

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210365Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 120055

MEETING MINUTES

GW Research Ltd.
Attention: Catherine Maher, Ph.D., RAC
Head of Regulatory Affairs
15 T.W. Alexander Drive, P.O. Box 13547
Research Triangle Park, NC 27709

Dear Dr. Maher:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cannabidiol Oral Solution.

We also refer to the meeting between representatives of your firm and the FDA on July 19, 2016. The purpose of the meeting was to obtain agreement with Division that the NDA can be reviewed under the standard of a single adequate and well-controlled study plus confirmatory evidence that provides substantial evidence of effectiveness for the use of Cannabidiol in the treatment of seizures associated with Dravet Syndrome.

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

If you have any questions, call Stephanie N. Parncutt, M.H.A., Senior Regulatory Health Project Manager, at (301) 796-4098.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: July 19, 2016; 3:00 – 4:00 PM EST
Meeting Location: CDER WO Room 1311

Application Number: IND 120055
Product Name: Cannabidiol Oral Solution
Indication: The adjunctive treatment of seizures associated with Dravet Syndrome (DS) in patients 2 years of age or older.
Sponsor/Applicant Name: GW Pharmaceuticals, Inc.

Meeting Chair: Billy Dunn, M.D.
Meeting Recorder: Stephanie N. Parncutt, MHA

FDA ATTENDEES

Billy Dunn, M.D.
Eric Bastings, M.D.
Ellis Unger, M.D.
Norman Hershkowitz, M.D.
Teresa Buracchio, M.D.
Angela Men, Ph.D.
Jagan Parepally, Ph.D.
Stephanie N. Parncutt, MHA
Martin Rusinowitz, M.D.
Jacqueline Ware, Pharm.D.
Kun Jin, Ph.D.
Colleen Locicero
Tristan Massie, Ph.D.
Cara Alfaro
Dominic Chiapperino, Ph.D.
Naomi Lowry
Kevin Krudys, Ph.D.
Laura Jawidzik, M.D.

EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein

SPONSOR ATTENDEES

Dan Checketts
James Crawforth, Ph.D.
Tilden Etges, MSc, QPPV
Catherine Maher, Ph.D.
Alice Mead, JD, VP
Gilmour Morrison, HNC
Mark Paternoster, Ph.D.
Claire Roberts, Ph.D.
David Solomon, BPharm
Ken Sommerville, MD
Colin Stott
Kevan VanLandingham, M.D., Ph.D.
Xiaoting Wang, Ph.D.
Stephen Wright, M.D.

1.0 BACKGROUND

Specific objectives for this meeting include reaching agreement on the following:

- The Dravet syndrome NDA meets the standards required for review of an NDA on the basis of a robust single multicenter study GWEP1332 with substantial supporting efficacy data from secondary endpoints, along with safety and efficacy data from the open-label extension study, the supportive Phase 1 studies, and the expanded access program;
- Phase 1 program and proposal for PopPK modeling;
- The nonclinical and clinical studies constituting the abuse liability program;
- Confirmation of agreement on the nonclinical program, which studies can be submitted within 30 days of the initial NDA submission, and that the mouse carcinogenicity study will be a post approval commitment;
- A priori agreement on the secondary efficacy measures appropriate to include in labeling;
- The likelihood of an Advisory Committee meeting and the appropriate committee;
- Deferment of rolling submission proposal;
- Confirmation that the planned statistical analyses are sufficient;
- The plan for the 120-day Safety Update;
- Input on the definition of the new basic class for re-scheduling purposes and the next steps for review of the basic class definition.

FDA sent Preliminary Comments to GW Pharmaceuticals, Inc. on July 18, 2016.

2. QUESTIONS

SUMMARY OF SPONSOR QUESTIONS AND FDA RESPONSES

1. [CLINICAL question submitted in the June 15, 2016 Briefing Document]

QUESTION 1: (a) Does FDA agree that the plan to provide data from the single adequate and well-controlled, multicenter study GWEP1332, along with the available data from the open-label extension study (GWEP1415), expanded access program, and the Phase 1 and 2 program, provides sufficient data to allow assessment of the efficacy and safety of CBD-OS in patients with DS?
(b) Additionally, does FDA agree that the unmet medical need of patients with DS warrants consideration for an expedited priority review?

FDA Preliminary Response

- a. On face, Study 1332 (Part B) appears to be an adequate and well-controlled study that may be sufficiently persuasive to allow it to serve as a single study providing evidence of effectiveness in support of a marketing application. With the additional safety data from the open-label extension studies, Phase 1 and 2 studies, and expanded access studies, it is possible that it may be sufficient to support an application for Dravet syndrome. The final determination as to whether these data are sufficient for approval will be a review issue. In addition, we note that you have recently released positive topline results for Study 1423 in LGS. It is possible that an application based upon a sufficiently persuasive Dravet study could include the results of the LGS study and ultimately support an indication for both conditions.

We note that topline results from Study 1414 in LGS will likely be available prior to your NDA submission and topline results from Study 1424 in Dravet may be available during the time that an NDA submission is under review. The results of these studies would also warrant consideration. We welcome the opportunity to discuss these issues with you at our meeting.

In order for data from the expanded access programs to support safety, you must provide support for the accuracy, completeness, and quality of these data (e.g., that patients were carefully assessed and consistently followed and that adverse events were adequately captured, documented, and coded).

GW Response

GW would like to confirm that the study report for GWEP1414 will be included in the LGS NDA. Unfortunately we do not anticipate results for GWEP1424 until 2H2017 and cannot at this point commit to providing top line results during the NDA review. Were results to become available during review, we would be grateful for guidance from the Division on the format of data to be provided during NDA review.

GW would like to discuss with the Division the interdependency of the efficacy sections for Dravet and LGS. For example, the effect of CBD on convulsive seizures in each indication may be supportive of the efficacy of CBD in the other indication.

In light of the results from LGS study GWEP1423, we intend to submit a fast track application and request priority review. We would also like to clarify whether the Division would still prefer a separate NDA for each indication with cross-application linking for Modules 3, 4, and 5 and certain documents within Modules 1 and 2. In order to facilitate streamlining of the review, GW requests parallel priority review of both indications. Is the Division able to indicate that this is acceptable?

Finally, GW would like to discuss with the Division the process for data collection in the US expanded access programs. The data originating from the US expanded access program is considered observational and has been collected as part of an organized data collection process. The expanded access programs Investigators were requested under agreement to provide complete safety data and all adverse events to GW. The safety data collected is standardized across these investigator-led INDs. Once received at GW, the data handling follows standard procedures for follow-up, quality checks and coding. The data will be provided in the ISS as a pooled dataset.

Meeting Discussion:

GW clarified that both clinical efficacy studies in LGS, GWEP1423 and GWEP1414, would be included in the NDA submission for LGS. They currently plan to submit the NDA for LGS concurrently with the NDA submission for Dravet syndrome. GW projects that the NDA submissions would occur at the end of the 1st Quarter of 2017.

Based upon the information provided by the sponsor, the Agency recommended that a single NDA be submitted for both LGS and Dravet indications, which contain the three completed efficacy studies (GWEP 1423 and GWEP1414 in LGS and GWEP 1332 in Dravet). The two LGS studies may potentially be considered as confirmatory evidence for the Dravet indication, based upon the review of the single Dravet study; however, the studies would be reviewed independently. The submission should include a discussion of the pathophysiology of LGS and Dravet and a rationale as to why the two indications can support one another. GW inquired whether the data for the two indications should be integrated into a single Summary of Clinical Efficacy (Section 2.7.3) or whether separate summaries would be required for each indication. The Agency indicated that a single summary would be acceptable but that it is not necessary to integrate the data across indications, as the Agency will be reviewing the studies independently. The efficacy data should be summarized in the way that GW feels is most appropriate and useful.

GW indicated that they plan to submit a Fast Track application for LGS based on data from Study GWEP 1423 and request a priority review. The Agency clarified that, although GW may submit a request for Fast Track designation for LGS, determination of a priority review is made independently of the Fast Track designation; the determination of priority

review occurs at the time of the NDA submission. If it is determined that one of the indications warrants a priority review, the entire NDA will be reviewed under the priority review timeline.

GW requested input on how results of GWEP1424 should be submitted to the NDA if results become available during the NDA review. The Agency indicated that if topline results for Study GWEP1414 become available during the NDA review, a brief summary report may be adequate.

GW provided further details regarding the collection of safety data from the expanded access programs. The Agency noted that GW's description of the procedures for collecting safety data in the expanded access programs appears to be adequate. In general, it is important that safety data have been collected in a systematic way and that adverse events are followed until resolution, with final outcomes included in the safety database. The Summary of Clinical Safety in the submission should address the identified safety signals of transaminase elevations and include evaluation by an external expert in liver disease. Interactions with clobazam should also be addressed in the safety summary.

- b. The determination of whether an NDA application will receive an expedited priority review will be made at the time of the NDA submission.**

GW Response

No discussion needed.

II. [PHARMACOKINETICS question submitted in the June 15, 2016 Briefing Document]

**QUESTION 2: (a) Does the FDA agree that the Phase 1 program available at initial NDA submission will provide sufficient data to support assessment of the DS NDA?
(b) Does the FDA agree with the sponsor's proposal for PopPK modeling?**

FDA Preliminary Response

- a. On face, the list of Phase 1 clinical pharmacology-related studies and data on changes in AED levels in the presence of CBD-OS in DS patients for CLB, N-CLB, VAL, STP, levetiracetam, and topiramate (study GWEP1332A) proposed to be submitted with the initial NDA appears to provide support of the proposed NDA. However, we strongly recommend submission of the data from DDI studies GWEP1543 [REDACTED] ^{(b) (4)} with the initial NDA submission so as to provide adequate time for the review of the complete package. The adequacy of the submitted information will be a matter of review of the NDA.**

GW Response

In the initial NDA, PK and AED data will be available from GWEP1332A (Dravet children), GWEP1428 (epilepsy patient clobazam DDI study), and from Dravet and LGS studies, using a population PK analysis exploring concomitant medications as a covariate. Healthy volunteer DDI study GWEP1543 may be available for the initial NDA, (b) (4)



b. Your plan to conduct a population PK analysis is acceptable. We also encourage you to explore the relationship between exposure metrics and efficacy and safety endpoints. The results of these analyses should be used to support your proposed dosing regimen. The following are the general expectations for the submission data and models for such analyses:

- All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- For the population analysis reports, we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line, and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also, provide in the summary of the report a description of the clinical application of modeling results.
- The codes should be submitted under the "module5/datasets/poppk/analysis/programs/" folder (such as run1.ctf.txt, run1.lst.txt, plot1.R.txt) with a define pdf file to explain the role of each file and sometimes with a pdf file as the revieweraid.pdf to explain the flow of running the code if necessary. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file.

GW Response

No discussion needed. GW plans to provide the population PK analysis plan to FDA for information in the coming months.

III. [ABUSE POTENTIAL question submitted in the June 15, 2016 Briefing Document]

QUESTION 3: The Sponsor believes information from the proposed nonclinical and clinical program allows for a comprehensive quantification of abuse liability.
Does the FDA agree?

FDA Preliminary Response

Yes, on face, we agree. CSS's review of the nonclinical and clinical data will determine the adequacy of your NDA submission.

GW Response

No discussion needed.

IV. [NONCLINICAL question submitted in the June 15, 2016 Briefing Document]

QUESTION 4: (a) The API (Purified CBD) present in CBD-OS is purified from (b) (4) (b) (4) *Cannabis sativa* L. plants. A thorough nonclinical program with CBD, the API present in CBD-OS, is ongoing (see list of studies provided in the Company Position), and the final reports will be available at the time of initial NDA submission, except where noted in question 4(b). Some of these studies have been conducted with the finished product formulation, CBD-OS. The remainder of the studies have been conducted with CBD BDS.
Taken together with the safety data from humans exposed to CBD in clinical studies, including those conducted by the Sponsor and studies published in the literature, the Sponsor believes that no additional nonclinical safety studies are required for NDA.
Does the FDA agree?

(b) As agreed with FDA on 29 February 2016, the 90-day toxicology study (with 28-day interim kill) (b) (4) in rats will be submitted within 30 days of submission of the original NDA. (b) (4)

(b) (4) In addition to (b) (4) has also been identified as present in the drug substance (b) (4) is currently controlled in the specification as an unspecified impurity at a limit of not more than (b) (4) % w/w and will be introduced in the specification as a specified impurity at NMT (b) (4) % w/w by the time of NDA submission. As with (b) (4) has been evaluated for structural alerts using software DEREK for Windows® with respect to its genotoxic, mutagenic, and carcinogenic potential. No structural alerts were predicted.

Therefore for both (b) (4) and (b) (4) at the time of initial NDA submission, the following studies will be included: *in vitro* and *in vivo* genotoxicity assessment (rat) and an embryofetal development study (rat), plus a 90-day (with 28-day interim kill) toxicity study (rat) for (b) (4)

only. Because of difficulties synthesizing (b) (4), GW proposes to submit the 90-day toxicology study of (b) (4) by the time of the 120-day Safety Update. For clarity, a similar battery of toxicology qualification studies for (b) (4) and (b) (4) (other API impurities) will be included in the initial NDA submission.

Does the FDA agree?

(c) In response to GW's mouse carcinogenicity protocol submission to the Carcinogenicity Assessment Committee on 08 December 2015, the CAC responded on 21 January 2016 that sufficient information to justify the doses selected was not provided. GW is awaiting toxicokinetic data and will resubmit to the CAC in coming months.

Since the initial NDA will include the rat carcinogenicity study report (Study JJG0003) conducted under (b) (4), does the FDA agree that completion of the mouse carcinogenicity study can be a post approval commitment?

FDA Preliminary Response

a) Based on the information provided, the completed and planned or ongoing nonclinical studies appear sufficient to support an NDA. However, the adequacy of the studies will be a matter of review.

b) Your proposal for providing qualification data for the (b) (4) and (b) (4) impurities is acceptable.

c) As previously agreed, the mouse carcinogenicity study may be submitted post-approval.

GW Response

No discussion needed.

V. [REGULATORY questions submitted in the June 15, 2016 Briefing Document]

QUESTION 5: GW requests FDA feedback on the Target Product Profile (Appendix 2). Specifically, as recommended in the 22 October 2015 Type C written responses, GW requests discussion and an *a priori* agreement on the secondary efficacy measures to include in labeling.

FDA Preliminary Response

Labeling is a review issue. However, we have the following general advice:

- **The proposed graph in Figure 2 which shows the [REDACTED] (b) (4) may not be acceptable for labeling. We do allow descriptive information similar to this in epilepsy labels, but prefer to have some consistency in its presentation across different products. Thus, you should refer to the histogram of “proportion of patients by category of seizure response” that can be found in recent labels such as the prescribing information for Briviact.**
- **Other secondary endpoints that you have included in the Target Product Profile, “percent reduction in total seizures” and [REDACTED] (b) (4), have not previously been discussed with the Agency prior to unblinding. We remind you that for secondary endpoints to be labeled we usually require that (1) they cover domains that are distinct from the primary endpoint, (2) there is a statistical correction for multiple comparisons, (3) the finding should be replicated, (4) a validated endpoint is used, and (5) there is a prior agreement to such labeling; this should occur before unblinding. The secondary endpoints, which you note, do not appear to fulfill these criteria.**

GW Response

The histogram of proportion of patients by category of seizure response for GWEP1332 varies slightly from the Briviact label. Is the draft display provided below acceptable to the Division?

Percentage of Patients Experiencing Worsening, No Change, or Improvements in Convulsive Seizure Frequency During the Treatment Period: Part B (ITT Analysis Set)

GW requests guidance from the Division on the process for agreeing on the secondary endpoints for GWEP1414 in advance of requesting the LGS Pre-NDA meeting.

Meeting Discussion:

The Agency re-emphasized that labeling is a review issue; however, it was noted that histograms typically use quartiles or quintiles and that the range of (b) (4) % to (b) (4) % in the proposed histogram is too broad to be interpretable. Although the Agency would like to have consistency in labeling, the sponsor may propose alternate ways to present the data.

GW sought clarification regarding prior agreement with the Agency on secondary endpoints for labeling. GW indicated that for study GWEP1423 in LGS, they included a correction for multiplicity for secondary endpoints in the final statistical analysis plan (SAP) prior to unblinding, but they had not submitted the SAP to the IND. They sought input on how they could come to agreement with the Agency on secondary endpoints for study GWEP1414 prior to unblinding.

The Agency emphasized that it is important that secondary endpoints represent different domains and do not simply replicate the primary endpoint. Typically, ordering of secondary endpoints is pre-specified in the SAP and submitted to the Agency for review prior to unblinding. GW should propose what they would like to include in the label with the NDA submission and provide support for the proposal. Final determinations regarding the inclusion of secondary endpoints will be made during the NDA review.

QUESTION 6: The Sponsor is aware that under Food and Drug Administration Amendments Act of 2007, an advisory committee meeting must be held for all new molecular entities unless adequate justification for not holding an advisory committee meeting is provided. Under Prescription Drug User Fee Act V, an advisory committee meeting is to be held during month 6 of an 8-month priority review clock. The applicable advisory committee is expected to be the Peripheral and Central Nervous System committee. **Does the Agency anticipate at this point that an advisory committee meeting is necessary and that PCNS would be the review committee?**

FDA Preliminary Response

This is determined after submission of an acceptable marketing application.

GW Response

No discussion needed.

QUESTION 7: The Sponsor requests the opportunity to submit for the Division's review, details of a plan for possible rolling submission at least 4 months before initiating the first NDA submission. **Does the FDA agree?**

FDA Preliminary Response

This is acceptable, but we remind you that the review timeline does not start until all necessary components of the NDA submission have been received and the application is considered complete.

GW Response

No discussion needed.

VI. [STATISTICS question submitted in the June 15, 2016 Briefing Document]

QUESTION 8: The integrated analysis plan for safety described below has been based on the FDA recommendations provided on 22 October 2015. Feedback from FDA has been incorporated into the presentations and pooling strategy described in the Company Position.

- (a) Does FDA agree with the plan outlined below for the ISS?**
- (b) Does FDA agree that an ISS report in Module 5 is not necessary and that the Clinical Summary of Safety can be used as the sole summary of the integrated safety data?**
- (c) Does FDA agree with a 9-month data cut of supportive data from the open-label extension study GWEP1415 and the expanded access program? Late breaking**

suspected unexpected serious adverse reactions (SUSARs) will be included until 2 months prior to the submission.

FDA Preliminary Response

- a. On face, the plan for the ISS appears to generally reflect the recommendations we provided in the October 22, 2015, Type C Meeting minutes and appears to be acceptable. However, narratives of SAEs and deaths from the ongoing Study 1424 in Dravet syndrome should also be included in the submission.**
- b. No, we do not agree. The analysis of safety will be complex as the safety data will be coming from a variety of sources; therefore, an ISS will be necessary.**
- c. Yes, your proposal for a 9-month data cut is acceptable.**

GW Response

No discussion needed.

VII. [120 DAY SAFETY UPDATE question submitted in the June 15, 2016 Briefing Document]

QUESTION 9: For the 120 day safety update, the Sponsor proposes to submit in NDA Module 5, Section 5.3.5.3 a safety update report in the same format as the Summary of Clinical Safety. The 120 day safety update will contain data from ongoing studies up to 9 months before its submission and late breaking SUSAR reports up to 2 months before its submission. The safety update report will summarize new safety data that may reasonably affect the statements of contraindications, warnings, precautions, and adverse reactions in the draft labeling and Medication Guide. New data included in the safety update will be pooled and presented in the same format for relevant pooled subsets of the ISS. The safety update will include additional discussion on the impact of the new data upon the labeling and Medication Guide.

(a) Does FDA agree with the plan outlined for the 120 day safety update?

(b) Does FDA agree with a 9-month data cut of supportive data from the ongoing open-label extension study GWEP1415 and the expanded access program (US expanded access and named patient supply)? Late breaking SUSARs will be included until 2 months prior to the submission.

FDA Preliminary Response

- a. Yes, your proposal for the 120 day safety update is acceptable.**
- b. Yes, your proposal for a 9-month data cut is acceptable.**

GW Response

No discussion needed.

VIII. [NEW BASIC CLASS question submitted in the June 15, 2016 Briefing Document]

QUESTION 10: As CBD is currently C-I, the sponsor proposes that the crystalline substance CBD should be (b) (4) rescheduled following the agency's approval of the sponsor's NDA for its CBD-OS product. The United States Adopted Name (USAN) for the sponsor's product has been adopted as "cannabidiol". The agency has recognized that the CBD active pharmaceutical ingredient (API) (b) (4). The sponsor intends to propose that the entity to be rescheduled (b) (4) should be the substance cannabidiol. **Does the Agency agree that the active pharmaceutical ingredient is the appropriate entity for rescheduling?**

(b) (4)

FDA Preliminary Response

The active pharmaceutical ingredient of your product, (b) (4) cannabidiol (CBD) as currently identified in your IND under eCTD section 3.2.S.1 (e.g., by CAS, IUPAC, and chemical structure) is considered appropriate for scheduling purposes under the Controlled Substance Act as the substance CBD.

(b) (4)

We remind you that FDA scheduling recommendations address scientific data characterizing the abuse potential of substances (e.g., receptor binding, possible mechanisms of action), but do not include recommendations to DEA as to how regulations, such as 21 CFR 1308, should be modified.

CSS is available for further discussion or clarification, as necessary.

GW Response

GW welcomes further discussion with CSS and the Division.

(b) (4)

Meeting Discussion:

The CSS scheduling recommendation of the drug will follow complete review of all abuse-related data in the NDA, when submitted, and if the drug is approved by the FDA. In addition to making a scheduling recommendation to the Commissioner of the FDA and the Assistant Secretary of Health (ASH/HHS), CSS will recommend language for Section 9 of the product labeling, and any other section of the labeling as necessary.

3.0 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).

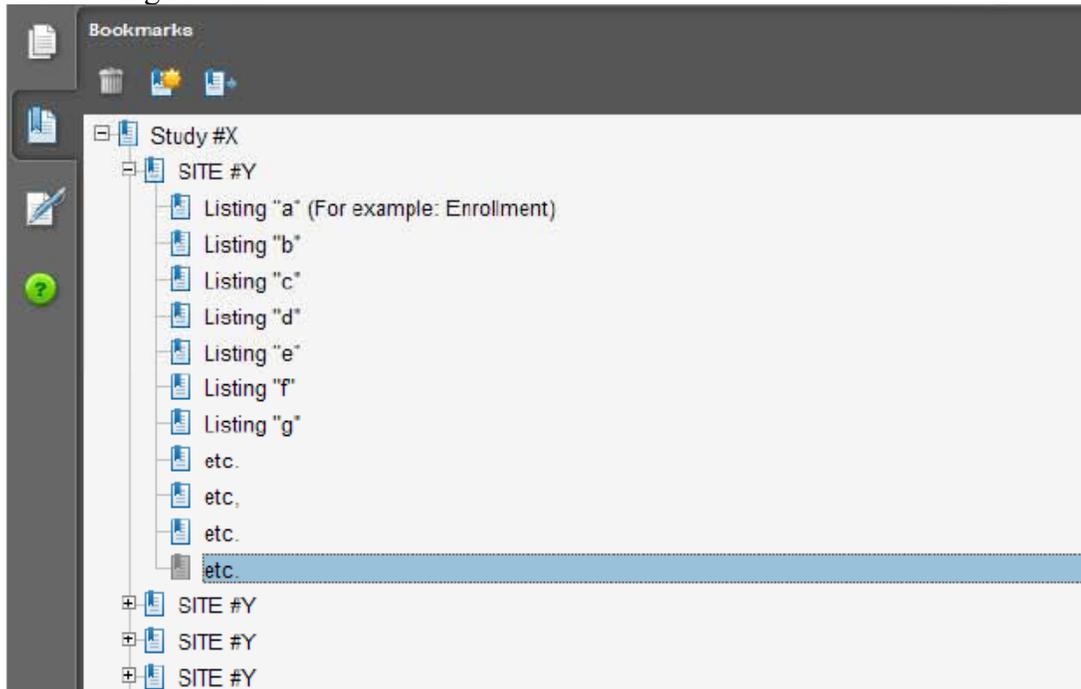
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator

- 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 Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [*PLR Requirements for Prescribing Information*](#) and [*PLLR Requirements for Prescribing Information*](#) websites including:

- 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 in the PI for human drug and biological products
- 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 42 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.

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

5.0 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. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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/s/

ERIC P BASTINGS
08/18/2016