CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022075Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22075

MEETING MINUTES

Kyowa Kirin Pharmaceutical Development, Inc.
Attention: Susan White
Director, Regulatory Affairs
212 Carnegie Center, Suite 101
Princeton, NJ 19067

Dear Ms. White:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Istradefylline Tablets (KW-6002).

We also refer to the meeting between representatives of your firm and the FDA on February 15, 2018. The purpose of the meeting was to discuss the presentation of the content and format of the efficacy and safety data for the NDA resubmission following the February 28, 2008, Not Approvable Action Letter.

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, Pharm, 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:	Pre-NDA
Meeting Date and Time:	February 15, 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:	NDA 22075
Product Name:	
Indication:	Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "OFF" episodes
Sponsor/Applicant Name:	Kyowa Kirin Pharmaceutical Development, Inc.
Meeting Chair:	Billy Dunn, MD
Meeting Recorder:	Stacy Metz, PharmD

FDA ATTENDEES
Ellis Unger, MD, Director Office of Drug Evaluation (ODE I)
Robert Temple, MD, Deputy Director for Clinical Science
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Nick Kozauer, MD, Associate Director
Dave (Gerald) Podskalny, DO, MPHS, Clinical Team Leader
Len Kapcala, MD, Clinical Reviewer
Lois Freed, Nonclinical Team Lead
Luann Mckinney, Nonclinical Reviewer
Martha Heimann, CMC Team Lead
Kun Jin, PhD, Statistical Team Lead
Junshan Qui, PhD, Statistical Reviewer
Atul Bhattaram, PhD, Pharmacometrics Reviewer
Yasmeen Abou-Sayed, OSE/DRISK
Chad Morris, OSE/DMEPA Reviewer (via phone)
Cara Alfaro, OSI (via phone)
Katherine Bonson, PhD, CSS Reviewer (via phone)

Dahlia Walters, OPQ RPM (via phone)
Stacy Metz, PharmD, Senior Regulatory Project Manager

SPONSOR ATTENDEES
Gemma Clark, Senior Director, Drug Development
Jeffrey Humphrey, MD, Chief Medical Officer
Shinsaku Kihara, M.S., Project Leader, CNS Division
Minoru Kobayashi, Director, CNS R&D Unit
Linghui (Jennifer) Kong, PhD, Director, Clinical Pharmacology
Young (Chet) Kwon, Senior Manager, Regulatory Affairs - CMC
Stephen Letrent, PharmD, PhD, Senior Vice President, Drug Development
Junfang (June) Li, PhD, Vice President, Biometrics
Eri Ohta, PhD, Director, Biostatistics
Phyllis Salzman, PhD, Senior Director, Medical Science
Snehal Shah, PharmD, Vice President, Regulatory Affairs
Jennipher Truesdale, Associate Director, Regulatory Operations
Susan White, MS, MBA, Director, Regulatory Affairs
(b) (4), External Consultant

1.0 BACKGROUND

As recommended by the Agency in their October 5, 2017, Type C Written Responses, the Sponsor requests a Type B meeting to discuss the content, format, and navigability of the NDA resubmission following the Agency's Not Approvable Action Letter dated February 28, 2008.

Objectives of the meeting include:

- To gain a clear understanding of the Agency's expectations regarding the presentation of the content and format of the efficacy and safety data.

FDA sent Preliminary Comments to Kyowa Kirin Pharmaceutical Development, Inc. on February 13, 2018.

2. DISCUSSION

2.1. Content and Format Questions

Question 1:
Does the Agency agree that the proposed strategy, content, and analyses for the Integrated Summary of Efficacy will be acceptable for the filing of the Resubmission and enable a complete review?

FDA Response to Question 1:

- You need to present the results of the protocol specified primary endpoint using the prespecified analysis and the prespecified plan to control Type I error for each study supporting effectiveness. We recommend that you provide a pooled efficacy analysis for all controlled Phase 2/3 trials and a separate analysis that excludes studies in which no overall treatment effect was demonstrable (Study 6002-014). The ISE should include analyses of demographic (e.g., age, gender and race-only if there is sufficient basis for comparison) subpopulations and an efficacy analysis showing the effect from trials both within and outside of Japan, and comparisons of results in U.S. and non-U.S. populations.

- Please provide a hyperlink to the final versions of the Protocol and SAP, and to the Final Study Report for each trial, at the end of the sections of the ISE presenting efficacy results for all pivotal efficacy trials.

- Please submit copies of each version of the study protocols and the Statistical Analysis Plans (SAPs) with a summary of changes for each revision to the three new pivotal trials.

- Please provide a comprehensive table of contents giving the location of all tables, figures, and listings (including in-text and post-text items) in the ISE, with a functioning hyperlink to each item.

- We will send shortly after this meeting a request to include additional efficacy and safety analyses for inclusion in the ISS and ISE.

Meeting Discussion:

- FDA stressed the importance of ensuring the navigability of the submission. The clinical review team will send a request for additional presentations of the efficacy and safety data in the ISS and ISE (sent by email to the sponsor 3/7/2018). If the Sponsor has question about the ISS, ISE or the clinical team's requests, FDA encourages the sponsor to submit their question by email to Dr. Metz.

- MMRM analyses will be used for the pooled analyses of efficacy.

- A major focus of the pooled efficacy analyses that excludes studies with no overall treatment effect will be to look at treatment effects in subgroups.

- The sponsor confirmed its plan to submit analyses as outlined in the first bullet of the FDA's response to Question 1.

Question 2:
To fulfill the requirement to submit a safety update report as part of a Complete Response to an Action Letter, the Sponsor intends to provide a revised Integrated Summary of Safety (ISS). Does the Agency agree that the proposed approach to the content and format of the ISS will be acceptable for the filing of the Resubmission and enable a complete review?

FDA Response to Question 2:
We will need to review your submission to determine whether it is acceptable for filing. Preliminarily, we have the following comments:

- We agree with the strategy for safety data Pools 1 through 4; however, Pool 5 (all istradefylline-treated subjects in Pools 1, 2, and 3 excluding placebo-treated subjects) is not necessary.

- Please conduct pooled safety analyses for the following pools:
  - Studies 6002-0608, 6002-009 and 6002-014
  - Studies 6002-0608, 6002-009.

- Please include the reported laboratory value and the high and low reference values for each laboratory parameter for studies 6002-0608, 6002-009 and 6002-014.

- You should present the incidence of adverse events as the number and percentage for each study population analyzed (individual studies and pooled studies) for all Adverse Events (AEs), AEs with a fatal outcome, and nonfatal serious AEs, in addition to your planned presentation of the incidence per Patient-Years.

- Please provide an overall, comprehensive table of all tables, figures, listings (including in-text and post-text items) in the ISS with page specification for each item and a hyperlink to each item.

- We will have several additional requests for safety analyses of treatment-emergent adverse events (TEAEs), vital signs, clinical laboratory analyses, and ECGs. Some are for revisions of your proposed analyses and others are supplementary to your proposed analyses. These requests will be sent in a separate email.

Meeting Discussion:

- The sponsor noted that fatal and non-fatal SAEs will be combined in the presentation of SAEs.

- FDA noted that its ISS appendix will include some requests for additional safety data presentations/analyses, recommendations for some different clinical laboratory analyte thresholds (for markedly abnormal results), and describe how safety results should be presented, including templates for presenting safety results.

Question 3:
Does the Agency agree with the Sponsor's proposal regarding the scope, format and documentation of the electronic datasets and programs to be submitted to enable a complete review?

FDA Response to Question 3:
Your approach is acceptable. The only issue is dataset "Visit" cannot be put into an ADaM folder if the data was derived from the raw data and did not follow the ADaM structure requirement. This data need to be put into the legacy folder, which may cause some confusion. We recommend that you create a custom domain to include "Visit" information, then create an ADaM of visit using this custom domain. If the visit dataset meets the requirement of an ADaM, this dataset can be put it into an ADaM folder.

Meeting Discussion:
The sponsor confirmed agreement that 'Visit' dataset cannot be put into an ADaM folder and proposed to submit the pooled VISIT dataset in ISS/tabulations/legacy folder rather than the ADaM folder. The sponsor further clarified that the dataset will not be changed, but rather placed it in the appropriate folder per FDA recommendation. FDA stated that the approach seemed acceptable, but provide a final response in the meeting minutes.

Post Meeting Note:
The sponsor's approach is acceptable.

Question 4a:
The Complete Response Resubmission will include data from nine clinical studies (two Phase 3 double-blind studies; one Phase 3 open-label, long-term study; one Phase 2b double-blind study; and five Phase 1 studies) not included in the original NDA submission. The Sponsor has identified 3 of the 9 studies (6002-0608, 6002-009, and 6002-014) as "covered clinical studies" as defined in 21 CFR 54.2.

Does the Agency agree with the Sponsor assessment that these 3 studies of the 9 studies to be included in the Complete Response Resubmission are "covered clinical studies"?

FDA Response to Question 4a:
We agree that studies 6002-0608, 6002-009, and 6002-014 are the "covered clinical studies" of the nine studies not included in the original NDA submission.

Meeting Discussion:
No further discussion at the meeting.

Question 4b:
Does the Agency agree that the Sponsor's efforts to obtain financial disclosure information from investigators in the "covered clinical studies" are sufficient to enable review of the Complete Response Resubmission?

FDA Response to Question 4b:

- This will be a matter of review of the submitted financial information and of the efforts made (due diligence) to collect information about disclosable financial relationships for study personnel who participated in the covered studies. Efforts should be made to obtain disclosable financial information from all other reasonably available sources. We refer you to The FDA's Guidance for Clinical Investigators, Industry, and FDA Staff-Financial Disclosure by Clinical Investigators.

- Financial disclosure information should be presented in 3 categories:
  1) investigators/sub investigators without financial information to disclose;
  2) investigators/sub investigators who have financial information to disclose;
  3) investigators/sub investigators for whom financial disclosure information was not able to be obtained

- For each category, specify the site (with the site number), and the investigators or sub-investigators for each covered study.

- For individuals with reportable financial relationships, provide specific details of the financial interest or arrangement, including its size and nature, and any steps taken to minimize the potential for study bias resulting from the interest or arrangement.

Meeting Discussion:
No further discussion at the meeting.

Question 5:
Does the Agency agree with the overall contents of the Complete Response Resubmission as outlined in the table below?

FDA Response to Question 5:

Your plan to submit information about the drug substance appears reasonable. We have the following recommendations:

- A drug substance from a new commercial supplier should be appropriately bridged to the clinical drug substance batches. This could be accomplished by comparison of drug substance batch data (3 batches from each supplier) and stability data (3 months long-term and accelerated from the new supplier).

- Confirm that the manufacturing process at the new facility is equivalent to that of the clinical supplier. If not, provide a tabular summary of significant changes in the manufacturing process.

- As a reminder, we generally expect a minimum of 12 months long-term testing on at least three primary drug substance batches at the time of NDA submission.

- NDA are required to include Clinical Summaries. In addition, your submission will include a substantial amount of new information including new post-marketing safety information, two Phase 3 double-blind studies; one Phase 3 open-label, long-term study; one Phase 2b double-blind study; and five Phase 1 studies.

Meeting Discussion:

FDA reminded the applicant that they would need to submit pharmacokinetic information to bridge between the clinical trial formulations and the to-be marketed formulation.

The Sponsor agreed to revised and update the Summary of Clinical Efficacy (SCE) and the Summary of Clinical Safety (SCS) for the NDA resubmission.

2.2. Administrative Questions

Question 6:
Based on the planned content of the Complete Response Resubmission, does the Agency agree that the Complete Response to the 2008 Action Letter will be considered a Class 2 Resubmission with a target 6-month review?

FDA Response to Question 6:
If we determine that your planned resubmission constitutes a complete response that addresses all deficiencies in the Agency's February 28, 2008, Action Letter, we will classify the resubmission as Class 2, and will complete our review and act on the resubmission within 6 months of the receipt date (21 CFR 314.110 and MAPP 6020.4 Rev 2).

Meeting Discussion:
No further discussion at the meeting.

Question 7:
The Sponsor acknowledges the Agency's October 5, 2017 feedback on the proposed contents of a waiver from disclosure of patient medical records. Does the Agency agree the following documents would fulfil the Agency request to provide documentation of disclosure prohibition to support a waiver request"?

FDA Response to Question 7:
We agree that submission of the Informed Consent Forms (ICFs) for studies 6002-0608 and 6002-009 and the Act on the Protection of Personal Information (APPI) would be acceptable documentation of disclosure prohibition for review in consideration of a waiver request.

Please comment as to whether redaction of patient personal information from medical records in preparation for review by FDA during a site inspection would be feasible.

Meeting Discussion:
The Sponsor has visited clinical sites in Japan in-person to clarify the Sponsor's understanding regarding disclosure of medical records containing patients' personal information in the context of the language in the ICFs and Japanese law. The Sponsor stated that they met with the clinical investigator at the sites who informed the Sponsor whether the FDA could review subjects' medical records according to language in the ICF used by the clinical site. The Sponsor identified 6 sites enrolling subjects in Study 0608 and 9 sites enrolling subjects in Study 009 that did not preclude FDA from reviewing subjects' medical records according to ICF language. The Sponsor stated that these sites represent the highest enrolling sites for these studies. The Sponsor also raised the possibility of redaction of subject identifiers from sites that preclude FDA review of medical records.

FDA asked whether the clinical investigator has the authority to determine whether the ICF language precludes FDA from reviewing subjects' medical records. FDA also asked whether ICF language differed that much between clinical sites so that some sites interpreted ICF language to preclude FDA from reviewing subjects' medical records, while other sites interpreted ICF language not to preclude FDA from reviewing subjects' medical records. FDA stated that, although the sites allowing FDA to review subjects' medical records are the highest enrolling sites, enrollment is only one attribute used when determining which clinical sites to inspect. FDA noted that OSI has inspected many Japanese clinical sites in the past and has not encountered similar issues with respect to FDA's ability to review medical records for subjects enrolled in clinical trials. FDA reiterated the importance of having the ability to review subjects' medical records as an integral part of their clinical site inspections. The Sponsor indicated that they would continue to address this issue and would work with the review division. FDA noted that this issue will need to be resolved prior to submission of the NDA.

Question 8:
Does the Agency agree with the Sponsor's proposal regarding the information to be provided for use by the Office of Scientific Investigations?

FDA Response to Question 8:
We agree with your proposal to provide the requested information for clinical studies 6002-0608, 6002-009 and 6002-014.

Meeting Discussion:
No further discussion at the meeting.

Question 9:
Does the Agency have any additional points for the Sponsor's consideration regarding the planned Resubmission?

FDA Response to Question 9:

- Navigability is important for a large submission. Please ensure that the pages of the ISE and ISS match the page numbers listed in the Table of Contents (TOC), that each listing

in the TOC has a working hyperlink, and that the page number in the TOC matches the page number shown of the PDF viewer and the page number on the PDF document.

- All cross-references in the ISE, ISS, revised summaries, and other documents should include a working hyperlink to the specific page containing the cross-referenced information.

- All requested analyses should show results for all randomized treatment group arms (including all istradefylline doses combined) on the same page, if possible.

- The Nonclinical Overview and Nonclinical Summaries should be updated to include all new nonclinical information.

- We remind you that a new request for a proprietary name review for your proposed name should be submitted when you respond to the application deficiencies. If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

    - Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

    - PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022 (https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm)

- The procedures for complying with pediatric study requirement under PREA have changed since your original submission. We refer you to the PREA Requirements section below. The links will take you to information explaining the procedure for requesting a waiver. We recommend that you submit an *initial* Pediatric Study Plan (iPSP) as soon as possible after this meeting. Your submission will need to include a Pediatric Study Plan (PSP).

- The NDA for istradefylline must contain an Abuse Potential assessment, as described in the "Preparing the NDA Submission" section of the 2017 Guidance for Industry: Assessment of the Abuse Potential of Drugs, which can be found on the Internet at: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf. We also refer you to the Abuse Potential Assessment in Section 3 below.

Meeting Discussion:

FDA received an email from the Sponsor with an additional question for discussion: "The Sponsor understands that if CSS determines during the review cycle of the resubmission that istradefylline is not a scheduled product than the Agency will not require a DEA review prior to

approval or is a DEA review always required for a CNS active substance. Is our understanding correct?"

CSS commented during the meeting that if their review of abuse-related data shows that a drug has abuse potential, CSS would prepare an Eight Factor Analysis (8FA) with a recommendation for scheduling on behalf of the Department of Health and Human Services (HHS). This 8FA is signed by the Assistant Secretary for Health at HHS and is transmitted to DEA. DEA then makes a final decision regarding scheduling and placement of a substance under the Controlled Substances Act. However, if CSS determines a drug does not have abuse potential, an 8FA is not prepared and DEA has no oversight of a drug product.

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.

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. 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.

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.

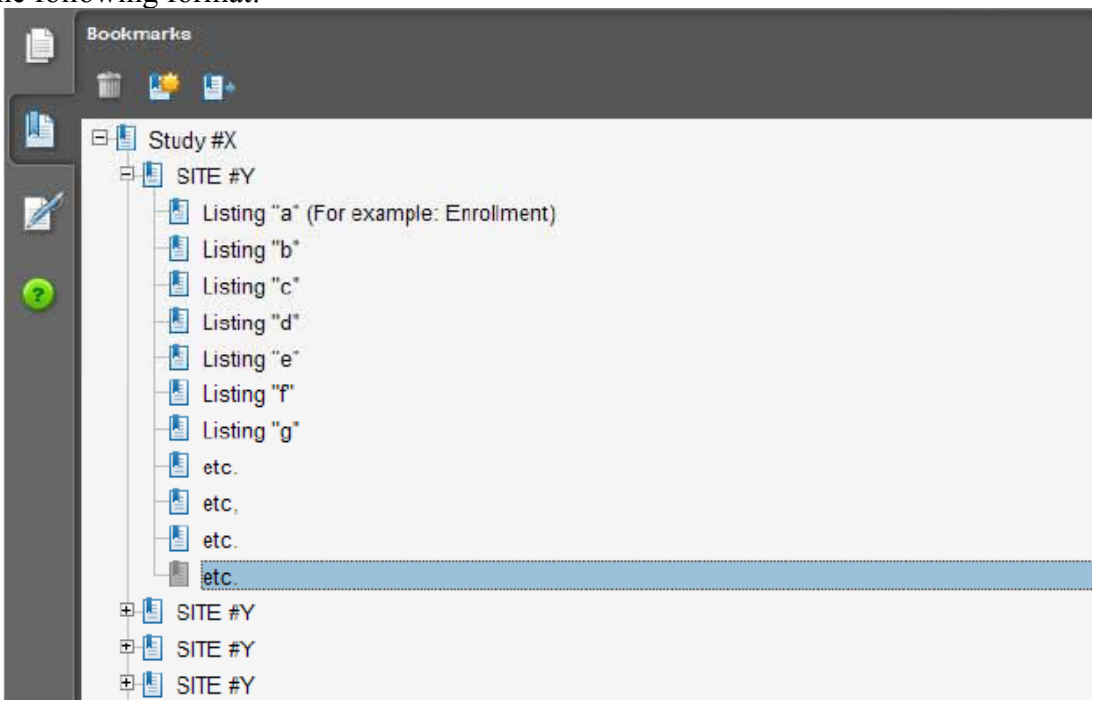
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere 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:

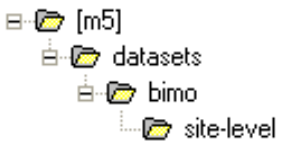
OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Please refer to discussion in Question 7.

5.0 ACTION ITEMS

None.

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
03/16/2018