CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211150Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 111842

MEETING MINUTES

Bioprojet Pharma
Attention: David Lucking, U.S. Agent
Voisin Consulting Life Sciences
222 Third Street, Suite 3121
Cambridge, MA 02142

Dear Mr. Lucking:

Please refer to your Pre-Investigational New Drug Application (PIND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Wakix (pitolisant).

We also refer to the meeting between representatives of your firm and the FDA on September 7, 2016. The purpose of the meeting was to discuss the data to be included in your NDA application.

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

If you have any questions, email Vandna Kishore, R.Ph., RPM, at Vandna.Kishore@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
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: B
Meeting Category: pre-NDA

Meeting Date and Time: September 7, 2016 at 10 AM EST
Meeting Location: White Oak, Building 22, Room 1415

Application Number: PIND 111842
Product Name: Pitolisant hydrochloride
Indication: (b) (4)
Sponsor/Applicant Name: Bioprojet Pharma

FDA ATTENDEES

DNP Director: Billy Dunn
Clinical: Nick Kozauer-Team Lead (TL), Veneeta Tandon-Medical Officer
OSE: RPM: Corwin Howard; DRISK-Laura Zendel
CMC: Martha Heimann-TL, Dahlia Woody, Dan Berger-drug product reviewer
Biopharmaceutics: Angelica Dorantes-Branch Chief, Okpo Eradiri-TL, and Banu Zolnik-reviewer
Nonclinical: Lois Freed-Supervisor, Melissa Banks-Muckenfuss-reviewer
Clinical Pharmacology: Sabarinath Sreedharan-TL, Xinning Yang-reviewer
Biometrics: Kun Jin-TL, Xiang Ling-reviewer
CSS: Mike Klein, Corrine Moody, Kit (Katherine) Bonson-reviewer
Safety: Alice Hughes, Sally Yasuda
Rare disease, OODP: John Milto-reviewer
(Eastern Research Group: Marc Goldstein)
RPM: Vandna Kishore

SPONSOR ATTENDEES

Dr Jeanne-Marie Lecomte, Pharm D, PhD, Executive Director
Prof Jean-Charles Schwartz, Pharm D, PhD, Scientific Director
Dr Isabelle Lecomte, MD, Clinical Director
Dr Catherine Scart-Grès, MD, Clinical Development
Dr Jean-Stéphane Julien, Pharm D, Pharmaceutical Affairs Director
Dr Philippe Robert, Pharm D, DMPK - Bioanalysis Head
Dr Pascale Vernade, Pharm D, EU Regulatory Affairs Manager
(b) (4) Consultant, (b) (4)

(b) (4)

(b) (4)

1.0 BACKGROUND

The purpose of the meeting is to discuss the technical aspects of the NDA to be submitted for Wakix (pitolisant).

(b) (4)

The pitolisant development plan includes Phase 1, Phase 2a, Phase 2b, and Phase 3 studies

2.0 DISCUSSION

2.1. Category/CMC

CMC Question 1: A Drug Master File (DMF) will be used for cross-reference for the active substance pitolisant HCl supplied by (b) (4) Bioprojet proposes to provide the following additional information in Module 3.2.S of the NDA:

- 3.2.S.3.2: Potential impurities of pitolisant hydrochloride
- 3.2.S.4.1: Specification for pitolisant applied by the finished product manufacturer for testing the active substance on receipt
- 3.2.S.4.2: Any non-compendial methods associated with the above specification
- 3.2.S.4.3: Analytical validation for the above methods, where appropriate
- 3.2.S.4.4: Batch data for 3 batches analyzed by finished product manufacturer in accordance with the above specification
- 3.2.S.6: Information on the reference standard used by the finished product manufacturer

Does the Agency agree that the above information is acceptable to support the active substance?

FDA Response to CMC Question 1: The proposed additional information to be submitted in Module 3.2.S of the NDA – to supplement that provided in the cross-referenced DMF – appears sufficient to support the drug substance. We remind you that General Properties of the API should also be described in the NDA (section 3.2.S.1.3). Note: Information on drug substance reference standards should be included in section 3.2.S.5 (not 3.2.S.6 as you outlined in Question 1). Additionally, we remind you that the pitolisant API specification applied by the finished product manufacturer should include any appropriate product-specific tests and acceptance criteria (e.g., particle size distribution) that may not be included in the drug substance specification of the (b) (4) DMF.

Meeting Discussion: None

CMC Question 2: The DMF for pitolisant HCl (b) (4) will include stability data to support a (b) (4) month retest period. Primary stability data up to 6 months will be available at the time of submission. Does the Agency agree that these data are sufficient and that Bioprojet does not need to provide additional stability data?

FDA Response to CMC Question 2: An appropriate retest period for pitolisant HCl will be assigned based on evaluation of the data available at the time of review. We agree that (b) (4) months of stability data for three production scale batches of pitolisant HCl manufactur from (b) (4) and 6 months of stability data for three additional production scale batches manufactured from (b) (4) are sufficient to file the NDA, provided all of these batches were manufactured using the same process at the same site (as you have stated). Batch data for these six batches should be provided in the NDA submission to demonstrate comparability of the two sets of batches. Per ICH Q1A(R2), a post-approval stability commitment to continue stability studies on the primary batches through the proposed retest period should be included in the NDA.

Meeting Discussion: None

CMC Question 3: The non-clinical and clinical studies were performed using active substance from different sources (b) (4) than that proposed in the NDA ((b) (4) In order to provide bridging information, comparative data between the active substances from the two suppliers and stability data for tablets manufactured with some of the different sources of active will be supplied. Does the Agency agree that these data will be adequate to demonstrate that the results of the non-clinical and clinical studies are valid for the proposed source of active ((b) (4)

FDA Response to CMC Question 3:
Drug substance data on impurity profiles, particle size distribution, solid state form, and density of API sourced from the two suppliers ((b) (4) along with appropriate drug product in vitro and stability data, should be adequate to demonstrate the comparability of the API batches.

The nonclinical and clinical data obtained using the various sources of pitolisant hydrochloride API appear valid to support the drug product manufactured using API from proposed commercial supplier (b) (4)

Confirm that all drug substance primary batches to be used in US clinical studies are manufactured by (b) (4) The adequacy of the data will be determined pending review.

Meeting Discussion: The Agency clarified that confirmation is needed that (b) (4) manufactures all drug substance batches used to manufacture drug product stability study batches.

CMC Question 4: The current dissolution method for release of film-coated tablets was set on the basis of the most discriminatory power of the method, i.e. [redacted] (b) (4) with a specification set at [redacted] (b) (4) (b) (4) . According to BCS study, pitolisant should be classified as highly permeable and highly soluble (i.e., BCS Class I). Does the Agency agree with the proposed dissolution method and specifications for routine quality control, i.e. [redacted] (b) (4) with a specification set at [redacted] (b) (4) dissolution in 30 min?

FDA Response to CMC Question 4: You have submitted dissolution data comparing the biconvex film coated to the cross-scored film tablets as well as over-encapsulated to the to-be-marketed tablets at two different rotation speeds. Provide all the comparative dissolution data with the proposed dissolution method. In the dissolution development report, include justification for the selection of the rotation speed for the proposed dissolution method. The final determination on the suitability of the dissolution method for the proposed drug product will be made, in part, on the outcome of the BCS Class 1 assessment. Please note that the acceptance criterion will be determined during NDA review.

Regarding the observed difference in pitolisant dissolution rate between over-encapsulated and non-encapsulated film-coated tablets, we are unable to make a full assessment because limited data and information are provided in the briefing package. However, note the following comments and address them in the NDA submission:

i. Please confirm if the formulations used in the pivotal trials are the same as the to-be-marketed formulation.
ii. The over-encapsulated film-coated tablets constitute the clinical trial product since they were used in the Phase III study. The uncoated film-coated tablets are the to-be-marketed (TBM) drug product. In order for the results of the Phase 3 studies to be attributable to the TBM drug product, it must be bridged to the over-encapsulated tablets. We acknowledge that you have made an attempt to establish the required bridge between the clinical trial and TBM drug products through comparative dissolution testing.
iii. Compare the dissolution profiles (sampling times: 10, 15, 20, 30, 45 min) of the clinical trial and TBM drug products by calculating the $f2$ values to demonstrate their similarity using the proposed dissolution method.
iv. Provide details of the over-encapsulation process in the NDA. For example, state if a filler or bulking agent and other excipients are used in the encapsulation process. Differences in dissolution profile between the clinical trial and TBM drug products should be explained to provide assurance that the observed differences do not result in bioavailability differences between the two products.

Meeting Discussion: None

CMC Question 5: A copy of the proposed finished product specification for the drug product is provided. Does the Agency agree that the specification is adequate to support release and stability testing of the finished product?

FDA Response to CMC Question 5: The specification appears to be adequate, pending further review. However, you should amend the specification to reflect tablet strengths of 4.45 mg pitisolant (from 4.5 mg) and 17.8 mg pitisolant (from 18 mg). The same tablet strengths should appear on all product labeling.

The proposal for skip lot testing may be allowed. However, it would be expected that the NDA submission will include historical data showing consistent and successful microbial limits results, a discussion of in-process microbial controls that could affect the microbial load of the drug product (i.e., processing times/holding times), a description of the microbiological monitoring and acceptance criteria for the identified control points, and a verification of the suitability of the testing methods.

Meeting Discussion: The Agency confirmed rounding up of the values is not acceptable.

Post Meeting Comments: We understand that you intend to engrave the 4.45 mg and 17.8 mg pilotisant tablet strengths (b) (4) respectively. Per 21 CFR 206.10(a), the code imprint on a solid oral dosage form, in conjunction with the product's size, shape, and color, permits the unique identification of the drug product and the manufacturer or distributor of the product. Your approach seems reasonable, although acceptability of the imprint code is a review issue.

CMC Question 6: Stability data will be provided in the NDA to support a shelf-life of 24 months with storage conditions of "(b) (4) " Does the Agency agree that these data are sufficient to support the proposed shelf-life?

FDA Response to CMC Question 6: The stability data supporting a shelf-life of 24 months may be adequate provided that you can show that the EP compliant excipients used are compliant with USP/NF standards. Alternatively, provide 12 month stability data for the tablets manufactured at the site for US supply ((b) (4)).
We recommend providing storage conditions: "Store at 20-25°C (68-77°F); limited excursions permitted to 15-30°C (59-86°F)." An additional statement may be added: "(b) (4) "

Meeting Discussion: None

CMC Question 7: A shipping study will be performed on the packaged finished product as per the validation protocol and the results will be included in Module 3.2.P.8. Does the Agency agree that this protocol will provide the data sufficient to support the planned NDA?

FDA Response to CMC Question 7: The protocol is adequate, pending review of the shipping study information provided in Module 3.2.P.8 which should include photostability evaluation data.

Meeting Discussion: None

CMC Question 8: The manufacturing facility used for the production of Wakix® tablets (b) (4) will be ready for inspection at the time of NDA submission. Based on a planned filing date for the NDA of January 2017, can the Agency advise of anticipated timing for the preapproval inspection of the (b) (4) facility?

FDA Response to CMC Question 8: At this time, FDA cannot comment on the anticipated timing for the preapproval inspection of the (b) (4) facility. Determination of whether a preapproval inspection is needed will be made after the NDA is received by the agency. All manufacturing, packaging, and control sites for both drug substance and drug product should be ready for inspection when the NDA is submitted to the agency.

Meeting Discussion: None

2.2. Category/Nonclinical

Nonclinical Question 1: Does the FDA agree that the nonclinical development is sufficient to register Pitolisant in the US for the targeted indication, (b) (4) "?

FDA Response to Nonclinical Question 1:
Based on the information provided in the briefing document, the nonclinical studies conducted on pitolisant appear sufficient to support an NDA; however, we have the following comments:

1. You should ensure that the pharmacological activity of all major human circulating metabolites has been adequately assessed in a comprehensive panel of in vitro binding assays.

2. You should ensure that all major human circulating metabolites have been adequately tested in the appropriate nonclinical studies, including assessment of carcinogenic potential in a single species (cf., Guidance for Industry, M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, Questions and Answers (R2), February 2013).

3. In the discussion of the repeat-dose toxicity studies in rat, safety margins were based on "the sum of BP2.649 and its metabolite BP1.2526…." Exposure margins should be calculated separately for parent and each metabolite.

4. The adequacy of the nonclinical studies will be a matter of review.

Meeting Discussion: The sponsor stated that a 6-month transgenic mouse study of the unique human metabolite (identified as a glycine conjugate) is planned and asked if submission of the study during the NDA review cycle would be acceptable. The Division stated that a final study report is typically required at the time of submission if the data are required to support approval of the NDA; however, the need for a carcinogenicity assessment is not clear based on the information provided in the briefing package. The Division encouraged the sponsor to provide additional information on the metabolite so that the need for the planned carcinogenicity study can be determined. The Division stated that feedback will be provided within 30 days of submission, workload permitting.

2.3. Category/Clinical

Clinical Question 1: Does the FDA agree with the proposed format and content of the Integrated Summary of Effectiveness (ISE) for Pitolisant, designed according to the guidance for industry "Integrated Summaries of Effectiveness" dated October 2015? Is it adequate to support the submission and filing of the NDA by the FDA?

FDA Response to Clinical Question 1: The proposed format and content of the Integrated Summary of Effectiveness (ISE) appears adequate to support a NDA submission.

Meeting Discussion: None

Clinical Question 2: Does the FDA agree with the proposed format and content of the Integrated Summary of Safety (ISS) for pitolisant? Is it adequate to support the submission of and filing of the NDA by the FDA?

FDA Response to Clinical Question 2: The proposed format and content of the Integrated Summary of Safety (ISS) appears adequate to support a NDA submission.

We remind you that adverse reactions, particularly those that would appear as a Warning as well as common adverse reactions, should be characterized overall and by demographic factors including age, sex, race, and renal function.

Please refer the attached document on General Clinical Safety Requests that will enable you to provide adequate information in terms of datasets and analyses for the ISS.

Meeting Discussion: The sponsor proposed to include a statement in the label to reflect the fact that the overwhelming majority of trial data was generated in Caucasians. The Division explained that a discussion about the specific language to be used in this scenario was premature at this time and advised the sponsor to include the available data with respect to race in the NDA application.

Clinical Question 3: Bioprojet Pharma plans to seek an indication for pitolisant in the treatment of (b) (4). Bioprojet Pharma plans to rely on two pivotal studies, HARMONY 1 (P07‑03), HARMONY CTP (P11-05) and on supportive studies HARMONY Ibis (P09‑15), HARMONY III (P09-10) and HARMONY IV (P10-01) for the demonstration of efficacy and safety.

Bioprojet Pharma believes that the design of and results from these trials are appropriate to support the safe and efficacious use of pitolisant as proposed in the NDA. Does the FDA agree that appropriate and adequately-designed trials were conducted in support of this NDA?

FDA Response to Clinical Question 3: As addressed in the May 2015 meeting minutes, the adequacy of the design and the results from the trials to support safe and efficacious use of pitolisant are review issues. On face, these trials appear appropriate to support the filing of a NDA application.

Meeting Discussion: None

Clinical Question 4: The FDA has previously noted that the pivotal trials had a relatively short duration of treatment in the context of the expected chronic drug treatment necessary for narcolepsy. The FDA has stated that this would be a review issue, not a filing issue. Bioproject believes that HARMONY III, an open-label trial with long-term follow-up (up to 5 years), provides strong evidence of safety and efficacy sufficient to supplement the pivotal trials of 7-to-8-week duration. Does the FDA agree that the open-label study can provide additional support for the proposed chronic indication in narcolepsy?

FDA Response to Clinical Question 4: An open-label study (HARMONY III) is unlikely to provide robust supportive evidence of efficacy because of design issues including lack of a well-matched comparator group. The adequacy of duration of the pivotal trials in the context of the expected chronic drug treatment necessary for narcolepsy remains an NDA review issue. Note that adding a randomized withdrawal component to an ongoing study such as HARMONY III may be capable of providing additional evidence of long-term efficacy.

Supportive information on safety can be obtained from the HARMONY III study as well as studies in other indications.

Meeting Discussion: None

Clinical Question 5: Regarding the extent of population exposure to assess clinical safety, as the targeted indication is a rare disease it is difficult to meet the numbers recommended by the ICH E1guidance (endorsed by the FDA March 1995) which suggests that 1500 patients exposed to the drug are needed for chronically administered drugs (300 - 600 exposed 6 months, and 100 for 1 year). However to date the number of subjects who received pitolisant is close to this requirement if one includes all the clinical trials conducted with pitolisant in different

indications, particularly the studies assessing the excessive daytime sleepiness in Parkinson's disease (HARPS studies) and in Obstructive Sleep Apnea (HAROSA studies) where patients received the drug during one year or 9 months if they were allocated to placebo in the double-blind period. The compassionate use was authorized in France by the French Medical Agency and additional patients with narcolepsy received pitolisant on a long-term basis. Bioproject believes that the data in the non-narcolepsy studies can be used to bolster the narcolepsy safety database to meet the ICH E1 guidelines. Does the FDA agree?

FDA Response to Clinical Question 5: The extent of exposure including the patients in non-narcolepsy indications appears adequate to support filing of a NDA application.

Meeting Discussion: None

Clinical Question 6: Bioprojet Pharma has performed Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for pitolisant during the pre-clinical and clinical development. Does the FDA agree with the completed plan? Bioprojet Pharma has proposed wording in the prescribing information (PI) characterizing QTc prolongation observed with pitolisant. Does the FDA agree with this approach?

FDA Response to Clinical Question 6: On face the completed plan for evaluation of the QT/QTc interval and proarrhythmic potential seems reasonable, although the adequacy will be a matter of review. Discussion of labeling at this time is premature.

Please include the following in your NDA submission:

- Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses.
- Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable).
- Data set whose QT/QTc values are the average of the above replicates at each nominal time point.
- Narrative summaries and case report forms for any:
    i. Deaths
    ii. Serious adverse events
    iii. Episodes of ventricular tachycardia or fibrillation
    iv. Episodes of syncope
    v. Episodes of seizure
    vi. Adverse events resulting in the subject discontinuing from the study
- ECG waveforms to the ECG warehouse (www.ecgwarehouse.com). If you use Holter recording and select 10-second segments to measure, submit either the entire Holter recording or at least the entire analysis windows.
- A completed Highlights of Clinical Pharmacology Table.

Advancing in this field – and possibly reducing the burden of conducting QT studies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at www.cardiacsafety.org/library.

Meeting Discussion: None

Clinical Question 7: Bioprojet Pharma does not plan to submit a REMS program with the NDA. A Risk Management Plan (RMP) has been approved by the EMA. Would this document be considered as relevant by the FDA?

FDA Response to Clinical Question 7:. At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application. We encourage the submission of the EU RMP to Section 1.16.1.

Meeting Discussion: None

Clinical Question 8: As pitolisant is a new molecular entity affecting the central nervous system, Bioprojet Pharma has provided in APPENDIX 10 the data required to allow the Controlled Substances Staff (CSS) to determine whether any additional abuse-related study will be needed. This data is from the completed *in vitro* and *in vivo* preclinical abuse potential studies, as well as the data from clinical studies including abuse-related AEs, over-consumption evaluation during all trials, and detection of withdrawal syndrome after abrupt termination of the treatment.
Since no abuse signal was detected by these various preclinical and clinical approaches, does the Agency confirm that this data in this dossier are adequate to assess the absence of risk for pitolisant to be considered as a drug that needs to be scheduled under the Controlled Substances Act (CSA)?

FDA Response to Clinical Question 8:
Ultimately, the need for a drug to be scheduled under the CSA is a review issue that is determined after the abuse-related data in your NDA are submitted, filed, and reviewed. As detailed below, the abuse-related studies included in the meeting packet are missing important information or were not designed based on CSS advice. We refer you to the draft *Guidance for Industry: Assessment of Abuse Potential of Drugs* (2010).

Notably, none of the protocols for your abuse-related studies were submitted to CSS prior to their initiation so that we could provide feedback on their design. In 2011 and in 2015, CSS requested the study reports for completed abuse-related studies in order to evaluate the adequacy of the studies and determine if additional studies would be needed, but you did not submit any information in response to these requests.

CSS has the following comments regarding the studies in the meeting package:

Mechanism of Action

- Pitolisant has activity at sigma-1 receptors (Ki < 10 nM), sigma-2 receptors (Ki = 52 nM), dopamine D3 receptors (Ki = 382 nM) and serotonin 5HT2A receptors (Ki = 544 nM), but an evaluation of functionality was not provided for these sites. Given that these sites are associated with drugs of abuse, it will be necessary to determine if pitolisant is acting as an agonist or antagonist at these sites.

Drug Discrimination Study

- The training dose of 10 mg/kg for cocaine was not justified. Typically, drug discrimination studies that use cocaine as the training drug use a dose of 5.6 mg/kg or less. Use of a very high dose of the training drug can skew responses from the test drug and prevent generalization.
- You should provide a justification for the doses of pitolisant that were chosen. Doses in animals should produce plasma levels that are equal to, as well as several multiples (frequently 2-3 times) greater than, the plasma levels produced by the highest proposed therapeutic dose in humans.
- Test sessions should occur at Tmax for each drug evaluated. It is unclear whether a 20 minute pretreatment period produces Tmax in animals that receive pitolisant.
- Use of an FR20 schedule of reinforcement is too high when evaluating a new molecular entity. CSS recommends the use of FR10.
- During the test session, responding on any lever should not be rewarded.
- Given that pitolisant has affinity for the 5HT2A receptor, if the drug acts as an agonist or partial agonist at this site, another drug discrimination study should be conducted using a 5HT2A agonist that is scheduled under the Controlled Substances Act as the training drug, in comparison to vehicle.

Self-Administration Study

- You should provide a statistical justification for the use of only 4 monkeys in the self-administration study, based on the anticipated effect size and the desired power of the statistical test used.
- The doses of pitolisant were not justified in relation to plasma levels produced by the highest proposed therapeutic dose in humans.
- Use of an FR50 schedule of reinforcement is too high when evaluating a new molecular entity. CSS recommends the use of FR10.
- All data from the study should be provided, including the data from the first of four test session days (which the protocol states were excluded from analysis).
- Throughout the testing period, pitolisant intermittently produced self-administration that was similar to that produced by cocaine. This is especially striking given that the schedule of reinforcement was FR50 or greater. In one of four animals (25%), the cumulative self-administration of pitolisant surpassed that of cocaine. These data demonstrate that under some conditions, pitolisant produces rewarding responses indicative of abuse potential.

- CSS does not recommend the use of progressive ratio as the schedule of reinforcement in studies conducted for regulatory purposes.

Conditioned Place Preference Study

- The doses of nicotine and cocaine were not justified.
- Pitolisant was tested at only one dose. A range of doses should be tested.
- The dose range should include a dose that produces plasma levels that are equivalent to and several multiples (usually 2-3 times) greater than the plasma doses produced by the highest proposed therapeutic dose in humans.

Animal Physical Dependence Study

- The range of doses of pitolisant tested should produce plasma levels that are equivalent to and several multiples (usually 2-3 times) greater than the plasma doses produced by the highest proposed therapeutic dose in humans.
- Doses of all drugs should remain stable across the administration period.
- Animals in all test groups should be evaluated in all measures prior to drug discontinuation as well as for at least one week after discontinuation (or for at least 5 half-lives, whichever is longer).
- Since pitolisant is a new molecular entity with a novel mechanism of action, the observation period should be at least 10 minutes to ensure that emergent behaviors will be observable.

Human Physical Dependence Study

- CSS informed you previously on more than one occasion (in 2011 and in 2015) that you need to study and evaluate physical dependence in humans. This was not part of the abuse assessment section of the meeting package.

Abuse-Related Adverse Events in Clinical Studies

- You state that there were no abuse-related adverse events observed during clinical studies. However, you did not provide data to support this statement. As we informed you in 2011 and 2015, the incidence of abuse-related AEs in comparison to placebo should be reported by study, population, and dose, and displayed in tabular format. Tables should be created for abuse-related higher level terms even if there were few patients or subjects who experienced a particular AE. The list of AEs is found in the *Guidance for Industry Assessment of Abuse Potential of Drugs (2010).*

After evaluating studies with the designs described above, a determination regarding the need for a human abuse potential study can be made.

Meeting Discussion: The sponsor presented summaries of abuse-related nonclinical studies conducted to date. The sponsor then stated that it intended to conduct a human abuse potential (HAP) study and would submit the protocol to CSS soon. CSS said they would provide feedback on the study design, but cautioned the sponsor that certain elements of the study might be difficult to determine, given the limitations of the nonclinical data. CSS encouraged the sponsor to justify all proposed elements in the HAP study protocol. CSS also requested that the sponsor submit the protocols for the human physical dependence

evaluations conducted at the end of the clinical efficacy studies so it could be determined if they were designed appropriately. Finally, CSS requested that the sponsor provide a tabulation of the abuse-related adverse events reported in post-marketing data following the recent EMA approval of pitolisant. CSS also said they would discuss the non-conjugated major metabolite of pitolisant with the Pharmacology/Toxicology team to determine if it would need an abuse assessment.

Clinical Question 9: Bioprojet Pharma has been granted orphan drug designation for pitolisant by the European Commission (07/10/2007, confirmed on 04/19/2016) and by the FDA (05/17/2010) (Orphan designation #10-3072). Bioprojet Pharma believes that pitolisant for this indication, (b) (4), still qualifies for an orphan drug designation and consequently will receive /benefit of 7 years exclusivity following the date of the drug's marketing approval by the FDA. Does the FDA agree?

FDA Response to Clinical Question 9: The criteria for orphan drug exclusivity upon marketing approval are as follows:

1. The approved indication must fall within the scope of the sponsor's orphan drug designation.
2. The "same dug" must not already have marketing approval for the same indication.

Eligibility for orphan drug exclusivity is made at the time of marketing approval. If you receive marketing approval for use of pitolisant for the treatment of (b) (4) (which does fall within the scope of your current orphan drug designation) and no other "same drug" has marketing approval for this same indication at the time of your marketing approval, then you would be eligible for orphan drug exclusivity.

Meeting Discussion: None

Clinical Question 10: Does the FDA agree that the format and content of the NDA as described in this pre-NDA briefing package is acceptable?

FDA Response to Clinical Question 10: From a technical standpoint (not content related), the proposed Table of Content for the NDA, appears acceptable. However, please see additional comments below:

- Provide proper bookmarks that are clear and indicative of the content. "Appendix 1" is not a proper bookmark.

- Do not create additional nodes in the eCTD structure (e.g., m2), beyond what is in the specifications. Please make sure your approach fits the DTD and the "Granularity Annex", located at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073261.pdf

- Providing Table of Contents in 4.1 is not necessary in the eCTD structure. Instead, it will be helpful to reviewers if sponsors can provide a linked reviewer's aid/reviewer's guide to briefly describe where information can be found throughout the application and place the document in m1.2.

- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 (tabular format), should be linked to the referenced studies in m5.

- Please submit the bioanalytical report and the data files for PK concentrations and PK parameters for each PK study.

- Please refer to the Division's previous response to your Type C meeting submission for our recommendation on the format and content of the population PK analysis and data files.

Meeting Discussion: None

Clinical Question 11: Is the format and content of the proposed prescribing information for Pitolisant adequate?

FDA Response to Clinical Question 11:
In general, the format of your proposed prescribing information follows the requirements of the Physician's Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR); however, please see section 3 of this document for further information regarding the correct format for the Prescribing Information.

The adequacy of the content of the Prescribing Information will be a matter of review. Prior to submission of your NDA, please review the following Guidances, which can be found on the *PLR Requirements for Prescribing Information* website, and make appropriate revisions to your Prescribing Information:

- Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling
- Adverse Reactions Section of Labeling
- Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format.
- Clinical Pharmacology Section of Labeling

- Please add the description about the food effect on PK of pitolisant, and the results from drug-drug interaction (DDI) studies between pitolisant andolanzapine, grapefruit juice, and itraconazole. If the ongoing DDI studies of pitolisant with midazolam, buproprion, probenecid, sodium oxybate, and modafinil are completed by the time of NDA submission, please also add the results from these studies into labeling.

Meeting Discussion: None

Additional Clinical Pharmacology Comments:

- Please clarify whether PK samples were collected from the Phase 3 trials. If so, we recommend that you explore the dose-exposure-response relationships for efficacy/safety of pitolisant.
- You state that the exposure to pitolisant increased by a factor of 2.5 in renally-impaired patients with creatinine clearance (CLcr) ranging from 15 to 89 mL/min. We recommend that you categorize these patients into different classes of renal impairment (i.e., mild, moderate, and severe) based on CLcr, and report the changes in pitolisant exposures relative to subjects with normal renal function for each group.
- We suggest that you use a "Clinical Pharmacology Summary Aid" to summarize the information related to clinical pharmacology for the NDA submission. The "Clinical Pharmacology Summary Aid" template is provided to you at the end of this document.

3.0 ADDITIONAL MEETING LANGUAGE

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 22, 2016 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric 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* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

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 draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

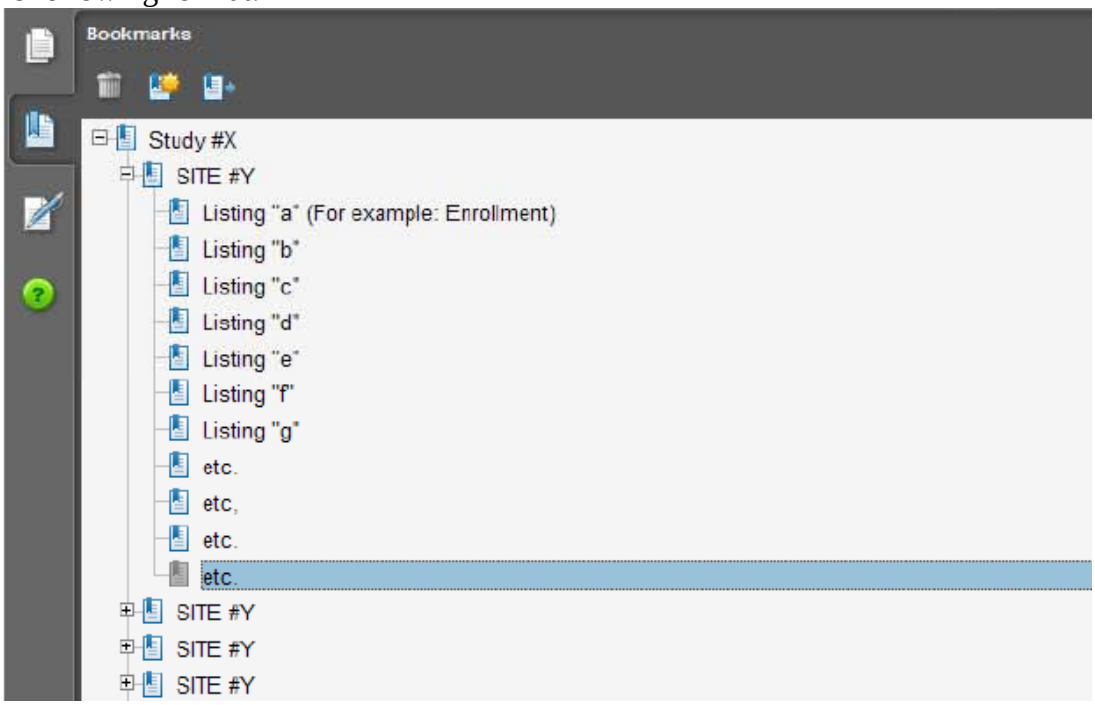
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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

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

[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

Pre-NDA General Clinical Safety Requests

Available Guidance's/resources--
For Electronic Regulatory Submission:

1. Follow the guidance documents and specifications regarding Electronic Common Technical Document (eCTD) submissions located at the following FDA webpage: eCTD
2. Refer to the following FDA webpage regarding the electronic submission of regulatory information to CDER: Electronic Regulatory Submission
3. The agency provides a process for submitting an eCTD sample for eCTD validation tests. Further instructions are listed at this FDA webpage: Sample eCTD Submission
4. Send any questions and general information regarding the preparation of submissions in electronic format to esub@fda.hhs.gov

For Datasets:

5. Refer to the following FDA webpage on Study Data Standards Resources
6. Follow the following Guidance Documents:
   a. Providing Regulatory Submissions in Electronic Format-Standardized Study Data
   b. Study Data Technical Conformance Guide – Technical Specifications Document
7. The agency provides a process for submitting sample standardized datasets for validation tests. Further instructions are listed here: Standardized Data Sample Submission
8. Open CDISC is one possible tool to check for conformance to the CDISC standard.
9. Send any questions regarding the submission or structure of datasets to eData@fda.hhs.gov

For General submission of safety data:

10. 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, accessible at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm 071665.pdf.
11. Provide an assessment of safety as per the FDA Guidance to Industry: Premarketing Risk Assessment, accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/u cm072002.pdf.
12. 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

Requests for General Submission Content:

1. For the integrated safety analyses, the main subject analysis pools must be: 1) All Safety Population subjects in placebo-controlled studies for the indication; and 2) All Safety Population subjects in repeat dose open label studies for the indication. 3) All Safety Population subjects in placebo controlled and open label studies for the indication. All major analyses should be performed using these subject pools. If safety data from other

indications are to be included in the analysis, the other indications safety pool should be separate for the placebo and open label studies.

2. 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.
3. 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.
4. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
5. Submit an annotated version of the pre-NDA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.
6. 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.
7. Include active hyperlinks from the lists of references to the referenced article.
8. For each study, we request the total number of subjects screened, total number of subjects who failed screening, and a list of inclusion and exclusion criteria that lead to screening failures (with the number of subjects that met each criterion).

	Number of Subjects
Total screened	
Total Number of Subjects who Failed Screening	
Exclusion criterion 1	
Exclusion criterion 2	
Inclusion criterion 1	
Inclusion criterion 2	

Request for Datasets:

1. Provide a data definition file to describe the format and content of the submitted datasets.
2. As outlined in Section 2.2 of Study Data Technical Conformance Guide – Technical Specifications Document:
    a. Include a Study Data Reviewer's Guide in the eCTD Module 5 that describes the use of study data standards and their conformance validation (this is in addition to the Reviewer's Guide in eCTD Module 1 that provides a high level overview of modules 1 through 5 with hyperlinks).
    b. As outlined in Section 4.1, use SDTM data format specifications for clinical tabulations datasets and ADaM for analysis datasets. Analysis datasets should be traceable to the tabulations datasets.

i. As outlined in Section 4.1.1.2, each individual subject should be assigned a single unique identifier across the entire application (e.g., including open label extensions of the trials).
ii. As outlined in Section 4.1.4.5, the data definition file, define.xml, should be included to describe the format and content of the submitted SDTM and ADaM datasets.

c. As outlined in Section 6.3.1, the preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
d. As outlined in Section 8.3.2, specify whether Legacy data has been converted to SDTM formatting. If this is the case, the rationale, methods, and approach to this conversion process will need to be discussed with our data standards team (eData@fda.hhs.gov). Submit both the original (legacy) and the converted (SDTM) data for these trials. If Legacy data has not been converted to SDTM formatting, provide the rationale.

3. Provide instructions on how to replicate the main adverse event, vital sign, and laboratory analyses (for the placebo-controlled population and repeat dose population) using the provided datasets.
4. Submit all SAS codes used to create your analyses for the ISE and ISS. If a SAS code contains a macro, please also include the macro code.
5. 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.
6. Provide an integrated subject-level dataset of all randomized subjects that has one line per subject, similar to Analysis Data Model (ADaM) dataset ADSL. This dataset should include (but not be limited to):
    a. A single unique identifier for each individual subject should be assigned across the entire application (e.g., including open label extensions of the trials)
    b. Variables indicating each study in which each subject participated
    c. Variables indicating whether the subject is part of the Safety population and whether the subject is part of the Intent to Treat (ITT) population
    d. Demographic variables (e.g., age, sex, race, other relevant factors)
    e. Disease factors (e.g., disease onset, disease severity). Include a variable indicating whether the subject was ambulant at baseline.
    f. Assigned treatment (drug and dose)
    g. Actual treatment received (drug and dose)
    h. Other possible prognostic factors that might affect response
7. The integrated adverse event dataset should include (but not be limited to) variables to indicate:
    a. Whether each adverse event occurred in a placebo-controlled study.
    b. The subject's universal study ID
    c. The study in which the adverse event occurred
    d. Whether the adverse event met the regulatory definition of a Serious Adverse Event
    e. Study treatment received (i.e., drug or placebo) and dose
    f. Study treatment start date and time
    g. Adverse event start date and time

h. Adverse event end date and time
i. The number of days from the date of the first study dose to the adverse event start date
j. Cumulative dose at the adverse event start time (all studies)
k. Date and time of the subject's first dose
l. The number of days from the date of the subject's first dose to the adverse event start date
m. Date of last dose relative to the adverse event start date
n. The number of days from the date of last dose of to the adverse event start date
o. The verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy

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 as well as the alternative MedDRA coding paths.
3. Provide a summary Table listing the different verbatim terms from which the TEAE of interest was coded to.
4. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
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.
8. Provide summary table(s) of analyses of the TEAE by gender, age category, race, dose, concomitant therapy, duration of TEAE, and time to first occurrence of TEAE. Perform an analysis of median duration exposure by treatment groups. Provide this for each safety pool.
9. If the given TEAE is associated with a laboratory, electrocardiogram or vital sign abnormality, then provide a summary table of the relevant parameter listing the abnormal values over time (provide reference values for each parameter).
10. Provide graphical display by treatment group of common TEAEs whose incidence either increases or decreases over time.

Request for Analyses of Laboratory Measurements:

1. Provide a table summarizing the frequency of each laboratory test routinely measured during each study in the clinical development program.
2. Provide the normal reference ranges for every laboratory value, as well as the thresholds for analysis of outliers.

3. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests: SI Units
4. Using integrated data from placebo-controlled studies, we request analyses of routinely measured laboratory parameters at baseline, as well as post-treatment change from baseline (median, interquartile range, and range), for each treatment group by visit. Provide the number of subjects included in each analysis.
5. Using integrated data from placebo-controlled studies, provide shift analyses for all routinely measured laboratory parameters. 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. For laboratory parameters with no available CTCAE toxicity grades, provide shift analyses with clearly defined criteria for mild, moderate, and severe post-baseline changes.
6. Ensure that analyses shift analyses of blood sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, and platelets in placebo-controlled studies are provided. If any of these laboratory tests were not measured, please specifically state that they were not measured.
7. 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
8. For each treatment group, please provide outlier analyses of the number of subjects with post-treatment vital sign changes compared to baseline listed below:
    - Systolic blood pressure (SBP) increment > 20 mm Hg
    - SBP increment > 40 mm Hg
    - SBP decrement > 20 mm Hg
    - SBP decrement > 40 mm Hg
    - Diastolic (DBP) increment > 10 mm Hg
    - DBP increment > 20 mm Hg
    - DBP decrement > 10 mm Hg
    - DBP decrement > 20 mm Hg
    - Heart rate increment > 15 bpm
    - Heart rate increment > 30 bpm
    - Heart rate decrement > 15 bpm
    - Heart rate decrement > 30 bpm
    - Treatment-emergent body temperature > 38.0 °C
9. Please provide outlier analyses of laboratory measures.
10. Summarize the protocols for collecting ECG data. Summarize the frequency of post treatment QTc >450 ms, >480 ms, and >500 ms.

Request for Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, all study discontinuations, subjects who had SAEs, AEs leading to withdrawal. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request.
2. Provide a word file (and excel spreadsheet) that indicate the subjects for whom a narrative was submitted. This file should list the subject name, reason for the narrative (e.g., death, discontinuation, SAE) along with a hyperlink to the narrative.
3. Provide both narratives and CRFs for all discontinuations (including Lost to follow-up, Other, Physician/investigator decision, Patient decision, Withdrew consent). Provide a tabular listing of all subjects with discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for discontinuation; for reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation.
4. Provide reports for any autopsies conducted during any of the studies.
5. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law lab criteria.
6. 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.
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):
    - Patient age/gender
    - Study number
    - The subject's universal study ID
    - Reason for the narrative (e.g., death, discontinuation, SAE,)
    - Study treatment received (i.e.,drug or placebo) and dose
    - Study treatment start date and time
    - Adverse event start date and time
    - Adverse event end date and time
    - Cumulative dose at the adverse event start time (all studies)
    - Date and time of the subject's first dose
    - The number of days from the date of the subject's first dose to the adverse event start date
    - Date of last dose relative to the adverse event start date
    - The number of days from the date of last dose to the adverse event start date
    - Signs and symptoms related to the adverse event being discussed
    - An assessment of the relationship of exposure duration to the development event
    - Pertinent medical history
    - Concomitant medications with start dates relative to the adverse event
    - Pertinent physical exam findings
    - Any abnormal vital sign measurements
    - Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
    - Discussion of the diagnosis as supported by available clinical data

- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

Other requests:

1. 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:
   - Age
   - Sex
   - Dates of screening, randomization and starting therapy
   - Whether the patient completed or did not complete the study, with dates and reason for withdrawal
   - 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)
   - Prior medications and concomitant medications with dates of start and end
   - Vital signs and laboratories, sorted by date, with reference ranges *
   - Full reports for radiologic studies, ECG, MRI, pathology results, and special studies with dates and reference ranges *
   - Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)

   * 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.

CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

In addition to summarizing the relevant findings the goal of the Clinical Pharmacology Summary is to focus sponsor and reviewer on the critical review issues of a submission. To better communicate the expectations of the Agency and to guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions a Clinical Pharmacology Summary Aid was created. The document consists of a generic questionnaire and instructions clarifying what the answers to the questions should address. The questions cover the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired backbone of the Clinical Pharmacology Summary in NDA and BLA submissions. The questions and instructions included in this aid are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

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 dose, 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 2.2.1 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?

3

4 **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?

5

6 2.3 General Clinical Pharmacology

7

8 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.

9 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.

10 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.

11 2.4 Exposure-Response

12 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 pivotal and other appropriate trials. Provide evidence that the exposure-response analysis supports 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 commonly known covariates are not identiiable, 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 effectiveness variables if 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.

13 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.

14 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.

15 2.4.4Is 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 pivotal trials. 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.

16 2.5 What are the PK characteristics of the drug?

17 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.

18 **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.

19 **2.5.4 What are the characteristics of drug absorption?**

Indicate absolute bioavailability of drug of parent drug 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.

20 **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.

21 **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 radioactivities are too small to be assignable to specific metabolites provide an estimate for their contribution to circulating total radioactivity.

22 **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 (mL/min) 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.

23 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) 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.

24 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.

25 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.

26 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: 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 (dose or interval) 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

27 2.6.2.4 Elderly

28 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

29 2.6.2.7 Renal Impairment

30 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, CL/F, CLr, V/F 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.

31 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 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, CL/F 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.

32 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.

33 2.7 Extrinsic Factors

34 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

35 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.

36 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.

37 2.7.5 Are there other metabolic/transporter pathways that may be important?

38 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.

39 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 the 90% confidence intervals about the geometric mean ratio for AUC and Cmax for the drug of interest in the presence and absence of each of the co-administered drugs. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

40 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. Report 90% confidence intervals about the geometric mean ratio for AUC and Cmax of each of the co-administered drugs in the presence and absence of the drug of interest.

41 2.7.8 Does the label specify co-administration of another drug?

42 2.7.9 What other co-medications are likely to be administered to the target population?

43 2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

44

45 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

46 2.8.1Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

47 2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

48 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%?

49 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?

50 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 clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

51 2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?

52 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.

52.8.12 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?

53 2.9 Analytical Section

54

55 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?

56 List all assays used and briefly describe the individual methods.

57 2.9.2 Which metabolites have been selected for analysis and why?

58 2.9.3 For all moieties measured, is free, bound, or total measured?

59 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.

60 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.

2.8.5 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.

61 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.

62 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 $\leq -20^{\circ}$ C.

63 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.

Applicable to therapeutic proteins only

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

Briefly describe the methods and summarize the assay performance.

2.9.5.6 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.

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Sponsor will submit detailed protocols for the abuse potential inquiries.	Sponsor	
Sponsor will submit the actual structures of the metabolites for further FDA feedback, as to whether further carcinogenicity assessment is needed.	Sponsor	Timely, prior to NDA submission. If a carcinogenicity study is required, that data would need to be submitted in full at time of NDA submission.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's slides at the meeting.

14 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

ERIC P BASTINGS
10/05/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 111842

ADVICE/INFORMATION REQUEST

Bioprojet Pharma
Attention: Robert Schiff, Ph.D.
U.S. Agent
1129 Bloomfield Avenue
West Caldwell, NJ 07006

Dear Dr. Schiff:

Please refer to your Pre-Investigational New Drug (PIND) file concerning pitolisant.

We further refer to you request for an End-of-Phase 2 meeting request to discuss the development of pitolisant (b) (4).

We note that efficacy studies of pitolisant in narcolepsy are either completed or ongoing. While the Division encourages discussion about study design before studies are initiated, e.g. through an End-of-Phase 2 meeting or Special Protocol Assessment, once studies are underway or completed, most questions about study design become issues that can be addressed meaningfully only through NDA review. If your phase 3 studies are 'adequate and well-controlled' (described in 21 CFR 314.126), as suggested in your meeting package, then we recommend when the ongoing study is completed, that if you believe findings would support approval, you request a meeting with the Division.

In the context of the above, we have the following responses to the specific questions contained in your briefing package:

1. Does the Agency agree that the primary endpoint, Epworth Sleepiness Scale (ESS) score, is suitable to measure/assess the efficacy of BF2.649 in the treatment of EDS in narcolepsy (b) (4)?

   FDA Response:
   This has become a review issue since phase 3 studies are completed or ongoing. Efficacy for excessive sleepiness should be supported by positive findings in two adequate and well-controlled studies, on both an objective measure of sleepiness and a subjective measure of improvement that supports the clinical meaningfulness of the objective finding.

2. Does the Agency agree with the choice of Modafinil as the comparator arm in the proposed pivotal Phase III studies?

FDA Response:
An active comparator arm is generally not required to support FDA approval.

3. Does the Agency agree with the dose regimen comprising initially an individual titration (5, 10, 20 mg/d) with 20 mg o.d. being the top therapeutic dose?

FDA Response:
Studies in which dose is individually adjusted based on patient response are not useful to establish dose/response. You should consider conducting a fixed-dose study to characterize dose/response (note that an initial titration period can be used in such a fixed-dose study).

4. (b) (4)

5. Does the Agency agree that the data in our briefing package justifies the non-necessity of a specific drug abuse liability study?

FDA Response:

- **Pitolisant is a new molecular entity (NME). Pitolisant has a novel mechanism of action, affects the CNS, and may produce stimulant-like effects.**

- **Without reviewing detailed protocols and primary data from the completed *in vitro* and preclinical abuse potential studies, controlled-substance staff cannot comment at this time on whether additional studies are needed. Without information on study designs (e.g., dose selection, species selection, pretreatment times and justification of comparator drugs) a thorough assessment cannot be performed.**

- **In preclinical studies, a comparison to modafinil (schedule IV) should be performed.**

- **A negative signal for abuse in preclinical animal studies does not mean that the drug being studied has no abuse potential. An NME with a unique mechanism of action may have a unique abuse potential profile dissimilar to other drugs of abuse. Thus, a negative signal in preclinical studies might not eliminate the need for more specific abuse potential studies.**

- **To further characterize the abuse potential of pitolisant we recommend that you collect and evaluate abuse-related adverse events (AEs) from all clinical studies. The incidence of AEs in comparison to placebo should be reported by study, dose, and displayed in tabular format. For a list of AEs of interest as well as for general guidance on the abuse potential assessment of drugs, we refer you to the draft guidance: "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf .**

- **We remind you that if an NDA is submitted, the NDA should include an assessment of studies and other information related to the abuse potential of the drugs. See 21 CFR 314.50(d)(5)(vii).**

6. Does the Agency consider that the pivotal Phase 3 studies HARMONY I, HARMONY Ibis, HARMONY CTP HARMONY III, designed to assess the efficacy and safety of BF2.649 (pitolisant) can support the labelling "(b) (4) " for Marketing Application in the US?

   FDA Response:
   This claim would need to be supported by positive findings in 2 adequate and well-controlled trials, (b) (4)
   The extent of patient exposure you describe appears, on face, adequate to support NDA filing.

Additional Comments

Statistics:

(b) (4)

CMC:

(b) (4)

Clinical Pharmacology:

- **Depending on the overall contribution of CYP2D6 on the metabolism of pitolisant, it is recommended that you evaluate the effect of CYP2D6 polymorphisms on the pharmacokinetics of pitolisant and if necessary genotype the patients in the phase 3 study.**
- **Sparse PK samples should be included in the phase 3 studies at adequate time**

points.

- **You propose to encapsulate the tablets in capsules for blinding purposes. You must conduct dissolution studies to establish the link between the capsules and the tablets using f2 comparisons. The results of the dissolution studies must be provided in Module 3 of the NDA.**
- (b) (4)
- **It is recommended that you conduct a drug interaction study with a strong inducer of 3A4.**

Studies in humans may not be conducted under this PIND. Before you may conduct studies in humans, you must submit a full Investigational New Drug Application (IND, see 21 CFR Part 312, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm) by amending this PIND with the required information. Include the above PIND number in Box 6 of the form FDA 1571 submitted with your IND. Send your IND submission in triplicate to the address below.

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, contact Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

RUSSELL G KATZ
06/15/2011