tables, figures, listings, and datasets. All appendices must have a hyperlinked Table of Contents that uses logical names that describe its contents. If an appendix contains subsections, the TOC for the appendix should contain hyperlinks or bookmarks to each subsection. Create a Master TOC that lists the order and title of each of the appendices. The Master TOC should contain functioning hyperlinks or bookmarks that bring the reader to the location of each appendix listed. The ISE needs to be clearly labeled and navigable.

The study reports, ISE and ISS should include a discussion of the data findings for all required subgroups analyses and adverse events of special interest.

Question 5:

Does the Division have any additional comments on the structure and analyses included in the ISE that would aid review of the OPC NDA?

FDA Response to Question 5:

Please see our response to Question 4.

2.2. Integrated Summary of Safety

Question 6:

Does the Division agree with the proposed strategy to summarize the Phase 3 data within the ISS in the pools as described, and that safety data from Phase 1 and Phase 2 studies will be summarized separately?

FDA Response to Question 6:

In the ISS, pool randomized, placebo-controlled and blinded studies separately from the open-label studies. We agree that Phase 1 and Phase 2 studies that you will not rely upon to provide evidence of safety or effectiveness in your NDA can be presented separately.

Question 7:

Does the Division agree with the proposed strategy to summarize exposure data within the ISS?

FDA Response to Question 7:

We have the following comments:

- Count the number of individual subjects exposed to a given dose using the actual dose subjects received during the period of exposure rather than the group mean dose. For example; only subjects treated with 50 mg each day in the exposure period should be counted

in the group treated with 50 mg in the period. A group of subjects treated with a mean of 50 mg for a defined period of exposure would not be acceptable method for counting exposure.

- Count the number of individual subjects exposed for a defined period using the actual number of days that subjects were treated with a specific dose of opicapone. For example; only subjects treated with an actual dose of opicapone 50 mg for 30 days would be counted as having been exposed to 50 mg for 30 days. A group of subjects treated with opicapone 50 mg for a mean period of 30 days is not an acceptable method for counting exposure. Please see the table shell below.

	Actual Dose			
	OPC <25 mg, n	OPC 25 mg n	OPC >50 mg n	Any OPCn
Exposure Actual Number of days on dose				
1 day				
30 to < 180 days				
180 to <365 days				
≥ 365 days				

- A summary table of exposure listing individual studies with the number of subjects by dose and duration in days is useful.

- Please indicate clearly the numbers of subjects included in the active treatment arm (by dose) versus the placebo arm in Studies 301 and 302, and those subjects who continued into open-label treatment (by dose) in each study.

- Exposure for subjects treated with the non-micronized formulation should not be included with subjects treated with the to-be -marketed formulation. Otherwise, your plan to calculate exposure for subjects treated with the non-micronized formulation in the Phase 1 and 2 studies separately is acceptable.

- The adverse event tables should include a column that provides the actual dose patients received when the adverse event was first reported (e.g., DOSEON column).

- We encourage you to submit a supplemental exposure dataset for the ISS that is one row per patient covering both the DB and OL phases of the clinical studies and provides the dates treatment with a dose started and ended, the actual dose administered, the number of study of days exposed for the dose that combines exposure in the placebo-controlled and open-label studies.

Question 8:

Does the Division agree with the proposed categories and strategy of analysis of AESIs for the ISS?

FDA Response to Question 8:
Yes. Please include diarrhea to the list of AESIs. Include a discussion of whether subjects with diarrhea were withdrawn from opicapone, rechallenged, and whether diarrhea reoccurred following rechallenge.

Question 9:

Does the Division agree with the subgroups planned for inclusion in the ISS?

FDA Response to Question 9:
Please see our response to Question 3

Question 10:

Does the Division agree that the ISS can be split across Module 2 and Module 5, with the narrative portion located in the Summary of Clinical Safety (SCS) Module 2.7.4, and the ISS appendices of tables, figures, and datasets located in Module 5.3.5.3?

FDA Response to Question 10:
Our response to Question 4 applies to the ISS as well. However, because of the number of subjects exposed to opicapone and the number of studies performed, the space constraints of the SCS may prevent it from adequately presenting all the findings that a complete ISS must contain. The SCS should not contain information or tables not discussed or explained in the ISS.

Question 11:

Does the Division have any additional comments on the structure and analyses included in the ISS that would aid review of the OPC NDA?

FDA Response to Question 11:
See our responses to Questions 6 through 10, above.

2.3. Clinical Pharmacology

Question 12:

Does the Division agree that the OPC metabolite profile has been adequately characterized and the available data will support an NDA filing?

FDA Response to Question 12:
Based on the steady state plasma AUC ratio of metabolites to parent (Study 126), it seems that the sulfated metabolite is the only major metabolite. Based on this study, all other metabolites have less than 25% of exposure relative to the parent. Additionally, at steady state, the minor active metabolites appear to not contribute to ≥50% of parent activity, based on the relative exposure to parent and the in vitro potency findings. Therefore, on face, OPC metabolite profile has been adequately characterized. The available data support an NDA submission.

2.4. Chemistry, Manufacturing and Controls

Question 13:

Does the Division agree that the considerable amount of stability data on the packaged product from the registration lots, augmented by data on supportive lots, will allow the Division to accept the NDA for filing in the absence of stability data from the product packaged at the proposed commercial packager, and would be sufficient to conduct a substantial review of the application and make a shelf life determination?

FDA Response to Question 13:

Your proposal is acceptable, provided that the container closure components for the commercial packaging configurations are identical to the registration batches, and that the packaging procedures and controls used by Bial and (b) (4) for the registration batches are comparable to the procedures and controls to be used at the commercial site, (b) (4)

2.5. Environmental Assessment

Question 14:

Does the Division agree that OPC qualifies for an environmental assessment claim of categorical exclusion?

FDA Response to Question 14:

Based on the information provided in the July 13, 2018 amendment, we agree that a claim for exclusion under 21 CFR 25.31(b) would be appropriate. Please provide a statement of no extraordinary circumstances per 21 CFR 25.15, in the claim when you submit the NDA.

2.6. Procedural

Question 15:

If the NDA is submitted on electronic media, does the Division have a preference for the media used for the submission?

FDA Response to Question 15:

Please refer to the Transmission Specifications. If the submission is over 45 GB, you should utilize a USB Drive.

Question 16:

Does the Division agree that the proposed content and format of the OPC NDA constitute a fileable marketing application?

FDA Response to Question 16:

The adequacy of a NDA submission can only be determined following initial review by the appropriate review disciplines after we receive the application.

From a technical standpoint (not content related), the proposed format of the planned NDA is acceptable. However, please see additional comments below:

- Please do not provide reviewer's aid in m1.11.4, m3.3 and m5.2. Providing a single hyperlinked reviewer's aid/ reviewer's guide in module m1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application, would be helpful to reviewers.
- For archival purposes, submit a pdf file of the labeling document submitted in word. Also, when you submit word documents, make sure the leaf title includes "word", so reviewers can quickly identify the word version of the document.
- Do not provide duplicate sections (e.g. 3.2.p.1.3, 3.2.p.2.4, etc.,) for same documents. Documents for "Bottles" (b) (4) " can be submitted under a single 3.2.p.1.3. or 3.2.p.2.4 section, making sure the leaf titles are clear, and reviewers can differentiate between "Bottles" (b) (4) " documents
- Periodic Safety Update Report should be provided as a single pdf file with bookmarks, table of contents and hyperlinks in the eCTD section, m5.3.6. Please ensure that the leaf title of the report includes the reporting period, (e.g., PSUR-Jan20-2018-Jan-19-2018), so reviewers can quickly differentiate one report from another.
- Include "bimo" in the leaf titles of all BIMO documents
- Please note that Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6. Each study should have an STF, and all components regarding that study should be tagged and placed under the study's STF including case report forms (crfs) and datasets. Case Report Forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form".

Additional Clinical Comment:
Provide the meaning for all coded, sponsor-created and derived variables in plain language and in the Reviewer's Guide.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our May 31, 2018, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on

submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

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 subjects 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 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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format.

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.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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 the 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

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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/

STACY M METZ
09/06/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104380

MEETING MINUTES

Neurocrine Biosciences, Inc.
Attention: Kika Teudt, MS
Director, Regulatory Affairs
12780 El Camino Real
San Diego, CA 92130

Dear Ms. Teudt:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BIA 9-1067 (opicapone).

We also refer to the meeting between representatives of your firm and the FDA on January 18, 2018. The purpose of the meeting was to obtain the Division's comments on the sufficiency of the opicapone development program data package to support a new drug application.

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 Stacy Metz, Senior Regulatory Project Manager, at (301) 796-2139.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
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:	End-of-Phase 2
Meeting Date and Time:	January 18, 2018; 3:00-4:00 PM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Application Number:	IND 104380
Product Name:	BIA 9-1067 (opicapone)
Indication:	Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "OFF" episodes.
Sponsor/Applicant Name:	Neurocrine Biosciences, Inc.
Meeting Chair:	Billy Dunn, MD
Meeting Recorder:	Stacy Metz, PharmD

FDA ATTENDEES
Robert Temple, MD, Deputy Director for Clinical Science
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Dave (Gerald) Podskalny, DO, MPHS, Clinical Team Leader
Ken Bergmann, MD, Clinical Reviewer (via phone)
Mariam Ahmed, PhD, Clinical Pharmacology Reviewer
Kun Jin, PhD, Statistical Team Lead
Xiangmin Zhang, PhD, Statistical Reviewer
Dave Jones, MD, Clinical Reviewer
Stacy Metz, PharmD, Senior Regulatory Project Manager

SPONSOR ATTENDEES
Chris O'Brien, MD, Chief Medical Officer, Neurocrine Biosciences, Inc.
Malcolm Lloyd-Smith, MSc, Chief Regulatory Officer, Neurocrine Biosciences, Inc.
Grace Liang, MD, Medical Director, Neurocrine Biosciences, Inc.
Gordon Loewen, PhD, Vice President, Preclinical Development, Neurocrine Biosciences, Inc.
Josh Burke, MS, Director, Biostatistics/Clinical Programming, Neurocrine Biosciences, Inc.
Kika Teudt, MS, Director, Regulatory Affairs, Neurocrine Biosciences, Inc.
Eiry Roberts, MD, Clinical Consultant, Neurocrine Biosciences, Inc.

Paula Costa, PharmD, Director, Global Regulatory Affairs , BIAL- Portela & Ca, S.A.
Helena Gama, MD, Head of Clinical Development, BIAL – Portela & C[a], S.A.
Patricio Soares da Silva, MD, PhD, Director, Research and Development, BIAL- Portela & Ca, S.A.

1.0 BACKGROUND

The Investigational New Drug (IND) application for opicapone was opened by BIAL – Portela & C[a], S.A (BIAL) in March 2011. The IND was transferred from BIAL to Neurocrine Biosciences, Inc. (NBI) in March 2017.

The purpose of this Type B EOP2 meeting is to obtain Division agreement on the sufficiency of the opicapone development program data package to support a New Drug Application.

The specific objectives of this meeting are to gain Division alignment on the following:

- Adequacy of the completed Phase 3 pivotal studies to support an NDA.
- Adequacy of the clinical pharmacology program to support an NDA.
- Adequacy of the nonclinical program to support an NDA.
- Proposal for submission of a Pediatric Waiver Request.

FDA sent Preliminary Comments to Neurocrine Biosciences, Inc. on January 16, 2018.

2.0 DISCUSSION

2.1. Clinical Questions

Question 1a:
Does the division agree that the design and duration of the Phase 3 BIA-91067-301 and BIA-91067-302 studies are sufficient to assess opicapone safety and efficacy in the target population and, thereby, fulfill the requirement for two adequate and well-controlled studies required to support a New Drug Application?

FDA Response to Question 1a:
On face, Study 301 and Study 302 show a statistically significant reduction for the change in Off time (primary endpoint) in patients with Parkinson's disease (PD) treated with opicapone, compared with placebo. Whether your studies provide adequate safety and efficacy information in support of the proposed indication is a matter of review.

We note that a considerable proportion (20-25%) of patients in both studies were treated with concomitant amantadine. Your NDA should include a description of the proportion of patients treated with amantadine at baseline for all treatment groups in Study 301 and Study 302, and exploratory analyses of the potential impact of amantadine treatment on the primary and key secondary efficacy endpoints in both studies.

Meeting Discussion:
No further discussion at the meeting.

Question 1b:
Does the Division agree that ON-time without troublesome dyskinesia could be considered an acceptable secondary efficacy endpoint for inclusion in the prescribing information?

FDA Response to Question 1b:
Provide that you provide an adequate plan for controlling Type I error, ON-time without troublesome dyskinesia could be considered for description in labeling.

Meeting Discussion:
No further discussion at the meeting.

Question 2:
Does the Division agree that patient exposure data from the opicapone clinical development program fulfills the ICH and FDA Extent of Population Exposure requirements and would be sufficient to support an NDA for the long-term use of opicapone for the treatment of Parkinson's disease?

FDA Response to Question 2:
On face and subject to review, your proposed safety database of 700 PD patients treated continuously for at least one year, with doses used clinically of the to-be-marketed formulation, would be adequate. At least half of these patients would need to have received the highest recommended opicapone dose.

Sponsor's Pre-Meeting Comments
The opicapone clinical database fulfills the ICH E1A requirements for exposure to dosage levels intended for clinical use (50 mg) for at least one year. In view of this, the sponsor would like to clarify the specific requirement of having "at least half of these patients" dosed for at least a year at the highest recommended dose? We look forward to further discussion of this topic at the meeting.

Meeting Discussion:
The discussion clarified the response to Question 2 to mean that the long-term safety database needs to contain information from 100 patients treated continuously for at least a year with dosages of opicapone intended for clinical use. At least half of these patients (50) would need to have received the highest recommended dose of opicapone for the year.

Question 3:
Does the Division agree that Phase 3 studies BIA-91067-301 and BIA-91067-302 conducted outside the United States (in accordance with 21 CFR 314.106 Foreign Data, and 21 CFR 314.120 Foreign Clinical Studies Not Conducted Under an IND) are sufficient to serve as the basis for an evaluation of safety and efficacy in the target population in an opicapone New Drug Application?

FDA Response to Question 3:
Your application should include detailed justification as to how your study populations are applicable to the PD population in the US. We refer you to the guidances below for general requirements. Please note that full and unfettered access to data is needed to insure reliability, transparency and traceability from case report form to the study datasets. You must comply with U.S. regulations to provide financial disclosure for all investigators in studies supporting the safety and effectiveness in your NDA. The clinical sites must be available for FDA site inspection.

https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm124939.pdf

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm294729.pdf

Meeting Discussion:
No further discussion at the meeting.

2.2. Clinical Pharmacology Questions

Question 4:
Does the Division agree that the biopharmaceutical data package is sufficient to support a New Drug Application for opicapone?

FDA Response to Question 4:
In your briefing package (page 62), you indicated that the 25 mg is not intended for marketing in US. This will limit the ability to adjust dosing based on intrinsic and extrinsic factors. Please clarify why you do not intend to market the 25 mg capsule.

Sponsor's Pre-Meeting Comments
The only identified intrinsic or extrinsic factor resulting in altered pharmacokinetics potentially warranting a lower dose is moderate hepatic impairment. (b) (4) We look forward to further discussion of this topic at the meeting.

Meeting Discussion:
(b) (4)

Question 5:
Does the Division agree that the completed and planned Clinical Pharmacology studies are sufficient to support a New Drug Application for opicapone?

FDA Response to Question 5:

We have the following comments:

1) You need to conduct a study in subjects with severe hepatic impairment.
2) Based on your briefing package, opicapone is also substrate for BCRP and OAT1P3. As per FDA guidance for clinical DDI studies, you need to study the effect of these transporters inhibitors on opicapone disposition.

Sponsor's Pre-Meeting Comments

Based on the observed 2-fold increase in opicapone exposure in subjects with moderate hepatic impairment, and an even larger magnitude of effect anticipated in patients with severe hepatic impairment, (b) (4) Therefore, a study in subjects with severe hepatic impairment is not warranted.

As was described in the meeting briefing document, the sponsor is currently conducting clinical studies evaluating the effect of a P-gp inhibitor (quinidine) on opicapone absorption, and the effect of a CYP2C8/OATP1B inhibitor (repaglinide) on opicapone pharmacokinetics. We will evaluate the results of these studies to determine how predictive the in vitro models were for in vivo effects. These data will clarify the need for additional drug-drug interaction studies, if any. We look forward to further discussion of these topics at the meeting.

Meeting Discussion:

The sponsor's proposals included in the pre-meeting comments are acceptable.

2.3. Abuse Liability Question

Question 6:

Does the Division agree that formal nonclinical and clinical abuse liability studies are not warranted for opicapone, a peripherally-acting COMT inhibitor?

FDA Response to Question 6:

No, we do not agree. We have the following recommendations:

1. For all Phase 1, 2 and 3 clinical studies, you should report all potential abuse-related adverse events (AEs). Also, you should provide a list of terms that will prompt these reports, such as euphoria, dissociative effects, hallucinations, psychosis, changes in mood, impaired cognition, attention, psychomotor effects, dopamine dysregulation syndrome, inappropriate affect, patient dropouts, overdoses, misuse, lost or unaccounted for medication and unjustified dose increases.

2. Your evaluation of dependence and withdrawal should include all new AEs occurring after drug discontinuation that are reported during the post-study visit for patients with PD as well as in healthy subjects.

3. Provide receptor binding data for serotonin receptors, particularly 5-HT 2A for opicapone and its active metabolites. The current receptor binding assay contains only serotonin non-selective receptor data.

4. If performed, please summarize the status and results of animal studies related to abuse potential and withdrawal.

Meeting Discussion:
No further discussion at the meeting.

2.4. Nonclinical Question

Question 7:
Does the Division agree that the data package for the nonclinical studies (pharmacology, safety pharmacology, ADME, chronic toxicology, reproduction and development toxicology, genotoxicity, and carcinogenicity) have adequately characterized the non-clinical properties of opicapone and would support a New Drug Application for opicapone?

FDA Response to Question 7:
Based on the information provided in the briefing document, it appears that the nonclinical program for opicapone would be sufficient to support an NDA. However, we have the following comments:

1) You should ensure that all circulating major human metabolites (i.e., ≥ 10% of total circulating drug-related material) have been adequately assessed in the appropriate nonclinical studies (see ICH M3(R2), January 2010; ICH M3(R2) Q&A, February 2013).
2) It is unclear whether all potentially genotoxic impurities have been adequately assessed (see ICH M7, May 2015). We ask that you provide a summary table for potential impurities from the current manufacturing process that includes the following information:
    a. Code number and any previously used code numbers
    b. Chemical structure
    c. Source of impurity (e.g., synthesis intermediate, byproduct)
    d. Results from in silico or in vitro genotoxicity assessment, and the location of the corresponding reports
    e. For each potential genotoxic impurity, clarify whether you will control the impurity in the drug substance or provide data to demonstrate the impurity is purged during the manufacturing process.

The adequacy of the nonclinical data will be a matter of review.

Meeting Discussion:
No further discussion at the meeting.

2.5. PREA Question

Question 8:
Does the Division agree with the proposed strategy for the opicapone Initial Pediatric Study Plan and waiver request submission?

FDA Response to Question 8:
New treatments for Parkinson's disease typically qualify for a drug specific waiver. We refer you to the PREA Requirements in Section 3 of this letter for additional information. Please note, your initial Pediatric Study Plan (iPSP) needs to be submitted to the IND within 60 days of this End of Phase 2 meeting.

Meeting Discussion:
No further discussion at the meeting.

3.0 OTHER IMPORTANT MEETING INFORMATION

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 Pedsdrugs@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 (cder-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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** 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.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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.

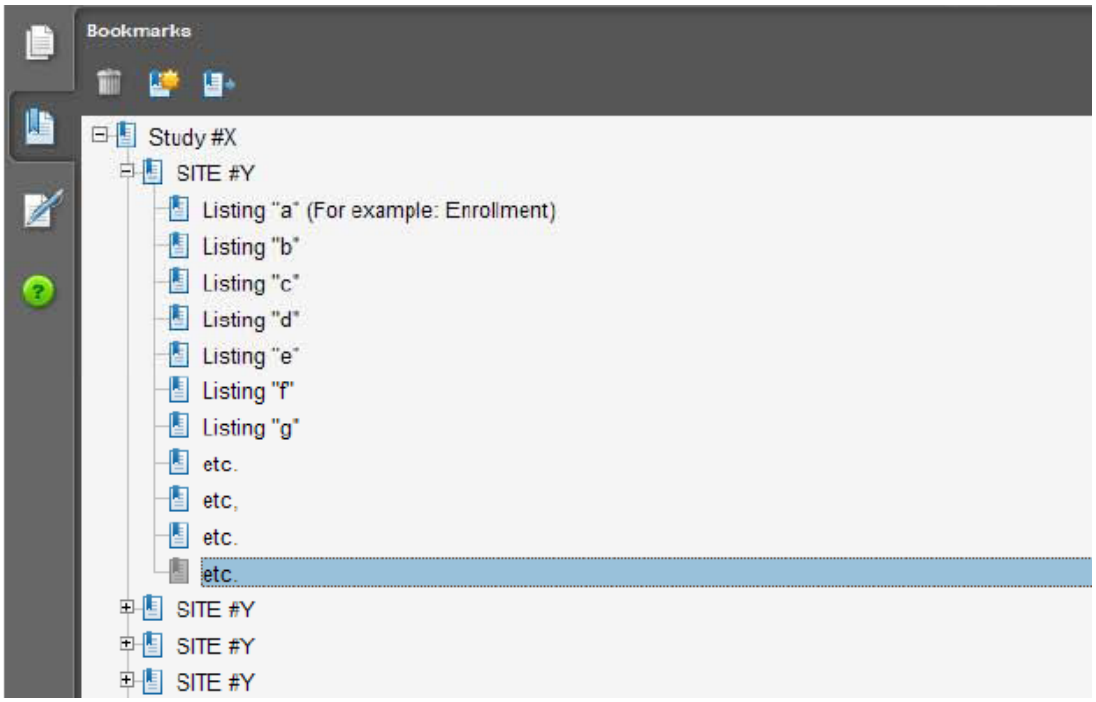
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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.

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

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

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

There are no action items.

6.0 ATTACHMENTS AND HANDOUTS

None.

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

/s/

ERIC P BASTINGS
02/13/2018