CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217026Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 114319

MEETING MINUTES

Acadia Pharmaceuticals, Inc.
Attention: Heather Bradley, MPH
Executive Director, Regulatory Affairs
12830 El Camino Real, Suite 400
San Diego, CA 92130

Dear Ms. Bradley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for trofinetide (ACP-2566).

We also refer to the teleconference between representatives of your firm and the FDA on February 25, 2022. The purpose of the meeting was to discuss the content and format of the planned NDA submission for trofinetide for the treatment of Rett syndrome.

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

If you have any questions, contact Brenda Reggettz, PharmD, Regulatory Health Project Manager, by email at Brenda.Reggettz@fda.hhs.gov or by phone at (240) 402-6220.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Attachments 1 and 2
- Sponsor meeting slides

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 25, 2022, at 11:00 am (ET)
Meeting Location: Teleconference

Application Number: 114319

Product Name: Trofinetide (ACP-2566)
Indication: Treatment of Rett syndrome

Sponsor Name: Acadia Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES

Office of Neuroscience
Billy Dunn, MD, Office Director
Michelle Campbell, PhD, Stakeholder Engagement and Clinical Outcomes

Division of Neurology 1
Teresa Buracchio, MD, Director
Laura Jawidzik, MD, Deputy Director (Acting)
Emily Freilich, MD, Clinical Team Leader
Michael Dimyan, MD, Clinical Reviewer
Veneeta Tandon, PhD, Clinical Reviewer
Ami Mankodi, MD, Clinical Reviewer
Christopher Corosella, MD, Clinical Reviewer

Office of Clinical Pharmacology
Bilal AbuAsal, B.Pharm, PhD, Team Leader
Xiaohan Cai, PhD, Reviewer

Office of Biostatistics
Kun Jin, PhD, Statistical Team Leader
Minjeong Park, PhD, Reviewer

Division of Regulatory Operations-Neuroscience
Susan Daugherty, RN, BSN, Senior Regulatory Project Manager
Brenda Reggettz, PharmD, Senior Regulatory Health Project Manager
Terry Harrison, PharmD, Safety Regulatory Project Manager

Controlled Substances Staff
Edward (Greg) Hawkins, PhD, Reviewer

Division of Medication Error Prevention and Analysis
Stephanie Degraw, Team Leader
Chad Morris, PharmD, MPH, Safety Evaluator

Division of Rare Diseases and Medical Genetics
Cynthia Welsh, MD, Rare Diseases Team

Office of Surveillance and Epidemiology
Lopa Thambi, PharmD, Safety RPM

SPONSOR ATTENDEES

Srdjan (Serge) Stankovic, MD, MSPH, President
Steve Davis, JD, Chief Executive Officer
Jon Pilcher, BSc (Hons), FCA, Chief Executive Officer, Managing Director, Neuren Pharmaceuticals
Kathie Bishop, PhD, Sr. Vice President, Chief Scientific Officer and Head of Rare Disease
Daryl DeKarske, MPH, Sr. Vice President, Global Head of Regulatory Affairs and Head of Translational Sciences
Mary Ellen Turner, MD, MPH, Sr. Vice President, Pharmacovigilance and Corporate Safety Officer, Head R&D Quality Assurance
Jim Youakim, MD, Vice President, Clinical Development
Dimitrios Arkilo, MD, Vice President, Clinical Development Rare Disease
Mona Darwish, PhD, Sr. Director, Head of Clinical Pharmacology
Yufan Zhao, PhD, Executive Director, Biostatistics
Di An, PhD, Sr. Director, Biostatistics
Heather Bradley, MPH, Executive Director, Regulatory Affairs
Kristina Manvelian, Sr. Manager, Regulatory Affairs
Ryan Neville, IT Support

1.0 BACKGROUND

Acadia Pharmaceuticals is developing trofinetide (ACP-2566) for the treatment of Rett syndrome under IND 114319. Trofinetide is a synthetic analogue of the N-terminal tripeptide, glycine-proline-glutamate (GPE), of the insulin-like growth factor 1 (IGF-1) protein, a peptide that occurs naturally in the brain. Acadia is developing trofinetide as a ready-to-use, oral solution drug product.

This product received orphan designation (11-3631) on February 11, 2015, for the treatment of Rett syndrome. Fast Track designation was granted on June 4, 2013, for trofinetide for the treatment of Rett syndrome, and Rare Pediatric Disease designation

(RPD-2019-262) was granted on March 2, 2020. Acadia will request Priority Review and a Priority Review Voucher with their planned NDA submission.

On December 17, 2021, Acadia requested a Type B meeting with the Division to discuss the content and format of a planned upcoming New Drug Application for trofinetide (ACP-2566). On January 14, 2022, Acadia submitted a CMC-only, Type B, Pre-NDA meeting request, which has been granted by the Office of Pharmaceutical Quality.

The Agency's preliminary responses to the questions contained in the sponsor's January 26, 2022, background package follow below.

FDA sent Preliminary Comments to Acadia Pharmaceuticals on February 23, 2022.

2.0 DISCUSSION

[Recommend, if appropriate, to organize questions by categories and/or disciplines. Each category and/or discipline receives a subheading. Insert each question submitted by sponsor. In unusual cases where there are not specific questions and answers, substitute agenda topics with a brief description of each]

2.1. Category/Discipline A

2.1. Clinical

Question 1: Does the FDA agree that the statistically significant and clinically meaningful results from Study 003, along with supportive evidence including two Phase 2 studies, provides substantial evidence of the efficacy of trofinetide for the treatment of Rett syndrome to support an NDA review?

FDA Response to Question 1:

On preliminary review, we acknowledge the positive results from Study 003 in support of the use of trofinetide for the treatment of Rett syndrome. The available data appear adequate to support the review of the proposed NDA submission. However, we note that there were a large number of dropouts in the trofinetide group due to adverse events, which could potentially impact the interpretability the study results. The future NDA submission should adequately address concerns regarding dropouts and associated missing data. The ability of Study 003 to serve as a single study that provides substantial evidence of efficacy to support approval will be a matter of review of the data at the time of the NDA submission. You should include in your application a discussion of the how the data you have generated provides, in your estimation, substantial evidence of effectiveness.[1]

[1] Draft Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products https://www fda.gov/media/71655/download

Meeting Discussion:
The sponsor presented the prespecified sensitivity analyses performed to assess the impact of the missing data according to the Study 003 Statistical Analysis Plan (SAP) for each of their co-primary endpoints.

The Division acknowledged the sponsor's analyses and noted that all of the prespecified analyses documented in the SAP should be presented in the NDA submission. The proposed analyses to understand the impact of missing data appear appropriate. The adequacy of the analyses to support the primary efficacy analysis would be a matter of review.

Question 2: Does the FDA agree that the key secondary endpoint in Study 003, the Communication and Symbolic Behavior Scales Developmental Profile™ Infant Toddler Checklist – Social Composite Score, could (b) (4) support of the proposed indication for trofinetide for the treatment of Rett syndrome?

FDA Response to Question 2:

The ability to describe this secondary endpoint (b) (4), if approved, will be a matter of review.

(b) (4)

Meeting Discussion:
The sponsor presented additional background on the secondary endpoint, the CSBS-DP-IT-SCS and noted the relevance of the scale to assess communication in children with Rett Syndrome. The sponsor also indicated that it does consider the CSBS-DP-IT-SCS distinct from the primary endpoint (RSBQ), as only 1 of the 45 items in the RSBQ directly relates to communication.

The Division indicated that the adequacy of the outcome measure, results, (b) (4) would be a matter of review. To aid in our review, the Division recommended that at the time of NDA submission the sponsor should provide:

1) *justification for the use of the outcome measure in the age range enrolled in the study,*

[2] https://www.fda.gov/media/72140/download

2) *justification regarding the importance of social communication in this population,*
3) *all individual patient level responses at each time point,*
4) *information on the recorder/rater at each time point.*

Question 3: Can the FDA provide further detail on the expectation of an Integrated Summary of Efficacy (ISE) in the trofinetide NDA? The supporting datasets, tables, figures, and listings of the long-term efficacy analysis of Study 004, relative to Study 003 Baseline, is the only planned integration of trofinetide efficacy data across studies.

FDA Response to Question 3:

Please see our responses dated November 1, 2021, for the expectations regarding the ISE. We do not anticipate pooling of any efficacy data; additionally, data from the pivotal study (Study 003) intended to support efficacy should not be combined with data from the open-label extension study (Study 004).

The Summary of Clinical Efficacy (SCE) can serve as the Integrated Summary of Efficacy (ISE) if the appropriate data can be included within the space limitations of the SCE. However, the ISE is effectively being split across Module 2 and Module 5, with the narrative portions located in the SCE (Module 2.7.3), and the tables, figures, and datasets located in Module 5.3.5.3, as described in FDA's Guidance for Industry – *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*.[3] The texts should contain functioning hyperlinks to the information found in the appendices, tables, figures, listings, and datasets for the ISE.

Meeting Discussion:
The sponsor clarified the plan to submit a bridging efficacy analysis for patients enrolled in Study 003 who continued into Study 004 and inquired if this type of exploratory analysis should be included in the submission.

The Division indicated that the controlled efficacy data from Study 003 would be the primary source of data to determine the efficacy of the product. The Division noted that the proposed analysis integrating Study 003 and 004 can be submitted with the NDA but would be considered exploratory.

Question 4: Does the FDA agree with the revisions to the proposed pools of safety data for the trofinetide Integrated Summary of Safety (ISS), incorporating FDA comments from the Type C WRO issued 01 November 2021? (revisions underlined):

[3] https://www.fda.gov/media/75783/download

1. **Pool of double-blind, placebo-controlled studies in subjects with RTT (Pool RTTDB):**
   - **Includes:**
     - **RTT Phase 3 Study 003**
     - **RTT Phase 2 Studies RETT-001 and RETT-002**
     - **Note: Trofinetide-treated subjects in Study 003 by itself will also be presented side-by-side to the RTTDB pool columns, where appropriate, and analyzed as part of the CSR for Study 003**

2. **Pool of long-term trofinetide treatment in Phase 3 RTT double-blind and OL Studies (Pool RTTLT)**
   - **Includes:**
     - **Trofinetide-treated subjects in RTT double-blind Study 003**
     - **RTT OLE Studies 004, 005**
   - **Excludes:**
     - **RTT OL Study 009 in Subjects with RTT aged 2 to 5 years**

3. **Pool of long-term trofinetide treatment in Phase 3 OL Studies (Pool RTTOL)**
   - **Includes: RTT OL Studies 004, 005**

4. **Pool of double-blind, placebo-controlled studies in all indications (Pool ALLDB):**
   - **Includes:**
     - **RTT Studies RETT-001, RETT-002, and 003**
     - **FXS Study Neu-2566-FXS-001**
     - **TBI Study Neu-2566-TBI-003**
     - **Note: Trofinetide-treated subjects in Study 003 by itself will also be presented side-by-side to the ALLDB pool columns, where appropriate, and analyzed as part of the CSR for Study 003**

FDA Response to Question 4:

We agree with the proposed pools for the ISS analysis.

Meeting Discussion:
No discussion occurred.

Question 5: Does the FDA agree that previously discussed targets for number of subjects with long-term exposure to trofinetide (approximately 35 subjects treated for 12 months, 70 subjects treated for 9 months, 107 subjects treated for 6 months) can be submitted with the Day 120 Safety Update?

FDA Response to Question 5:

Any data necessary to support safety of the drug should be submitted at the time of the original application submission. The intent of the 120-Day Safety Update is to share new safety information learned about the drug that may reasonably affect any contraindications, warnings, precautions, and adverse reactions in the draft drug labeling.

The safety database should be as close to possible to the previously agreed upon estimated safety database at the time of NDA submission. We note that the 35 patients treated for 12 months is the minimum number of patients we would expect to find acceptable for chronic exposure to adequately assess the safety of your drug, based on our current understanding of the drug's safety profile. We also note that the number of analysis dropouts in your treatment group is high and you should anticipate future dropouts in assessing the adequacy of your safety database.

Please also refer to the standard Division of Neurology 1 pre-NDA safety requests in Attachment 1. We note that not all of the listed analyses may be appropriate for the Rett syndrome patient population; however, you should conduct those analyses that apply to your study population.

Meeting Discussion:
The sponsor presented the planned exposures at the time of NDA submission and 120-Day Safety Update and confirmed there would be safety data available for 35 patients treated for 12 months with trofinetide in the safety database at the time of NDA submission.

The Division responded that this number would be adequate for filing but that adequacy of the safety database to support a determination of safety would be a matter of review. The sponsor also indicated that the number of patients with expected 12-month exposure at the time of the 120-Day Safety Update was a conservative estimate to account for discontinuation rates.

Question 6: Does the FDA agree that the Day 120 Safety Update can be submitted as an updated Summary of Clinical Safety (Module 2.7.4) with supporting datasets, tables, figures or listings in Module 5.3.5.3?

FDA Response to Question 6:

In accordance with the requirements of 21CFR 314.50(d)(5)(vi)(b), we recommend the safety update include the same information as required in the integrated safety summary and contain case report forms for all deaths, SAEs, and discontinuations due to adverse events.

Meeting Discussion:
No discussion occurred.

Question 7: Does the FDA agree that an interim CSR of Study 009 in subjects with RTT aged 2 to 5 years is an acceptable to facilitate NDA review, including to inform labeling and fulfill PWR requirements?

FDA Response to Question 7:

No, we do not agree with your plan for the submission of Study 009. The 120-Day Safety Update is not intended for submission of new data to inform labeling. Any safety and PK data intended to inform labeling should be submitted at the time of initial submission.

If Study 009 is to be completed subsequent to the NDA submission, it can be submitted post-approval as an efficacy supplement and to fulfill the PWR. Please see prior correspondence regarding the Pediatric Written Request dated October 8, 2021, in which we provided instructions regarding "Timeframe for submitting reports of the study(ies)".

Meeting Discussion:
The sponsor clarified that at the time of NDA submission, Study 009 data will include safety, tolerability, and PK data from 10 patients aged 2 to 5 years treated for 12 weeks, and safety and tolerability data in an additional 5 patients treated for <12 weeks. The sponsor also confirmed that this population will include at least 4 patients under age 4 years, which was previously agreed upon. Additional safety data on patients treated for more than 12 weeks will be submitted at the 120-Day Safety Update.

The Division noted that if the safety and PK data are submitted at the time of the original NDA submission, then the data may be considered during the review of the NDA application. The adequacy of the data to inform labeling in this population would be a matter of review of the data.

The sponsor also indicated its plan to provide a synoptic Study 009 study report at the time of NDA submission, with descriptive results in the appropriate summary documents, along with the datasets. The Division indicated acceptability of this approach.

Question 8: Does the FDA agree to Acadia's proposal to submit study-level data in CDISC format for all individual clinical studies, in addition to:

- **Statistical Analysis System (SAS) programs to create all Analysis Data Model (ADaM) datasets for the ISS, the Phase 3 pivotal double-blind Study 003, and the 003/004 bridging efficacy analysis**

- **SAS programs to create all ISS tables and figures**
- **SAS programs to create the tables and figures for the co-primary and key secondary efficacy analyses for the Phase 3 pivotal double-blind Study 003 and the 003/004 bridging efficacy analysis**

FDA Response to Question 8:

From a technical perspective, the proposed study data submission package is acceptable. Please also make sure to submit all macros used in the programs.

Meeting Discussion:
No discussion occurred.

Question 9: ***Does the FDA agree with the proposed MedDRA coding for all adverse events and medical history for ISS pools and individual study reports?***

FDA Response to Question 9:

We agree with the proposed MedDRA coding plan.

Meeting Discussion:
No discussion occurred.

Question 10: Does the FDA agree to the planned Bioresearch Monitoring (BIMO) clinical data submission plan for the NDA?

FDA Response to Question 10:

We agree with the plans to submit the site level dataset and summary-level clinical site dataset (clinsite.xpt) for Study ACP-2566-003 (Study 003).

We note that Study 003 includes a semi-structured caregiver diary. In your NDA submission, please provide the following:

- Please specify whether this diary was paper, electronic (eDiary), or some other format.
- If an eDiary was used, please submit the user manual.
- In preparation for BIMO inspections, please indicate the data available at the clinical investigator sites for verification of raw diary listings. For example, for paper diaries, do the sites collect caregiver diaries as source for date entered into the eCRF? If eDiaries are used, will there be certified CDs (including audit trails) available or access to a web portal?

Meeting Discussion:
No discussion occurred.

2.2. Nonclinical

Question 11: Does the FDA agree with the toxicology studies for which Acadia plans to submit SEND datasets?

FDA Response to Question 11:

For an NDA, SEND datasets are required for single-dose toxicology, repeat-dose toxicology, and carcinogenicity studies that were initiated after December 17, 2016, and for respiratory and cardiovascular safety pharmacology studies initiated after March 15, 2019. At this time, there is no requirement for SEND datasets for a fertility and early embryonic development study. For additional information on study data standards, please refer to the Study Data Standards Resources web page[4].

Meeting Discussion:
No discussion occurred.

2.3. Regulatory

Question 12: Does the FDA agree with the proposed Table of Contents for the NDA?

FDA Response to Question 12:

From a technical perspective (and not content related), the Table of Contents (TOC) found in Appendix B is acceptable. Further guidance on acceptable submission format per Module is available in the Guidance for Industry M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use[5].

Meeting Discussion:
No discussion occurred.

Question 13: In accordance with 21 CFR Part 54.4, Acadia plans to include financial certification for all applicable Investigators from the adequate and well-controlled Phase 3 Study 003. Does the FDA agree?

[4] https://www.fda.gov/forindustry/datastandards/studydatastandards/default htm
[5] https://www.fda.gov/media/71551/download

FDA Response to Question 13:

We agree that financial certification should be provided for all Investigators of covered clinical studies, which include any studies that are relied upon in the application to provide support for the effectiveness of a product; Study 003 is considered a covered clinical study. Refer to the FDA Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosures by Clinical Investigators[6].

Meeting Discussion:
No discussion occurred.

2.4 Additional Comments

Clinical Pharmacology

If the to-be-marketed formulation is different than the formulation used in pivotal clinical trial(s), you will need to establish a bridge between these formulations.

Please provide a "review aid" for Clinical Pharmacology in the NDA submission. A template is attached as an appendix (Attachment 2).

Additional Meeting Discussion
The sponsor indicated plans to submit the NDA in June 2022 and indicated that there are no minor components to be submitted within 30 days of the initial submission. The sponsor also indicated that datasets for all PK analyses will be included in the NDA submission.

2.5 Post-meeting Question from Acadia

Acadia is planning to submit selected modeling and simulation reports under sections within Module 5 based on their subject matter. These modeling and simulation reports pertain to the following areas listed below (with CTD section numbers). As these are modeling and simulation reports, and not clinical study reports, the accompanying data packages (including datasets and programs) will be provided in data formats intended to be viewed and processed using modeling and simulation software, and are not in CDISC format.

- **5.3.3.3 Intrinsic factor PK Study reports and related information**
- **5.3.3.4 Extrinsic factor Study reports and related information**
- **5.3.4.2 Patient PD and PK/PD Study reports and related Information**

[6] https://www.fda.gov/media/85293/download

We have noted that, based on recent updates to FDA eCTD validation criteria (validation criteria versions 3.9 and onward), placement of reports in the sections listed above without CDISC data packages may result in high severity errors, and therefore could lead to technical rejection of the NDA submission.

We also note that, based on general feedback provided by FDAs ESUBS team, placement of modeling and simulation reports with non-CDISC data packages in the sections below will not generate validation errors; however these CTD sections do not fully align with the subject matter of the modeling and simulation reports Acadia is planning to submit.

- **5.3.3.5 Population PK Study reports and related information**
- **5.3.5.4 Other Study reports and related information**

Can the review division and/or FDAs ESUBS team provide further guidance regarding where these reports can or should be placed in a way that aligns with report content, but will not result in high severity validation errors (with respect to inclusion of CDISC data packages)?

FDA Response:

If your submission (modeling and simulation reports) in m5.3.3.3, m5.3.3.4, and m5.3.4.2 does not include any .xpt files then the technical rejection criteria will not be triggered. However, if you are submitting any .xpt files in these sections then please submit simplified ts.xpt to avoid the validation error 1734.

Refer to The Technical Rejection Criteria for Study Data document[7] for addition details (and examples) on simplified ts.xpt.

3.0 OTHER IMPORTANT INFORMATION

PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR IN CLINICAL PROTOCOLS

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be

[7] https://www.fda.gov/media/100743/download

included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology 1.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

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

- We did not have a preliminary discussion on the need for a REMS, other risk management actions or the development of a Formal Communication Plan; however, at this time it is not anticipated that there will be a REMS for this application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. There are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting is scheduled for March 16, 2022. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

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.

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[8] and Pregnancy and Lactation Labeling Final Rule[9] websites, which include:

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

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

[8] https://www fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[9] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[10]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[11]

ABUSE POTENTIAL ASSESSMENT

1. Your NDA submission should include abuse-related information and cross-linkage in appropriate sections of the NDA, as follows:
    a. Section 1.11.4 should contain your proposal and rationale for placing or not placing the drug substance or product into any schedule of the CSA.
    b. Section 2.7.4 should contain a subsection devoted to details of your abuse potential assessment, including a description of data, interpretation, and discussion of all abuse potential data provided in the NDA under other modules, including any drug accountability discrepancies and an analysis of abuse-related adverse events. Section 2.7.4 should also contain a comprehensive table of contents that provides links to all studies (nonclinical and clinical) and references in the NDA submission related to the assessment of abuse potential.

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.

[10] http://www fda.gov/ectd
[11] http://www fda.gov/ForIndustry/ElectronicSubmissionsGateway

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[12] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[13]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

[12] https://www.fda.gov/media/84223/download
[13] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[14]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion were identified.

5.0 ACTION ITEMS

Not applicable

6.0 ATTACHMENTS AND HANDOUTS

Included are attachments 1 and 2, provided by FDA to Acadia with FDA's preliminary meeting comments. Also attached are meeting slides provided by Acadia that were displayed during the meeting discussion.

[14] https://www.fda.gov/media/85061/download

Attachment 1.

Division of Neurology Pre-BLA and Pre-NDA Meetings
General Clinical Safety Requests

Datasets:

1. Each individual subject should be assigned a single unique subject identifier across the entire application (e.g., including open label extensions of the trials). Include the unique subject identifier in the ISS and individual studies' datasets.
2. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.

For additional guidance refer to the FDA webpage on Study Data Standards Resources.

General Submission Contents:

1. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application
2. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment
3. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
4. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
5. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
   a. Title of the table or figure in the application
   b. A hyperlink to the location of the table or figure with page number
   c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
6. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review.
7. Include active hyperlinks from the lists of references to the referenced article.

8. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
10. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
5. Ensure that all adverse events are presented, and not only events deemed "drug-related."
6. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
7. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request. Narratives should be integrated. For subjects who had more than one event requiring a narrative (whether in the same trial or in the core study and an extension) present a single narrative (rather than separate narratives for the various events).
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the narrative and CRF.
3. Provide reports for any autopsies conducted during any of the studies.

4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law laboratory criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation. The Division may want to request selected narratives/CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA/BLA submission.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
    a) Patient age and gender
    b) Adverse event onset and stop dates (presented as relative Study Day number)
    c) Signs and symptoms related to the adverse event being discussed
    d) An assessment of the relationship of exposure duration to the development of the adverse event
    e) Pertinent medical history
    f) Concomitant medications with start dates relative to the adverse event
    g) Pertinent physical exam findings
    h) Any abnormal vital sign measurements
    i) Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
    j) Discussion of the diagnosis as supported by available clinical data
    k) For events without a definitive diagnosis, a list of the differential diagnoses
    l) Treatment provided
    m) Re-challenge results (if performed)
    n) Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests:
   SI Units.
2. Provide the normal reference ranges for every laboratory value.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs, and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.

5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
    - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
    - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
    - Pulse Rate: <60 bpm, >100 bpm
    - Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
    - Temperature: >38.0 °C, <36.0 °C
    - Respiratory rate: <12 breaths/min, > 20 breaths/min
6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Patient profiles
   Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
    a) Age
    b) Sex
    c) Dates of screening, randomization and starting therapy
    d) Whether the patient completed or did not complete the study, with dates and reason for withdrawal
    e) Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
    f) Prior medications and concomitant medications with dates of start and end
    g) Vital signs and laboratories, sorted by date, with reference ranges *
    h) Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
    i) Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges
    j) Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.
    k) For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

   Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

2. Please submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies prior to submitting your NDA.
3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the NDA. This process could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

Attachment 2.

CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

The goal of this Aid is to facilitate the creation of an optimal Clinical Pharmacology Summary that summarizes the relevant Clinical Pharmacology findings and focuses sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions the Aid provides a generic questionnaire that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address. A special Section of the Clinical Pharmacology Summary should identify and discuss the critical findings and issues and indicate how the unresolved issues are addressed.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies*)* and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple doses, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t1/2 and AUC.

2.4 Exposure-Response

2.4.1 Does the exposure-response relationship support evidence of effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from randomized and well controlled trials

(RCT) and other appropriate studies. Provide evidence that the exposure-response analysis supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, Cmax or Cmin is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints.

Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, Cmax or Cmin is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) Cmax and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the RCTs. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [Cmax, tmax, AUC, Cmax,ss, Cmin,ss, Cmax,ss/Cmin,ss, tmax,ss, AUC0-τ, CL/F, V/F and t1/2 (half-life determining accumulation factor), accumulation factor,

fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?
Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?
Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, Cmax, Cmin, CL/F and t1/2 of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?
Indicate absolute and relative bioavailability, lag time, tmax, tmax,ss, Cmax, Cmax,ss and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?
Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?
Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?
Provide identification for ≥ 90% of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivity is too small to be assignable to individual metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.11 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min or mL/min/1.73m^2) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) Cmax and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.13 How do the PK parameters change with time following chronic

dosing?
Indicate whether the mean ratio of AUC0-τ at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.5.14 Is there evidence for a circadian rhythm of the PK?
Indicate whether Cmax and Cmin of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?
Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, Cmax, clearance, volume of distribution and t1/2 for pairs studied (e.g. elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?
Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (change of dose or dose interval or both)) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Sex

2.6.2.3 Body Weight

2.6.2.4 Elderly

2.6.2.5 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.6 Race/Ethnicity

2.6.2.7 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, Cmax and t1/2 of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, Cmax and CL/F on Clcr for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment (dose or dose interval, or both) is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.8 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, Cmax, tmax and t1/2 of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of Cmax, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.9 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?
Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?
Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?
Summarize the results of the in vitro studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

2.7.2 Is the drug a substrate of CYP enzymes?
Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to Km, controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the in vitro findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?
Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for Ki, IC_{50} and Vmax for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the [I]/Ki ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

2.7.5 Are there other metabolic/transporter pathways that may be important?

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report t1/2, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and Cmax for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater

than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report t1/2, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and Cmax for each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.8 Does the label specify co-administration of another drug?

2.7.9 What other co-medications are likely to be administered to the target population?

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and Cmax after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

IR Product

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate the clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were the strengths bioequivalent or not?

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

MR product (if an IR is already marketed)

2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?
Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on Cmax, AUC and Cmin of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?

2.8.8 What is evidence that MR formulation displays less variability in Cmax, AUC and Cmin than IR formulation?

2.8.9 Does the MR product show dose dumping *in vivo*?
Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?
Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

2.8.11 Are the MR and IR products marketed simultaneously?
If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing

regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?

2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?
List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

2.9.3 For all moieties measured, is free, bound, or total measured?
Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?
Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?
For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?
For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?
For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.5.3 What is the sample stability under conditions used in the study?
For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at

room temperature and stability during long term storage at ≤ –20° C.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.5.5 What evidence is available demonstrating that neither the assay of the drug on interest is impacted by co-administered other drugs and vice versa?

Applicable to therapeutic proteins only

2.9.5.6 What bioanalytical methods are used to assess therapeutic protein concentrations?

Briefly describe the methods and summarize the assay performance.

2.9.5.7 What bioanalytical methods are used to assess the formation of the anti-product antibodies?

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

2.9.5.8 What is the performance of the neutralizing assay(s)?

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: October 12, 2017 11:00 AM to 12:00 PM (EST)
Meeting Location: White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: IND 114319
Product Name: Trofinetide (NNZ-2566)

Indication: Rett syndrome
Sponsor/Applicant Name: Neuren Pharmaceuticals, Ltd

Meeting Chair: Billy Dunn, MD
Meeting Recorder: LaShawn Dianat, PharmD

FDA ATTENDEES

Billy Dunn, MD	Director, Division of Neurology Products (DNP)
Eric Bastings, MD	Deputy Director, DNP
Nicholas Kozauer, MD	Clinical Team Leader, DNP
Veneeta Tandon, MD	Clinical Reviewer, DNP
Martha Heimann, PhD	Neurology CMC Lead
Bilal AbuAsal, PhD	Office of Clinical Pharmacology
Atul Bhattaram, PhD	Office of Clinical Pharmacology
Kun Jin PhD	Biometrics Team Leader
Junshan Qiu, PhD	Mathematical Statistician
LaShawn Dianat, PharmD	Regulatory Project Manager, DNP

SPONSOR ATTENDEES

Richard Treagus, MBChB, Executive Chairman, Neuren Pharmaceuticals
Larry Glass, Chief Science Officer, Neuren Pharmaceuticals
Nancy Jones, PhD, VP, Clinical Development, Neuren Pharmaceuticals
James Shaw, VP, Clinical Operations, Neuren Pharmaceuticals
James Bonnar, Director, Clinical Operations & Regulatory Affairs, Neuren Pharmaceuticals
Jon Pilcher, Company Secretary, Neuren Pharmaceuticals
Steve Kaminsky, PhD, Chief Science Officer, RettSyndrome.org

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1.0 BACKGROUND

The purpose of this meeting is to discuss development of trofinetide (NNZ-2566) oral solution for the treatment of Rett Syndrome.

Rett syndrome is a rare neurological disorder caused by mutations on the X-chromosome that almost exclusively affects females, with a worldwide incidence of approximately 1:10,000. It is a serious condition. Trofinetide is a new chemical entity that received Fast Track designation by the FDA in June 2013, and Orphan Drug designation in February 2015, as a potential new treatment for Rett syndrome.

Neuren completed Study Neu-2566-RETT-001, a Phase 2 study of NNZ-2566 in adolescent and adult patients with Rett syndrome.

The objectives of the meeting are to reach agreement on:

- The design of the Phase 3 study;
- The dose of oral trofinetide to be studied;
- The primary and secondary clinical endpoints to be used in the Phase 3 study;
- The approach to a prespecified statistical analysis;
- The required safety exposure data;
- Post approval commitments, clinical and nonclinical;
- Plans related to Chemistry, Manufacturing, and Controls.

FDA sent Preliminary Comments to Neuren Pharmaceuticals on October 9, 2017.

2. DISCUSSION

Clinical

Question 1:

The Sponsor proposes a Phase 3 pivotal study using a sequential parallel comparison design (SPCD) with 2 stages of 12 weeks each to evaluate the safety and efficacy of trofinetide for Rett Syndrome in children, adolescents and adults. Does the Division have any comments concerning the acceptability of the proposed Phase 3 study design as the pivotal study for the clinical package to support filing of an NDA?

FDA Response to Question 1:

We have not endorsed the SPC design in a confirmatory trial setting, largely due to uncertainty about the validity of the associated statistical methodology. For instance, the

validity of the test explored in Chen et al (2011) remains unclear in most scenarios. It is important to have thorough understanding of the pros and cons of this novel methodology before it is fully recognized. To minimize the risk of a failed SPC trial, we recommend that the statistical power at Stage 1 alone be adequate to support efficacy in case the validity of the associated statistical analyses remains uncertain by the time of your NDA submission. The final acceptance of the design with the associated statistical analyses to support a NDA submission will be a review issue. In addition, we have the following statistical comments.

1. Please clarify the definition of the index i for the test statistics T in the primary efficacy analysis.

2. Please state the distribution of T statistics and describe how to calculate the p-value.

3. You should provide a plan on how to handle missing data.

4. Sensitivity analyses should be planned for assessing the impact of missing data on the analysis results, especially when the amount of missing data is not ignorable.

5. You should provide a plan on subgroup analyses.

Additional Clinical Comment:

We note that the study protocol does not include any stratification based on MeCP2 gene mutation status. Please comment on whether imbalances in MeCP2 gene mutation are likely confound the interpretability of the study results.

Discussion:

The sponsor proposed significant changes to the protocol based on the Division's preliminary meeting comments. The sponsor explained that in order to eliminate the uncertainly in the analysis of the sequential parallel comparison design (SPCD) trial, it plans to conduct a single parallel group design of 6 months duration with 1:1 randomization to drug and placebo. The RSBQ and CGI-I will be designated as co-primary endpoints in this proposed study. The dosing and inclusion/exclusion criteria will remain the same as proposed in the SPCD. The sample size will accordingly be powered to detect a treatment difference based on the revised primary endpoint structure. The Division indicated that this proposal appeared to be acceptable, pending a review of the full study protocol.

The sponsor asked if the Division has any preference on approaches to address placebo response in a trial. The Division indicated that it had no specific recommendation, but had successful experience with placebo run-in designs, albeit for acute treatments in migraine trials. The Division asked if the sponsor had any specific concerns regarding placebo response specific to Rett syndrome, as this occurs in many trials. The sponsor indicated that its concerns were general in nature.

Regarding the MeCP2 gene mutation, the sponsor clarified that it did not plan on stratifying randomization based on MeCP2 mutation status as a clear genotype-phenotype relation with each mutation has not been established. In addition, the sponsor stated that there are over 200 MeCP2 gene mutations in Rett syndrome with approximately 12 being more common than the others, therefore there would only be at most a few subjects with any given mutation. The sponsor further indicated that it will collect information regarding mutation status in the study. The Division agreed with this approach and had no further comments.

Question 2:

The Sponsor proposes to use the Rett Syndrome Behaviour Questionnaire (RSBQ) as the primary endpoint and the Clinical Global Impression – Improvement (CGI-I) measure as a secondary endpoint to evaluate efficacy in the Phase 3 pivotal study. Does the Division have any comments on the RSBQ as the primary endpoint and the CGI-I as a secondary endpoint in the study?

FDA Response to Question 2:

The Rett Syndrome Behavior Questionnaire (RSBQ) may be an acceptable primary endpoint for your proposed trial. However, score changes for many of the items, particularly items that assess disease signs, do not directly reflect how patients feel or function in everyday life. A statistically significant positive treatment effect on the RSBQ that was not supported by a similar positive effect on the Clinical Global Impression – Improvement (CGI-I) scale would be very difficult to interpret. We also note that you plan to support any future planned NDA based on the results of a single positive adequate and well-controlled trial. For such an approach to be acceptable, it is especially important that the results of the trial are robust (i.e., supported by statistically significant and clinically meaningful effects on endpoints). Therefore, we strongly recommend that you analyze the CGI-I scale as a co-primary endpoint in your proposed trial.

With respect to the additional proposed secondary endpoints for your planned trial, for such measures to be considered appropriate for inclusion in any future product label, they should assess domains that are distinct from those evaluated by the primary endpoint. In addition, the analysis of the endpoints must be statistically controlled for Type I error.

Discussion:

See the discussion for Question 1.

Regarding the recommendation for CGI as a co-primary endpoint, the Division explained that for endpoints that evaluate a range of disease symptoms such as RSBQ, a score change does not necessarily directly assess whether a patient's life has changed as a result. A supportive measure, such as the CGI-I scale, is therefore necessary to understand the clinical meaningfulness of any observed score change in the RSBQ. The sponsor had no further comments.

Regarding secondary endpoints, the sponsor asked if the Division had any specific secondary endpoints in mind for inclusion into a clinical trial in Rett syndrome. The Division indicated that it did not have any specific recommendations. The Division further explained that a secondary endpoint that is a subset of the primary endpoint (as proposed), is likely to be positive if the primary endpoint is positive. Therefore, especially in the setting of a marketing application that intends to support a finding of effectiveness based on positive results of a single adequate and well-controlled trial, positive findings on secondary endpoints that assess different disease domains from the primary endpoint can help make the study results more persuasive. The Division also reiterated that the ability of positive results from such a single trial to support the effectiveness of a drug cannot be prespecified and are a matter of review.

Question 3:

The Sponsor proposes to compare a single active exposure group of trofinetide to placebo using weight-banded doses of 200 mg/kg, 260 mg/kg and 340 mg/kg BID to achieve comparable and optimal systemic exposure across all subject weights. Does the Division have any comments about this approach?

FDA Response to Question 3:

The approach is acceptable.

Additional Clinical Pharmacology Comments:

- You should evaluate the effect of food on the exposure of trofinetide. Based on the food effect, if any, your protocol should clearly indicate whether the drug be administered with or without regard to food.

- You should characterize the metabolism and elimination pathways of trofinetide. The need for hepatic and renal impairment studies should be evaluated based on the metabolism and elimination of trofinetide.

- Please clarify the rationale for excluding patients taking anticonvulsant medications with liver enzyme inducing effects from your proposed Phase 3 study. You should evaluate whether trofinetide is a substrate for major drug metabolizing enzymes and transporters and decide on allowed concomitant medications.

- We note the following exclusion criterion in your planned trial: “gastrointestinal disease which may interfere with the absorption, distribution, metabolism or excretion of the study medication.” Please clarify whether there are any factors/conditions that you have identified that may affect the absorption, distribution, metabolism, or excretion of trofinetide.

- You should record the dose and time of administration of any concomitant medications relative to trofinetide dosing and the PK sampling times. This will help

with pop-PK analyses for evaluating potential drug-drug interactions from your proposed Phase 3 study.

Discussion:

The sponsor stated that they will address these additional comments while revising the Inclusion/Exclusion criteria.

Question 4:

The planned safety database will include children, adolescents and adults who have been treated for 6 months (n=~107), 9 months (n=~70) and 12 months (n=~35). Does the Division have any comment on the planned safety database to support the filing of an NDA?

FDA Response to Question 4:

Your proposed safety database is likely to provide adequate safety data to support an NDA for Rett Syndrome. However, the final acceptability of these data are subject to the emerging safety findings from your future trials. Therefore, the adequacy of the safety database remains a matter for review of the application.

Discussion:

None

CMC

Question 5:

Does the Division have any comments about the Sponsor's approach to use a ready-to-use (RTU) drug product solution for oral administration to subjects in the pivotal Rett syndrome clinical study and as the "to-be-marketed" drug product, based on the information provided?

FDA Response to Question 5:

The ready-to-use drug product approach appears to be reasonable based on the provided information. In order to ensure the integrity of the drug product prior to administration to patients, identify an in-use period following removal of the drug product from the refrigerator for multi-dosing administration.

We have the following microbiology recommendations for a non-sterile aqueous multiple-dose formulation:

1. Microbiological testing of the drug product should be performed for release and stability per USP <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* and 62> *Microbiological Examination of Nonsterile Products: Tests*

for Specified Microorganisms with acceptance criteria as recommended in USP <1111> *Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* for non-sterile aqueous oral drug products.

2. Because the drug product will be supplied as a multiple-dose formulation, the NDA should include the results of antimicrobial effectiveness testing (AET) according to USP <51> or an equivalent method. Antimicrobial effectiveness testing should be conducted using the minimum acceptable concentration of the preservative(s) of the drug product, allowed for release or stability, whichever is lower. Additionally, AET should be conducted on at least one primary batch at shelf-life to demonstrate that the preservative system remains effective through the shelf-life of the drug product. See ICH Q1A *Stability Testing of New Drug Substances and Products* for additional information.

3. Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. Therefore, we recommend that the pending NDA microbiological release testing for this drug product include a test for the absence of BCC" with these additional considerations:

    a. Identify potential sources for introduction of BCC during the manufacturing process. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.
    b. The test method for identify BCC should be validated. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing. As there are currently no compendial methods for detection of BCC, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to ensure that the proposed recovery methods are adequate to recover organisms potentially present in the environment. Your NDA submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions.

Discussion:

The response to this question has been provided with the final meeting minutes and was therefore not discussed during the meeting.

Question 6:

Does the Division have any comments about the Sponsor's approach to support expiration dating of the RTU drug product solution, based on the information provided?

FDA Response to Question 6:

The overall approach to support expiration dating appears reasonable, but will be a matter for review based on the data provided for the final formulation. Your expiration dating approach should include confirmation of antimicrobial preservative effectiveness throughout its proposed usage and shelf-life as discussed in the response to Question 5.

It is our expectation that the NDA will include at least twelve (12) months of long-term stability data and at least six (6) months of accelerated stability data for 3 drug product batches at the time of submission. Although not considered a filing issue, we will evaluate the proposed expiration period based on the quantity and quality of the stability data provided in the submission. The proposed expiration period should ensure that the drug product is commercially viable. We would like to remind you that as stated in Guidance for Industry ICH Q1E Evaluation of Stability Data "where long-term data are not amenable to statistical analysis, the proposed shelf life can be up to one-and-a-half times as long as, but should not be more than 6 months beyond, the period covered by long-term data," if relevant supporting data is available.

Discussion:

The response to this question has been provided with the final meeting minutes and was therefore not discussed during the meeting.

Question 7:

Does the Division have any comments about the Sponsor's approach to establish the RTU drug product solution specification for impurities, based on the information provided?

FDA Response to Question 7:

Your approach to establish the RTU drug product solution specification for impurities in accordance with ICH guidelines appears to be reasonable. As drug product impurity levels increase rapidly at room temperature, an in-use period following removal of the drug product from the refrigerator must be established (as noted in our response to question 5).

Discussion:

The response to this question has been provided with the final meeting minutes and was therefore not discussed during the meeting.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

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

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

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

DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study

Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the

CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

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

ABUSE POTENTIAL ASSESSMENT

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

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*
4.	

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

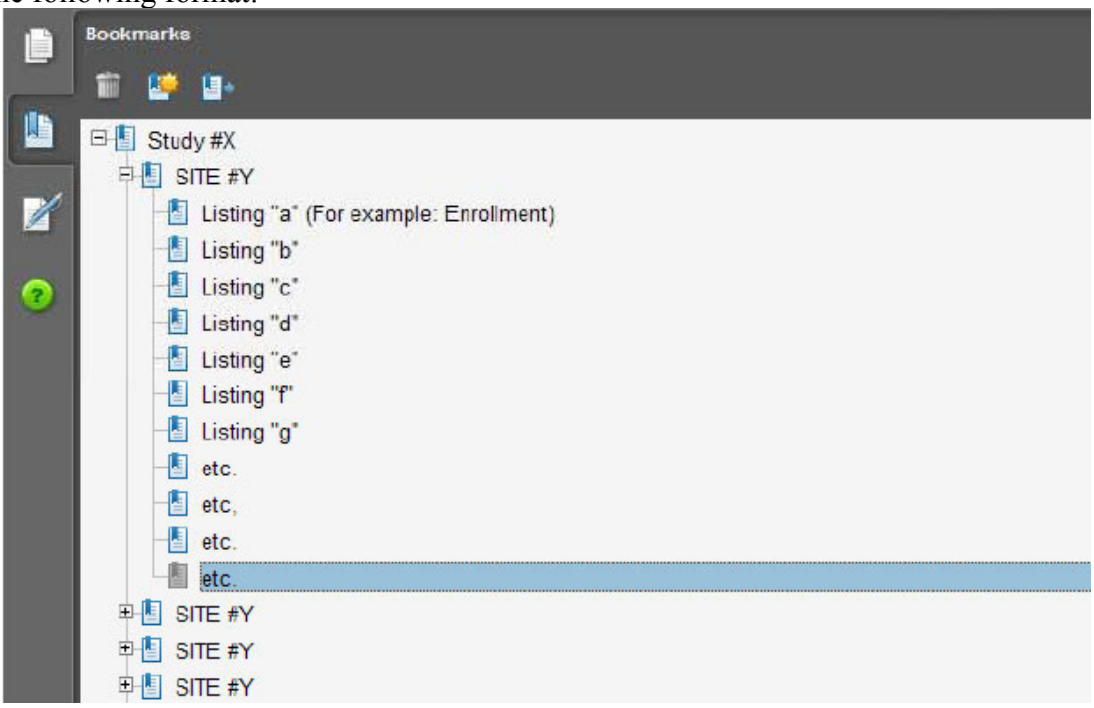
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND 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

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:

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

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

PATIENT-FOCUSED ENDPOINTS

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population

5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

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

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
10/24/2017