# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 210828Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 125673

**MEETING MINUTES**

UIHC-P-E-T Imaging Center
Attention: John Sunderland, Ph.D.
Director, PET Imaging Center
Director, Small Animal Imaging Core
University of Iowa
200 Hawkins Drive; 0911ZJPP
Iowa City, Iowa 52242
Dear Dr. Sunderland:

Please refer to your Pre-Investigational New Drug Application (PIND) file for $^{68}$Ga DOTATOC.

We also refer to the telecon between representatives of your firm and the FDA on October 3, 2017. The purpose of the meeting was to discuss the content and format of a 505(b)(2) application for marketing approval of Ga-68-DOTATOC use with PET for localization of somatostatin receptor positive NETs (b) (4) in adult and pediatric (b) (4) patients.

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

If you have any questions, call me at (301) 796-1348.

Sincerely,

*{See appended electronic signature page}*

Modupe Fagbami
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
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:** October 3, 2017, at 2:00 pm
**Meeting Location:** Teleconference (WO, Building 22, Conference Room 5266)

**Application Number:** PIND 125673
**Product Name:** $^{68}$Ga-DOTATOC

**Indication:** For localization of somatostatin receptor positive NETs (b) (4) in adult and pediatric (b) (4) patients.
**Sponsor/Applicant Name:** University of Iowa Health Center, P-E-T Imaging Center

**Meeting Chair:** Louis Marzella, M.D., Ph.D., Director, DMIP
**Meeting Recorder:** Modupe Fagbami, Regulatory Project Manager, DMIP

## FDA ATTENDEES

Louis Marzella, M.D., Ph.D., Director, DMIP
Alex Gorovets, M.D., Deputy Director, DMIP
Charles, Ganley, M.D. Director, ODEIV
Nushin Todd, M.D., Clinical Team Leader, DMIP
Cynthia Welsh, M.D., Medical Officer, DMIP
Ron Honchel, Ph.D., Pharmacology/Toxicology Reviewer, DMIP-On Phone
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, DCPV
Sam Habet, Ph.D., Clinical Pharmacology Reviewer, DCPV
Danae Christodoulou, Ph.D., Branch Chief, OMPT/CDER/OPQ/ONDP/DNDPII/NDPBVI
John Amartey, Ph.D., CMC Reviewer, OMPT/CDER/OPQ/ONDP/DNDPII/NDPBVI
Sue Jane Wang, Ph.D., Acting Deputy Division Director, OMPT/CDER/OTS/OB/DBI
Jyoti Zalkikar, Ph.D., Secondary Statistical Reviewer, OMPT/CDER/OTS/OB/DBI
Satish Misra, Ph.D., Primary Statistical Reviewer, OMPT/CDER/OTS/OB/DBI
Kui Xu, M.D., OMPT/OSMP/OOPD-On Phone
Modupe Fagbami, Regulatory Project Manager, DMIP

## SPONSOR ATTENDEES

John Sunderland, Ph.D., Director PET Imaging Center, UIHC-PET Imaging Center
Timothy Ginader, M.S., Biostatistician, UIHC- Holden Comprehensive Cancer Center
Michael Graham, Ph.D., M.D., Division Chief, Nuclear Medicine, UIHC-PET Imaging Center
Shannon Lehman, Research Specialists, UIHC-PET Imaging Center

(b) (4)

## BACKGROUND

On July 26, 2017, UIHC-P-E-T Imaging Center requested a Type B, pre-NDA meeting to discuss the content and format of their planned 505(b)(2) NDA for $^{68}$Ga DOTATOC. $^{68}$Ga DOTATOC is proposed for use with PET for localization of somatostatin receptor positive NETs (b) (4) in adult and pediatric (b) (4) patients. The sponsor intends to support their application primarily by reliance upon published literature, including a meta-analysis of 17 published articles reporting on the use of $^{68}$Ga DOTATOC for the assessment of NET disease, and a retrospective pivotal efficacy and safety study (RET-NET-01, based upon data collected from 3 investigator-initiated prospective studies conducted at the University of Iowa).

A pre-IND meeting was previously held on April 30, 2015, to discuss the published literature and data obtained from studies conducted at the University of Iowa to support submission of an NDA. For this pre-NDA meeting, the sponsor's meeting request was granted on August 2, 2017, and their background package was received on September 1, 2017.

FDA sent Preliminary Comments to University of Iowa Health Center, P-E-T Imaging Center on September 28, 2017.

## DISCUSSION

**Question 1** The retrospective Phase 3 study was an open-label study designed to demonstrate the efficacy of Ga-68-DOTATOC as an accurate imaging technique for use with PET/CT for management of somatostatin receptor positive NETs. Does FDA have any comments regarding the adequacy of the study design, specifically:

a) Patient population;

b) Sample size;

c) Comparator;

d) Efficacy assessments;

**e)** Statistical methods?

## FDA RESPONSE

**We plan to rely on the following sources of data to make a determination of safety and effectiveness of your drug:**

**1. Systematic literature review and meta-analysis**
**2. Data from each of the three individual studies supporting RET-NET-01, and**
**3. RET-NET-01.**

**We would like the data analyzed by tumor type, by age group, and by reader. Your application should include copies of all the protocols and amendments where applicable.**

**We note that the RET-NET-01 protocol has not been previously submitted to your IND and that we have not had opportunity to discuss the design prior to its conduct. Please provide a rationale for taking such an approach rather than analyzing and submitting the results of the studies upon which you based RET-NET-01. For example, the patient populations, pre-specified endpoints (e.g. sensitivity and specificity vs. concordance with a comparator), standard of reference and/or truth standard and reading methodologies may have differed among the studies.**

**Importantly, please clarify whether, for RET-NET-01, the images were re-read and how the patients and their images were selected for inclusion in RET-NET-01. Please also clarify the method for assessing the reference/truth standard in RET-NET-01 and whether it was pre-specified in the RET-NET-01 protocol.**

**On page 10 of your meeting package, you state that the RET-NET-01 was "designed to evaluate subjects who participated in at least one of the 3 ongoing prospective investigator-initiated studies of Ga-68-DOTATOC in patients with known or suspected NETs at the University of Iowa". Your meeting package did not identify or contain copies of those protocols nor did you identify which patients may have been in >1 study and how those cases were handled statistically. Patients whose data were used >1 times both within a single protocol and among multiple protocols should be identified. We have conducted a search and have identified studies to which you may be referring:**

1. **Comparator study of 68Ga DOTATOC PET/CT with Octreoscan + high resolution, contrast enhanced CT for diagnosis and staging of neuroendocrine tumors and other somatostatin receptor positive tumors**
2. **68Ga DOTATOC PET for diagnosis, staging, and measurement of response to treatment in somatostatin receptor positive tumors**
3. (b) (4)

**Furthermore, we have also identified 5 additional studies on clinicaltrials.gov (link below) that may or may not be the same studies as those whose titles are noted above.https://clinicaltrials.gov/ct2/results?cond=Neuroendocrine+Tumors&term=DOTATOC+Ga&cntry1=NA%3AUS&state1=NA%3AUS%3AIA&Search=Search**

**We understand that the studies you reference may be ongoing. We do not suggest that you close these studies. We agree with your cutoff date of September 2016. However we do consider that some of these three studies as well as any others you wish to include to support your application, might be adequately designed (prospective, predefined endpoints, blinded readings, controlled for bias) and conducted to determine safety and efficacy of your product and we anticipate that the protocols and data from each study would have to be analyzed separately. You may find it helpful to develop a table describing the various protocols. For example:**

| Characteristic | Study 1 | Study 2 | Study 3 |
|---|---|---|---|
| Design | | | |
| Patient population | | | |
| Number of patients | | | |

| | | | |
|---|---|---|---|
| **Tumor type** | | | |
| **Comparator** | | | |
| **Standard of reference / truth** | | | |
| **Endpoints** | | | |
| **Gaps in the protocol that contributed to developing a retrospective approach** | | | |
| **Etc.** | | | |

**Based upon the limited information submitted in your pre-NDA meeting package, we assume the RET-NET-01 study has been completed. We offer the following comments for you to consider when compiling your NDA package.**

**We agree with the concept of a "composite reference standard of truth". We note that there is no comparator. If there are sufficient number of patients with OctreoScan to serve as a comparator for performance data, we anticipate that those instances will be described and the analysis will be conducted.**

a. **To assess the adequacy of the patient population, in your NDA submission, as stated earlier, please identify and include copies of any protocols and their amendments, if applicable, from which you obtained the subjects for your retrospective study We understand that** (b) (4) **If you find that there is sufficient data in this population to establish efficacy, please provide those analyses.**

b. **We note that sensitivity and specificity calculations will ultimately be performed using the Ga-68-DOTATOC consensus reads in combination with the patient's disease status. We recommend reporting these results for each individual reader of Ga-68-DOTATOC images. Please provide the sensitivity and specificity calculations for each reader along with confidence intervals.**

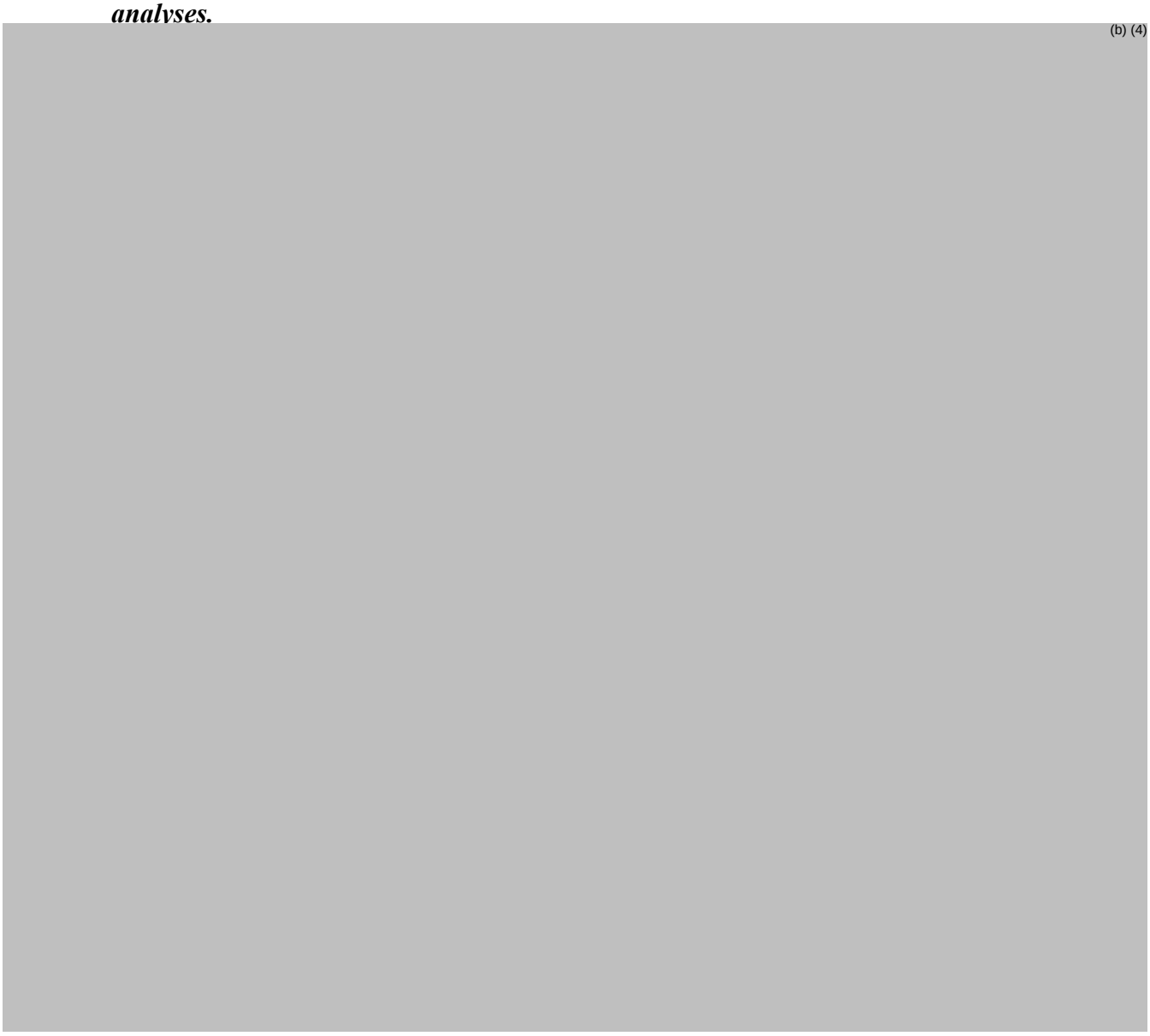
c. **Page 30 of the meeting package discusses use of CT scans. The discussion is unclear. Please clarify.**

d. **Describe the utility of** (b) (4) **. Describe how this information will be handled in the statistical analysis plan as well as in potential labeling.**

e. **Please provide Statistical Analysis Plan (SAP) and desired threshold on performance characteristics. Please capture the subjects who are "indeterminate" for efficacy and list the reasoning. Please include these subjects in your "missing data analysis" in your statistical analysis plan and include results from that secondary analysis of Full Analysis population in your NDA.**

***Meeting Discussion:***
***The Sponsor clarified that the SAP for RET-NET-01 was finalized prior to database lock. In the SAP, 2 categories of indeterminate subjects were identified. The first category of subjects included those whose disease status could not be defined based on the predetermined NET Disease Status Determination criteria (as provided on pages 29-32 of the briefing document). Since classification is not possible, no further analyses will be performed with these subjects. The second category of subjects included those in which consensus between readers was not obtained. For these subjects, sensitivity analyses on the primary efficacy analysis will be performed twice, once by assigning all indeterminate results as positive, and once by assigning all indeterminate results as negative.***
***The agency agreed with this approach. Additionally, Sponsor will include the data for all 72 patients who were classified as "indeterminate" to be excluded from the analyses.***

(b) (4)



(b) (4)

**Question 2** Does the Agency agree that the available efficacy data obtained in the Phase 3 retrospective pivotal study and the Ga-68-DOTATOC meta-analysis form an adequate basis for an NDA submission and no additional studies are needed?

**FDA RESPONSE**

**Please see our response to Question 1. We do not anticipate the need for additional studies. The adequacy of the application for approval will be a review issue.**

***Meeting Discussion: There was no meeting discussion on this item.***

**Question 3** Does the Agency agree that the available safety data obtained in the Phase 3 retrospective pivotal study (N=350) and the data from the meta-analysis (n=432) form an adequate basis for an NDA submission and no additional studies are needed?

**FDA RESPONSE**

**We assume that you have collected the adverse events and laboratory data of the subjects included in your study. Please clarify. The adequacy of the safety data will be a review issue.**

***Meeting Discussion: There was no meeting discussion on this item.***

**Question 4** Does FDA agree that there are adequate pediatric data in the Phase 3 retrospective efficacy and safety study in order to support a pediatric indication for Ga-68-DOTATOC?

**FDA RESPONSE**

**We note that Orphan Designation does not require submission of pediatric data (see the PREA Requirements section below). However, because you are seeking an indication for the pediatric population, we recommend that your NDA include confirmation that you have reviewed the literature for pediatric data and then describe your findings to inform labeling. For example, please describe how your product will be dosed and performed in pediatric patients relative to adults using clinical pharmacology information.**

**Please report your collected data and analyses for pediatric patients separately. The adequacy of the data and findings will be a review issue.**

***Meeting Discussion: There was no meeting discussion on this item.***

**Question 5** Does the Division agree with University of Iowa's plan to rely on the (b) (4) assessment report to support the clinical pharmacology aspects of Ga-68-DOTATOC in the NDA and no additional clinical pharmacology information is required?

**FDA RESPONSE**

**Please note that non-US regulatory authority assessments and non-US labeling may not be relied upon as substantial evidence of safety or effectiveness to support approval of a 505(b)(2) application, as such assessments are neither FDA's findings related to a listed drug nor are they published literature. However, it appears that the nonclinical and clinical pharmacology (as it pertains to Question 13) sections of the EMA assessment for (b) (4) may have been supported by published literature. If the studies upon which the non-US conclusions are based have been published, you may be able to rely upon that literature. Your application should include copies of the published literature articles that you intend to rely upon.**

***Meeting Discussion: There was no meeting discussion on this item.***

**Question 6** Does the Division agree with University of Iowa's literature search plans to support the Ga-68-DOTATOC NDA?

**FDA RESPONSE**

**Yes, we agree.**

***Meeting Discussion: There was no meeting discussion on this item.***

**Question 7** Based on the positive results achieved in the pivotal Phase 3 program (**Error! Reference source not found.**), does FDA agree that the data provided are sufficient to support the proposed Indication Statement section?

**FDA RESPONSE**

**Determination of the indication statement is a review issue.**

***Meeting Discussion: There was no meeting discussion on this item.***

**Question 8** Does the Division agree with providing datasets in legacy format for both pivotal studies?

**FDA RESPONSE**

**We prefer STDM format. We refer you to the additional information section below labeled Study Data Tabulation Model (SDTM) Issues.**

***Meeting Discussion: There was no meeting discussion on this item.***

**Question 9** Does the Division agree with our request to waive the requirements for an ISE and an ISS in the NDA?

**FDA RESPONSE**

**The NDA application must include an ISE and an ISS section. We refer you to the following guidance documents:**

**Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document**

**https://www.fda.gov/downloads/drugs/guidances/ucm136174.pdf**

**Note the following section from the guidance document:**

> C. Exceptions There may be situations in which sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety, would be sufficiently detailed to serve as the narrative portion of the ISE and ISS, respectively, while still concise enough to meet the suggested size limitations for Module 2. This situation is rare but can occur if the application is small and consists of a single study or a number of small studies. In our experience, the narrative portion of the ISE often is more amenable for inclusion in Module 2 than is the ISS. In such situations, the ISE and ISS can be split across Module 2 and Module 5, with the narrative portion located in section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in section 5.3.5.3. If the ISE or ISS is split across modules in this way, it is critical to include a clear explanation of where the parts are located. This explanation should be placed both in Module 2 (section 2.7.3 or 2.7.4) and in Module 5 (section 5.3.5.3).

***Meeting Discussion: There was no meeting discussion on this item.***

**Question 10** Does FDA agree with University of Iowa's NDA pooling strategy?

**FDA RESPONSE**

**We anticipate that you will provide and analyze the safety data for the subjects enrolled in the 3 protocols from which you obtained your patient population for RET-NET-01. We expect that you will then pool the safety data for that population with that found in the meta-analysis as well as from use of the product globally.**

***Meeting Discussions:***

***The Sponsor clarified that the 3 prospective studies included in RET-NET-01 were not included in the Graham et al. meta-analysis. The meta-analysis did not provide any specific or overall safety data because none of the original manuscripts presented any safety or adverse event data. Additionally, the Sponsor performed a literature search and has not identified any additional studies with safety data that could be included in the NDA. Therefore, the Sponsor proposed to include only the safety data from the 3 prospective studies included in RET-NET-01. The Agency agreed with the proposal. However, the adequacy of the safety data will be a review issue.***

**Question 11** Does the Division agree with not submitting patient CRFs, patient narratives, or patient profiles for the pivotal studies?

**FDA RESPONSE**

**Yes, we agree. However, please note that we may ask for selected information during the review process.**

**Please submit clinical management sheets / algorithm for clinical management and a summary table noting whether the change was beneficial to the patient.**

***Meeting Discussion: There was no meeting discussion on this item.***

**Question 12** Are there any other aspects of the clinical development plan or clinical sections of the NDA that the Agency would like to comment on, or that University of Iowa should take into consideration?

**FDA RESPONSE**

a. **Please provide a detailed description of the clinical management team members, their qualifications, and methodology (e.g. extent of blinding, randomization, individual determination vs. consensus) utilized for assessing the change in management portion of your study.**
b. **Please provide the NCT# for each investigator study (clinicaltrials.gov)**
c. **Your application should address the request outlined under the Patient Experience Data section below.**
d. **We request that you include a copy of the proposed labeling text with annotations indicating the source of information supporting the labeling content and where that information can be located within your application. We also refer you to the Prescribing Information section below.**

***Meeting Discussions:***
***The Sponsor clarified that they have not collected any information in their application that qualifies for Patient Experience Data, but will like to know where this information should be placed in the NDA submission.***

***Since this is a new requirement, the specific location cannot be specified at the meeting. Sponsor said that they will be submitting their NDA as soon as possible, but cannot specify time at this meeting.***

***Post meeting addendum:***

***The patient experience data is clinical in nature. Therefore, we recommend that this information be included in module 5. Please ensure that the location is identified in the Reviewer's Guide and the Table of Contents. Thank you.***

**Question 13** Does FDA agree with University of Iowa's plan to use the (b) (4) assessment report to fulfill the nonclinical safety requirements in the NDA and that no additional nonclinical studies are required?

**FDA RESPONSE**

**See the response to Question 5 regarding reliance on the EMA assessment report. Also, we recommend that you request a waiver from conducting reproductive toxicity studies as per the Medical Imaging Guidance. We do not anticipate the need for additional nonclinical studies at this time.**
**Guidance for Industry Developing Medical Imaging Drug and Biological Products Part 1: Conducting Safety Assessments**

https://www.fda.gov/downloads/Drugs/Guidances/ucm071600.pdf

***Meeting Discussion: There was no meeting discussion on this item.***

**Question 14** Are there any other aspects of the nonclinical sections of the NDA that the Agency would like to comment on, or that University of Iowa should take into consideration?

**FDA RESPONSE**

**We have no additional nonclinical comments based on the meeting package.**
***Meeting Discussion: There was no meeting discussion on this item.***

**Question 15** Does the Division have any comments regarding the NDA contents or content locations based on the TOC that has been provided?

**FDA RESPONSE**

**a. In section 5.3.5.1 please separate efficacy and safety data.**
***Meeting Discussion:***
***The Agency reiterated that the datasets should be separated into efficacy and safety datasets. Separate sections of the RET-NET-01 CSR should also describe efficacy and safety data. The Sponsor agreed, and promised to include in the NDA submission.***

**b. If you anticipate the use of a proprietary name, please include a request for propriety name review in section 1.12.4.**
**c. Include copies of all protocols including those from which you recruited subjects for RET-NET-01 as well as study reports in section 5.3.5.**

***Meeting Discussion:***
***The Agency would like to know if all the studies were conducted under the same IND, and also to look at each individual study to confirm that the primary analysis will be specified in the prospective protocol.***
***The Sponsor clarified that the prospective studies are on-going investigator-initiated studies, and that they do not have copies of all protocols and amendments, and the final study reports have not yet been prepared. The plan is for the Sponsor to obtain Right of Reference for the individual studies, and to analyze the subset of data collected only for this application, by study as well as for the RET-NET-01 study inclusive in the NDA in which only the endpoints will be specified.***
***The Agency does not necessarily disagree with this approach, however, requested the Sponsor to include in the NDA the results of each prospective study based on what was pre-specified in the original study protocols.***
***The Sponsor indicated that they would follow FDA's request as best as they could in the NDA, noting that: 1) their database was a subset of both patients and variables from the original prospective studies, and 2) the prospective study protocols may not have clearly identified efficacy and safety analyses.***

**Question 16** Does the Agency concur that this approach is acceptable?

**FDA RESPONSE**

**Your proposed product has received orphan drug designation. Therefore, your planned NDA would not be subject to an application fee unless it includes an indication for other than the rare disease or condition. You do not need to request a waiver of the application fee. Instead, you should claim the orphan exemption when completing the User Fee Coversheet (Form FDA 3397) and include a brief statement claiming the orphan exception in your cover letter.**

***Meeting Discussion: There were no meeting discussions on this item.***

**ADDITIONAL COMMENTS**

***Post-meeting Statistical Comment:***

> ***As Graham et al. meta-analysis will be one of the data sources we rely upon to make a determination of safety and effectiveness of your drug, it is important that you provide the detailed description of the statistical methodology used and assumptions made in your NDA submission..***

**Study Data Tabulation Model (SDTM) Issues**

1. The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed. Refer to the SDTMIG section on Conformance (3.2.3)

2. Domains
    a. There are additional domains listed below that are not included in the current DTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, use these domains.
        - (DV) Protocol deviations
        - (DA) Drug Accountability
        - (PC, PP) Pharmacokinetics
        - (MB, MS) Microbiology
        - (CF) Clinical Findings

    b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.

        - Tumor information
        - Imaging Data
        - Complex Inclusion/Exclusion Criteria

3. Variables

    a. All required variables are to be included.

    b. All expected variables must be included in all SDTM datasets.

    c. Variables (expected or permissible) for which no values will be submitted must be explicitly stated and discussed with the review division.

    d. A list of all Permissible variables that will be included and those that will not be included for each domain must be provided for review and discussed with the review division.

    e. A list and description of all variables that will be included in the Supplemental Qualifier dataset must be provided.

    f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.

4. Specific issues of note:

    a. SDTM formatted datasets must not provide replication of core variables (such as treatment arm) across all datasets.

    b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.

c. These issues can be addressed through the request for ADaM datasets

**Analysis Data Model (ADaM) Issues**

1. Specify which ADaM datasets you intend to submit.
2. Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
3. Discuss the structure of the datasets with the reviewing division and specify in the QSAP.

4. Within each adverse event analysis dataset, include all levels of the MedDRA hierarchy as well as verbatim term.

5. Indicate which core variables will be replicated across the different datasets, if any.

6. SDTM and ADaM datasets must use the unique subject ID (USUBJID). Each unique subject identifier must be retained across the entire submission.

**General Items**

Controlled terminology issues

a. Use a single version of MedDRA for a submission. Does not have to be most recent version

b. We recommend that the WHO drug dictionary be used for concomitant medications.

c. Refer to the CDISC terminology for lab test names.

d. Issues regarding ranges for laboratory measurements must be addressed.

| Unique Subject dentifier USUBJID) | Sequence Number (AESEQ) | Study Site Identifier (SITEID) | Unique Subject Identifier | Coding Dictionary Information | Reported Term for AE (Verbatim) | Lower Level Term MedDRA Code | Lower Level Term (LLT) | Preferred Term High Level Term (HLT) | High Level Group Term (HLGT) | System Organ Class (SOC | Secondary System Organ Class 2 (SOC2) | Secondary System Organ Class 3 (SOC3) | Secondary System Organ Class 4 (SOC4) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 01-701-1015 | **1** | **701** | **1015** | MedDRA version 8.0 | redness around application site | 10003058 | Application site redness | Application site redness | Administration site reactions | General disorders and administration site conditions | Skin and subcutaneous tissue disorders | | |

## 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

## PATIENT EXPERENCE DATA

Under 21st Century Cures Act, FDA is required to "make public a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of the application."

Applicants may either:

1) Confirm that no patient experience data was submitted with the application. **OR**
2) Identify all patient experience data, as defined in section 3001 of the 21st Century Cures Act that are included in the application. See https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf.

   Some examples of patient experience data might include the following, but are not limited to:

   - Clinical outcome assessment data
   - Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)

- Patient-focused drug development or other stakeholder meeting summary reports
- Observational survey studies designed to capture patient experience data (e.g., disease burden, treatment burden, etc.)
- Natural history studies
- Patient preference studies

Please include a summary table with patient experience data type and reference the section in the application where the data is described in detail. A sample table has been provided below.

| | | |
|---|---|---|
| □ | The patient experience data that was submitted as part of the application, include: | Section(s) and if applicable file names where data are located and discussed in the application |
| | □ Clinical outcome assessment (COA) data, such as | |
| | □ Patient reported outcome (PRO) | |
| | □ Observer reported outcome (ObsRO) | |
| | □ Clinician reported outcome (ClinRO) | |
| | □ Performance outcome (PerfO) | |
| | □ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | |
| | □ Patient-focused drug development or other stakeholder meeting summary reports | |
| | □ Observational surveys studies designed to capture patient experience data | |
| | □ Natural history studies | |
| | □ Patient preference studies (e.g., submitted studies or scientific publications) | |
| | □ Other: (Please specify) | |

**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.

**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.

**SECURE EMAIL COMMUNICATIONS**

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please

note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

**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. | | | | |

**505(b)(2) REGULATORY PATHWAY**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's

interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that

supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

| **List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature** | |
|---|---|
| **Source of information (e.g., published literature, name of listed drug)** | **Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)** |
| *1. Example: Published literature* | *Nonclinical toxicology* |
| *2. Example: NDA XXXXXX "TRADENAME"* | *Previous finding of effectiveness for indication A* |
| *3. Example: NDA YYYYYY "TRADENAME"* | *Previous finding of safety for Carcinogenicity, labeling section B* |

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

**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.

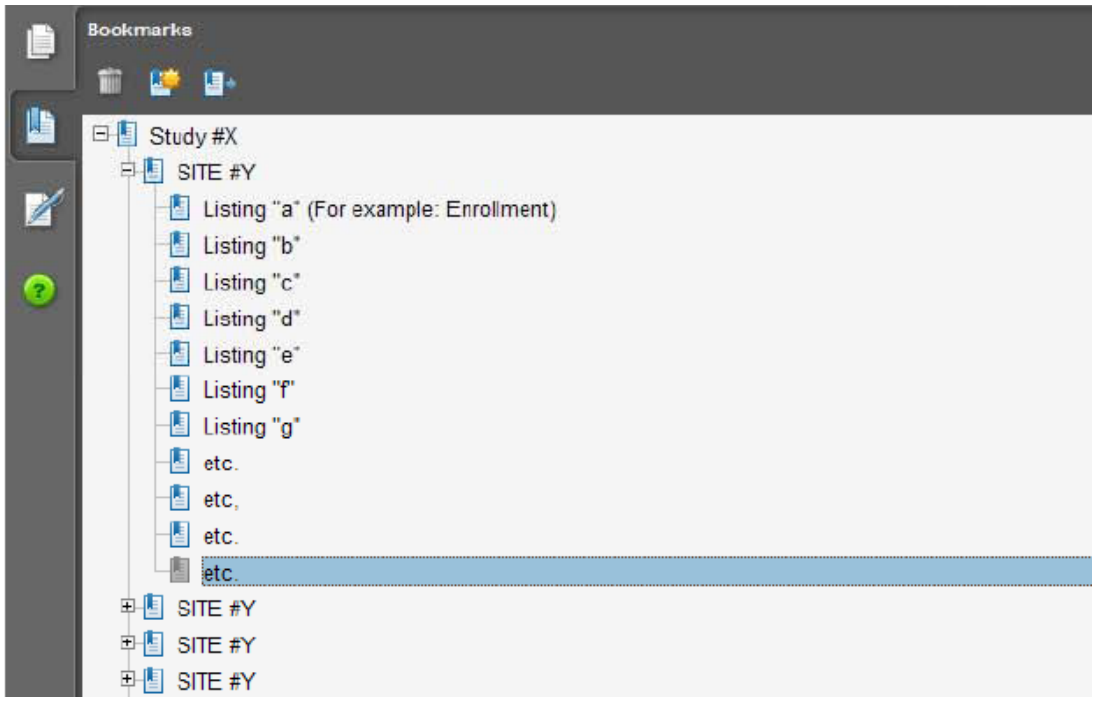
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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**

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

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

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/s/

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ALEXANDER GOROVETS
10/19/2017