CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212028Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 111871

MEETING MINUTES

Eisai Inc.
Attention: Amanda Goodwin
Director, Global Regulatory Affairs
155 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Goodwin:

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

We also refer to the telecon between representatives of your firm and the FDA on June 14, 2018. The purpose of the meeting was to discuss the format and content of your planned NDA for lemborexant, including acceptability of data for submission, projected submission date, proposed presentation of data, dataset structure, and labeling.

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

If you have any questions, contact LT Brendan Muoio, Senior Regulatory Project Manager at (240) 402-4518 or brendan.muoio@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry 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:	June 14, 2018, from 10 a.m. to 11 a.m. EDT
Application Number:	111871
Product Name:	lemborexant
Indication:	Treatment of insomnia disorder, characterized by difficulties with sleep onset and/or sleep maintenance, (b) (4)
Sponsor Name:	Eisai Inc.
Meeting Chair:	Mitchell V. Mathis, MD Director, Division of Psychiatry Products (DPP)
Meeting Recorder:	Brendan Muoio, PharmD, RAC Senior Regulatory Project Manager, DPP

FDA ATTENDEES

Mitch Mathis, MD	Director, DPP
Tiffany Farchione, MD	Deputy Director, DPP
Jasmine Gatti, MD	Clinical Team Leader, DPP
Bernard Fischer, MD	Clinical Reviewer, DPP
Amy Avila, PhD	Pharmacology/Toxicology Reviewer, DPP
Laura McGhee, PhD	Pharmacology/Toxicology Fellow, DPP
Douglas Warfield, PhD	Associate Director for Biomedical Informatics, DPP
Brendan Muoio, PharmD	Senior Regulatory Project Manager, DPP
Peiling Yang, PhD	Biometrics Team Leader, Office of Biometrics (OB)
Andrew Potter, PhD	Biometrics Reviewer, OB
Praveen Balimane, PhD	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Kelly Harbourt, PharmD	Safety Evaluator, Division of Pharmacovigilance I
Phuong Nguyen, RPh	Safety Regulatory Project Manager, Office of Surveillance and Epidemiology

SPONSOR ATTENDEES

Connie Chou, PhD	Director, Biostatistics, NBG
Shobha Dhadda, PhD	Vice President, Biostatistics and Clinical Development Operations, NBG

Martin Rabe	Vice President, Global Regulatory Strategy NBG
Amanda Goodwin	Director, Global Regulatory Strategy, NBG
Margaret Moline, PhD	Executive Director, Project Team Leader, Clinical Research, NBG
Patricia Murphy, PhD	Director, Clinical Research, NBG
Carlos Perdomo, PhD	Senior Director, Biostatistics, NBG
(b) (4)	Head of Regulatory Affairs, (b) (4)
(b) (4)	Director, Biostatistics, (b) (4)

1.0 BACKGROUND

Eisai Inc. is developing lemborexant (formerly E2006), a dual orexin receptor antagonist, for the treatment of insomnia (sleep onset and/or maintenance) under IND 111871, and (b) (4)

The Agency and Sponsor have met several times, as per Table 1.

Table 1. Past FDA-Sponsor Meetings.

Meeting	Date	Significant Agreements
End-of-Phase 2	11/19/2014	1. Agreement on proposed phase 3 program supporting proposed insomnia indication, including total subject exposures, proposed doses and overall number of enrolled elderly subjects. 2. Agreement on proposed approach for rebound insomnia, measures to assess residual sleepiness and assessment of cataplexy via adjudication committee. 3. Agreement on proposed population PK and PK/PD modelling plan. 4. Confirmation that Eisai will be incorporating an assessment of bone toxicity in the pre-post-natal development study in the rat including calcium, phosphorus, iron, histopathology and bone length. 5. Request to include two positive controls in the Randomization Phase of the human abuse liability study: a single dose of the Schedule IV sedative, zolpidem (40 mg), and a single dose of the Schedule IV dual orexin receptor antagonist suvorexant (40 mg). 6. Agreement with the approach to analyze adverse events related to drug abuse liability and with the proposed customized MedDRA queries. 7. Preliminary agreement with the proposed 3 regulatory GMP starting materials (b) (4) (b) (4) for lemborexant drug substance synthesis.
Type C (Written Response Only)	05/08/2015	1. Agreement on proposed revisions to phase 3 program (extending the treatment period of Study E2006-G000-

		303 from 6 months to 12 months and eliminating Study E2006-G000-307). 2. No objection to the proposed sequential gatekeeping approach although Division would also accept an alternative gatekeeping approach. 3. Agreement that wake-time-after-sleep-onset (WASO) is a reasonable measure of sleep maintenance if one assumes a standardized time-in-bed; this is a form of sleep-efficiency (total time slept/total time in bed). 4. No objection to the use of zopiclone as an active control from a safety point of view for study 106. 5. Agreement with Eisai's proposal to remove serum ferritin monitoring. 6. Division agreed that metabolite M10 appears to be adequately qualified in nonclinical species. However, Eisai still needs to provide AUC values for all major metabolites in rats and monkeys at steady state.
Type C Meeting	01/07/2016	1. Division agrees that WASO2H is a reasonable measure of sleep maintenance. 2. Comparative language in the PI will be matter of review. 3. Agreement on the proposed sequential gate-keeping technique. 4. No objection to the proposed population age distribution of Studies 304 and 108. 5. Concern that the current design of studies 304 and 108 will lead to under-dosing of the comparator drug (zolpidem ER). The Division requested that Eisai outline the strategy to prevent under-dosing of zolpidem in Study 304 and Study 108.
Type C Meeting (Cancelled)	Preliminary Comments 08/19/2016	1. ~12-hour half-life may make it difficult for Sponsor to adequately perform a training procedure with the test drug. 2. Agreement that the proposed study in zolpidem-trained rats is an appropriate alternative to the conduct of a drug discrimination study in suvorexant-trained rats.
Type C (Written Response Only)	02/22/2017	Agreement on abuse-related AE search terms that trigger individual subject narratives
Type C Meeting (Cancelled)	Preliminary Comments 01/26/2018	1. Revised exposure numbers are consistent with ICH guidelines. 2. Acceptability of 40% elderly enrolled in Phase 3 program (per End of Phase 2 Meeting) will ultimately be a review issue. 3. Agreement with the sleep-onset primary endpoint of PSG-determined latency to persistent sleep (LPS; Study 304); substantiated by subjective Sleep Onset

		Latency (sSOL; Study 303). However, to evaluate lemborexant's effect on sleep maintenance, we recommended using PSG-measured Wake After Sleep Onset (WASO) versus placebo as a key secondary endpoint. Subjective WASO could be used for substantiation in the second study.

The phase 3 development program for insomnia is presented in Table 2.

Table 2. Phase 3 Development for Lemborexant's Insomnia Program.

Study	Description	Subjects	Dosing	Status
303	Randomized, controlled, double-blind Period 1: placebo, 2 doses lemborexant 6 months Period 2: 2 doses lemborexant 6 months Primary endpoint: Sleep diary	N=966 (≥18 yrs)	Lemborexant: 5mg, 10mg	Ongoing
304	Randomized, controlled, double-blind, active comparator (zolpidem) 1 month Primary endpoint: Polysomnography	N=1006 (males ≥ 65 yrs, females ≥ 55 yrs)	Lemborexant: 5mg, 10mg Zolpidem ER: 6.25mg	Completed (Positive)

The purpose of this meeting is to discuss the content and format of a planned NDA for lemborexant, including acceptability of data for submission, projected submission date, proposed presentation of data, dataset structure, and labeling.

FDA sent Preliminary Comments to Eisai on June 8, 2018. Per Eisai's request, the meeting format was changed from a face to face meeting to a teleconference.

2.0 DISCUSSION

2.1. ACCEPTABILITY OF THE DATA PACKAGE FOR THE PROPOSED NDA

Question 1: Recently completed studies E2006-G000-304 and E2006-A001-108 demonstrated superior efficacy and safety as compared to market leader zolpidem tartrate extended release. Zolpidem, like other approved sedative-hypnotic GABA agonists, has established adverse consequences and efficacy limitations, particularly at the end of the sleep period. Given this, Eisai wishes to accelerate its planned NDA submission for lemborexant and proposes a data cut for Study E2006-G000-303 for all data received by 14 September 2018. Eisai expects that at the time of original NDA submission, the lemborexant database will comprise 87% (210,809 patient days) of all planned patient exposures, with the remaining 13% of patient exposures submitted as part of the 120-day safety update. Eisai believes that the proposed patient database resulting from this data cut is sufficient to permit a robust assessment of the efficacy and safety of lemborexant. Does the Division agree?

FDA Response to Question 1: This proposal appears reasonable. However, the ultimate decision regarding the amount of safety data needed for NDA filing depends, in part, on the nature of the reported AEs and will be made at filing.

Discussion: *No further discussion.*

Question 2: Eisai proposes to conduct the population PK/PK-PD analysis based on data obtained through 14 September 2018. Does the Division agree?

FDA Response to Question 2: Yes, we agree.

Discussion: *No further discussion.*

2.2. INTEGRATED SUMMARY OF EFFECTIVENESS (ISE) AND SUMMARY OF CLINICAL EFFICACY (SCE)

Question 3: Eisai does not propose to pool efficacy data from Phase 2 study E2006-G000-201 (Study 201) with efficacy data from the Phase 3 studies in the ISE. Where appropriate, efficacy data from 201 ("study-level data") will be integrated (presented and discussed) in the ISE. Does the Division agree with this approach?

FDA Response to Question 3: Yes, we agree that the data from the phase 2 study (E2006-G000-201) does not need to be pooled with the phase 3 studies in the ISE.

Discussion: *No further discussion.*

Question 4: Eisai proposes that pooled analyses in the ISE will include sleep diary data up to Month 1 from the two Phase 3 studies (Study 303 and Study 304). Where appropriate, additional efficacy data from Studies 303, 304 and 201 ("study-level data") will be integrated (presented and discussed). Does the Division agree?

FDA Response to Question 4: Yes, we agree with pooling sleep diary data from Month 1 and the Insomnia Severity Index from Studies 303 and 304. In addition, we remind you that we consider the ISE an exploratory analysis.

Discussion: *No further discussion.*

Question 5: Does the Division agree with the proposed subgroups for efficacy analyses?

FDA Response to Question 5: The Division agrees to the following exploratory, subgroups:

- Age group 1 (<65, 65 to <75, and ≥75 years old)
- Age group 2 (<65 and ≥65 years old)
- Sex (male and female)
- Race (white, black, Asian, and other)
- Region (North America, Europe and New Zealand, Asia)

BMI can potentially be confounded by sex. We request the BMI subgroup analysis be performed on the total sample as well as on males and females separately.

Discussion: *See attached response from Eisai.*

Question 6: Does the Division agree that the text of the ISE report can also be provided in Module 2 as the SCE?

FDA Response to Question 6: Yes, the Division agrees that the ISE can also be used as the SCE for this submission.

Discussion: *No further discussion.*

Question 7: Eisai proposes that the ISE report present sleep diary data to which sleep diary handling rules have been applied. If there are any differences in overall results (with and without sleep diary handling rules), these will be discussed in the ISE. The pooled datasets for the ISE will contain data with and without the sleep diary handling rules. The raw data (subject data), derived data at each day (e.g., sSOL, sWASO), and the derived data at each timepoint (e.g., first 7 days, month 1, month 3) will all be submitted to the Division with and without the sleep diary handling rules. At the study level, datasets, TLGs and the CSR will include sleep diary data with and without the sleep diary handling rules applied. Does the Division agree?

FDA Response to Question 7: If the full study reports for Studies 303 and 304 (submitted in eCDT Section 5) present results without the data handling rules applied, then the Division agrees that the ISE may present results with the handling rules applied (noting and discussing where there are differences with and without the handling rules applied).

Discussion: *See attached response from Eisai.*

2.3. INTEGRATED SUMMARY OF SAFETY (ISS) AND SUMMARY OF CLINICAL SAFETY (SCS)

Question 8: For the ISS, Eisai proposes to submit separate data files for (1) studies of healthy volunteers and (2) studies of subjects with sleep disorders (patient studies). Data from the healthy volunteer studies will not be pooled with patient studies. Does the Division agree?

FDA Response to Question 8: Yes, the Division agrees with not pooling data from patients and healthy volunteers.

Discussion: *No further discussion.*

Question 9: Does the Division agree that the text of the ISS report can be provided in Module 2 as the SCS?

FDA Response to Question 9: Yes, the Division agrees that the ISS can also be used as the SCS for this submission.

Discussion: *No further discussion.*

Question 10: Does the Division agree with the proposed summaries of selected adverse events (selected AEs) for all ISS data?

FDA Response to Question 10: Yes, the Division agrees with the proposed summaries for selected AEs:

- Cataplexy: Treatment Emergent Adverse Events (TEAEs) with Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) of "cataplexy" and "drop attack"
- Falls: TEAEs with MedDRA PT of "fall"
- Seizure: TEAEs with MedDRA PTs belonging to Standardized MedDRA Query (SMQ) of "Convulsions" (Narrow Terms)
- Abuse liability events: TEAEs with MedDRA PTs as detailed in the ISS SAP for Subjects with Sleep Disorders
- Sleep paralysis: TEAEs with MedDRA PT of "sleep paralysis"

To ensure your ISS has the greatest relevance to our review at the time of NDA submission, the Division requests pre-submission of your AE mapping (verbatim to preferred terms). This will allow us to come to an agreement regarding AE mapping prior to you composing your ISS. This AE mapping submission can take the form of a dataset with two columns: Verbatim terms and Preferred terms. Please note that verbatim terms representing more than one AE should be coded to the number of relevant preferred terms (e.g., a verbatim term of "broke arm in a fall" should be coded to a preferred term capturing the broken arm and a separate preferred term capturing the fall).

Discussion: *See attached response from Eisai.*

2.4. STUDIES OF HEALTHY VOLUNTEERS: ISS

Question 11: Eisai proposes to pool healthy volunteer subjects for ISS analyses. Data from other Phase 1 studies ("study-level data") with special populations will be integrated (presented and discussed) in the ISS. Does the Division agree?

FDA Response to Question 11: Yes, the Division agrees to exclude phase 1 special populations (e.g., subjects with hepatic or renal impairment) from the healthy volunteers ISS.

Discussion: *No further discussion.*

Question 12: Eisai proposes to present pooled safety data from the Phase 1 Studies of Healthy Volunteers separately for single-dose studies and multiple-dose studies. Does the Division agree?

FDA Response to Question 12: Yes, the Division agrees to separate single- and multiple-dose pooling for the healthy volunteers ISS.

Discussion: *No further discussion.*

2.5. STUDIES OF SUBJECTS WITH SLEEP DISORDERS: ISS

Question 13: Eisai proposes to present the safety summary for Studies of Subjects with Sleep Disorders as 4 summary sets to support the proposed indication. Does the Division agree?

FDA Response to Question 13: Yes, the Division agrees with your proposal for four summary sets in the sleep-disorder ISS:

- Subjects with insomnia disorder in pivotal Phase 3 studies
- All subjects with insomnia disorder
- All subjects with sleep disorders
- Subjects with sleep disorders other than insomnia

Discussion: *No further discussion.*

Question 14: Eisai proposes to present safety data from Studies of Subjects with Sleep Disorders per the following subgroup summaries. Does the Division agree?

Subgroup summaries will be presented for the following summary tables:

- Overview table of TEAEs, including number of subjects with TEAEs, treatment-related TEAEs, severe TEAEs, treatment-emergent serious AEs (TESAEs), deaths, TEAEs leading to study drug withdrawal

Note: TEAEs that occur during the Run-in Period will be summarized separately from those that occur after Randomization

- Incidence of TEAEs by SOC and PT
- Incidence of TESAEs by SOC and PT

The following demographic and baseline information will be used in the subgroup summary:

- Age group 1 (<65, 65 to <75, and ≥75 years old)
- Age group 2 (<65 and ≥65 years old)
- Sex (male and female)
- Race (white, black, Asian, and other)
- Region (North America, Europe and New Zealand, Asia)
- BMI (<25, 25 to 30, and >30)

FDA Response to Question 14: Yes, the Division agrees with your proposed subgroups except for BMI. As per our answer to Question 5, we request that the BMI subgroup analysis be performed on the total sample as well as on males and females separately.

Discussion: *See attached response from Eisai.*

Question 15: Eisai proposes to present safety data from Studies of Subjects with Sleep Disorders for the following subgroup summaries for clinical laboratory data. Does the Division agree?

Subgroup summaries will be presented for the following summary tables:

- Mean and mean change from baseline by visit
- Treatment-emergent markedly abnormal values (TEMAVs)

The following demographic and baseline information will be used in the subgroup summary:

- Age group 1 (<65, 65 to <75, and ≥75 years old)
- Age group 2 (<65 and ≥65 years old)
- Sex (male and female)
- Race (white, black, Asian, and other)
- Region (North America, Europe and New Zealand, Asia)
- BMI (<25, 25 to 30, and >30)

FDA Response to Question 15: See our answer to Question 14.

Discussion: *See attached response from Eisai.*

2.6. POPULATION PK/PD ANALYSIS

Question 16: Does the Division agree with the proposed population PK and PK/PD analyses for safety and efficacy (exposure-response) as outlined in the PK/PD analysis plan including:

- The proposed studies to be included (pooled) as part of population PK analyses
- The proposed studies to be included (pooled) as part of exposure-response (PK/PD) analysis of efficacy and safety
- The proposed endpoints considered for efficacy and safety exposure-response analyses

FDA Response to Question 16: We agree with the proposed studies and endpoints for population PK, efficacy and safety exposure-response analysis. However, we have the following recommendations:

1. In your analysis plan, you propose to evaluate the impact of pH modifiers and CYP3A inhibitors on the pharmacokinetics of lemborexant. The plan suggests that you would include information on the use of these concomitant drugs (Yes vs. No) at baseline. However, we could not determine if you would include information on the dose of these concomitant drugs as well as their intake time which can influence drug interaction potential. You should include this information in your analysis or provide a rationale for why you think it is unnecessary.

2. It appears that you have also performed PK/PD analyses from the driving study (Report CPMS-E2006-003R). You should also include the report and datasets/model codes for these analyses in your submission.

   Discussion: *No further discussion.*

2.7. DATA SUBMISSION PLAN

Question 17: In accordance with FDA Specifications for Preparing and Submitting Summary Level Clinical Site Data for the Center for Drug Evaluation and Research's (CDER's) Inspection Planning, Eisai proposes to construct the dataset based on the 2 Phase 3 studies (Study 303 and Study 304). Does the Division agree?

FDA Response to Question 17: If you intend to rely on data from Study 201 for your NDA, Summary Level Clinical Site Data from this study must be included as well.

Discussion: *No further discussion.*

Question 18: For all studies, Eisai proposes to submit study-level data in electronic Common Technical Document (eCTD) format in Module 5.3.5.1. Eisai will also submit:

- Statistical Analysis System (SAS) programs to create all Analysis Data Model (ADaM) datasets for all ISS and ISE data and all Phase 2/3 studies
- SAS programs for creating all safety tables and figures
- SAS programs to create the tables and figures for all primary and key secondary efficacy analyses for the 2 Phase 3 studies (Study 303 and Study 304)

All other data and program files will be provided to the Division upon request. Does the Division agree?

FDA Response to Question 18: In addition to the datasets (submitted in. xpt format) and SAS programs listed above, please submit:

- A detailed user guide describing how to recreate all the derived sleep diary variables for Study 303 using the submitted raw data

- A dataset containing all daily electronic sleep diary data to allow us to recreate the derived sleep diary variables

- All datasets and programs for Study 201. Include all datasets and programs needed to recreate the interim analyses and track the randomization ratio for each patient randomized.

- All documentation of how the randomization ratio was updated throughout Study 201.

Discussion: *No further discussion.*

Question 19: For all ISS and ISE data, Eisai proposes to pool select ADaM datasets only. SDTM datasets will not be pooled. Does the Division agree?

FDA Response to Question 19: This plan is acceptable to the Division.

Discussion: *No further discussion.*

Question 20: For all ISS data, Eisai proposes to update the MedDRA coding for all adverse events and medical history to either the most current version available at the time of submission or one version before the current version. Does the Division agree?

FDA Response to Question 20: This plan is acceptable to the Division.

Discussion: *No further discussion.*

Question 21: For all ISS data, Eisai does not intend to update the MedDRA coding at the study level datasets for adverse events. The coding updates will be implemented in the ISS ADaM datasets only. Does the Division agree?

FDA Response to Question 21: This plan could result in a review issue if ISS coding updates result in inconsistencies in the application. You should provide an explanation for coding updates in the Analysis Data Reviewer's Guide for ISS based on the Study Data Technical Conformance Guide (pg. 5).

Discussion: *No further discussion.*

Question 22: For the Studies of Subjects with Sleep Disorders ISS, Eisai does not propose altering the WHO Drug Dictionary from the version used at the time of database lock for each study. As such, prior/concomitant medications will not be upgraded to the same WHO Drug Dictionary version. Does the Division agree?

FDA Response to Question 22: This plan is acceptable to the Division.

Discussion: *No further discussion.*

Question 23: For all studies, Eisai requests a waiver on Appendix 16.4 Individual Data Listing, in the study-level clinical study report (CSR). The pertinent subject data listings will be presented in Appendix 16.2 Selected Patient Data Listing, in the CSR. Does the Division agree?

FDA Response to Question 23: This plan is acceptable to the Division.

Discussion: *No further discussion.*

Question 24: Eisai proposes to include a list of all subject narratives in the ISS report. This list will directly hyperlink to the location of previously-created patient narratives in individual CSRs as well as narratives that are newly created for the ISS report. Does the Division agree with this proposal?

FDA Response to Question 24: This plan is acceptable to the Division.

Discussion: *No further discussion.*

Question 25: Guidance for Industry Premarketing Risk Assessment (2005) suggests that "Case report forms (CRFs) submitted for subjects who died or discontinued a study prematurely due to an adverse event should include copies of relevant hospital records, autopsy reports, biopsy reports, and radiological reports, when feasible". Eisai proposes to provide this level of

documentation and Council for International Organizations of Medical Sciences (CIOMS I) forms only for those subjects who died. Does the Division agree?

FDA Response to Question 25: This plan is acceptable to the Division. However, as you point out, the Division may request follow-up information for specific subjects as needed for the review.

Discussion: *No further discussion.*

2.8. REGULATORY

Question 26: Does the Division agree with the Table of Contents for the proposed NDA?

FDA Response to Question 26: We agree.

Discussion: *No further discussion.*

Question 27: In accordance with 21CFR54, Eisai plans to include financial certification for all applicable investigators from the adequate and well-controlled Phase 3 clinical studies (Study 303 and 304) and Phase 2 Study 201. Does the Division agree?

FDA Response to Question 27: We agree.

Discussion: *No further discussion.*

Question 28: For lemborexant studies completed and submitted to IND 111871 prior to 31 December 2017 Eisai proposes to include only the final protocol, which incorporates all amendments, in CSR Section 16.1.1 (as previously submitted to the IND). Eisai also proposes to include only the final Statistical Analysis Plan in CSR Section 16.1.9 (as previously submitted to the IND). From 01 January 2018 CSRs will include copies of all protocol amendments and SAP amendments. Does the Division agree?

FDA Response to Question 28: No, we do not agree. Please submit all versions of the protocol. The protocols are included in the background materials provided to the Office of Regulatory Affairs (ORA) for BIMO inspections; it is important to provide all versions of the protocol so that the field investigator performing the inspection can reference the correct one(s) for each subject.

Discussion: *No further discussion.*

2.9. LABELING

Question 29: Top-line results from Study 304 (Section 16.1) demonstrate that lemborexant provides statistically significant and clinically meaningful benefit to patients with insomnia as compared to placebo, [redacted] (b) (4)
In addition, the observed TEAEs demonstrate a favorable safety profile in the lemborexant group compared to [redacted] (b) (4) placebo [redacted] (b) (4) Following a review of the top-line Phase 3 data and content of the proposed NDA, does the Division have any feedback or initial comments on the draft label (Target Product Profile provided as Section 16.3) in relation to:

a. Proposed comparative efficacy language that serves the purpose of anchoring lemborexant in a well-established context of efficacy for the class. Data from a well-controlled Phase 3 confirmatory trial shows that lemborexant has robust efficacy on sleep onset and maintenance [redacted] (b) (4)

b. Proposed comparative safety language as it relates to clinically important adverse reactions such as marked impairment of middle-of-the-night (MOTN) postural stability [redacted] (b) (4)

c. The proposed indication statement: "BRAND NAME is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance, [redacted] (b) (4)

FDA Response to Question 29: Labeling will be a review issue after submission of the NDA. [redacted] (b) (4)

Discussion: *No further discussion.*

Additional Comments

- Confirm that the final "to-be-marketed" formulation was used in the pivotal efficacy/safety studies as well as the key clinical pharmacology studies (i.e., food-effect study, drug interactions study etc.)
- We recommend the content and format of information found in the Clinical Pharmacology sections (Section 7, 12, etc.) of labeling submitted to support this application be consistent with FDA Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format. Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.
- Confirm that a comprehensive assessment for drug-interaction (i.e., in vitro potential for substrate, inhibition and induction for key CYP enzymes and transporters as well as in vivo clinical interaction studies, as needed) for the product has been conducted as per the recent guidances by the Agency. Confirm the appropriate characterization (i.e., determination of inhibition and substrate potential towards key metabolizing enzymes and transporters) for all major circulating metabolite(s).

- Confirm that organ impairment (i.e., renal and hepatic impaired) studies are planned or done.
- Submit a listing of all interactions with the Agency pertaining to this IND/NDA including serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings.
- Submit minutes of DSMB meetings.
- Clarify if the Phase 2 Study 201 will be submitted to the planned NDA in support of your efficacy claim.
- Provide an interpretation of the treatment effect estimated by your MMRM model using multiple imputation from a pattern mixture model with the complete case missing value indentifying assumption.

Discussion: *See attached response from Eisai.*

With regard to the final bullet point, Eisai explained that they decided to use the complete case missing value (CCMV) assumption because they believed that few patients will drop out of Studies 303 and 304.

During discussion about the CCMV-7 (-4 for study 304), Eisai stated that SAS imputes each missing data pattern (e.g., a patient is observed for the first 5 visits and drops out of the study after the 5th visit yielding two missing data points at visits 6 and 7) using a mixture distribution consisting of all missing data patterns with more observations. In the example, Eisai asserted that SAS imputes the missing data for visits 6 and 7 using a mixture distribution estimated from the patients who had all visits observed and the patients only missing visit 7. The Agency asked Eisai to submit all mathematical details including how SAS generates the mixture distributions.

The Agency raised concerns about the interpretability of Eisai's proposed tipping point analysis (TPA) because the current TPA examines how the results of Study 303 change when the imputation model is systematically shifted from an assumption that the data are missing at random (MAR) to an assumption that missing data are imputed from a distribution generated from the placebo completers. MAR is a stronger assumption than CCMV. Eisai proposed modifying the TPA to start with the CCMV and shifting the data towards the null hypothesis. The Agency stated this plan is reasonable on face, and recommended that Eisai submit an amended statistical analysis plan with the details of the revised TPA. Because Study 304 had been analyzed using the original TPA assuming MAR and only had approximately 4% missing, Eisai asked the Agency if it was acceptable to submit the results of the original TPA and present the revised TPA as a post hoc analysis in the integrated summary of efficacy. The Agency did not object to this plan.

Eisai stated that Study 201 was conducted by (b) (4) *Eisai will submit all study reports, data, and programs used to conduct the trial to the NDA.*

3.0 OTHER

PREA REQUIREMENTS

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

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

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

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit all mathematical details regarding the use of CCMV assumption in studies 303 and 304, including how SAS generates the mixture distributions.	Sponsor	Prior to NDA submission
Submit amended statistical analysis plan with details of revised TPA.	Sponsor	Prior to NDA submission
Submit all study reports, data, and programs used to conduct Study 201 to the NDA.	Sponsor	With NDA submission

6.0 ATTACHMENTS AND HANDOUTS

Eisai's June 12, 2018, response to the June 8, 2018, Agency preliminary comments.

Questions 5, 14 and 15: Per the Division's request, BMI subgroup analysis will be performed on the total sample as well as on males and females separately.

Question 7: For the full study reports for Studies 303 and 304 Eisai intends to present results **with and without** the data handling rules applied. The ISE will present results **with** the data handling rules applied (noting and discussing where there are differences with and without the handling rules applied).

Question 10: Per the Division's request, the proposed AE mapping strategy will be provided to the Division for endorsement prior to the NDA submission.

Additional Comment "Confirm that the final "to-be-marketed" formulation was used in the pivotal efficacy/safety studies as well as the key clinical pharmacology studies (i.e., food-effect study, drug interactions study etc.)": Eisai confirms that the final "to-be-marketed" formulation was used in the pivotal efficacy/safety studies as well as the key clinical pharmacology studies.

Additional Comment "Confirm that a comprehensive assessment for drug-interaction (i.e., in vitro potential for substrate, inhibition and induction for key CYP enzymes and transporters as well as in vivo clinical interaction studies, as needed) for the product has been conducted as per the recent guidances by the Agency. Confirm the appropriate characterization (i.e., determination of inhibition and substrate potential towards key metabolizing enzymes and transporters) for all major circulating metabolite(s)": Eisai confirms that a comprehensive assessment has been completed per recent guidances and all major circulating metabolites are appropriately characterized.

Additional Comment "Confirm that organ impairment (i.e., renal and hepatic impaired) studies are planned or done": Eisai confirms that the hepatic impairment study (E2006-A001-104, Sequence 0143) and renal impairment study (E2006-A001-105, Sequence 0142) are ongoing.

Additional Comment "Clarify if the Phase 2 Study 201 will be submitted to the planned NDA in support of your efficacy claim": The safety and effectiveness of lemborexant will be based on Studies 303 and 304, with Study 201 providing supportive efficacy information only.

Additional Comment "Provide an interpretation of the treatment effect estimated by your MMRM model using multiple imputation from a pattern mixture model with the complete case missing value identifying assumption": It is Eisai's understanding that the Division is requesting that Eisai provides, as part of the discussion in the results section of the Clinical Study Reports for Studies 303 and 304, an interpretation of the treatment effect estimated using the Complete Case Missing Value (CCMV) identifying assumption in the pattern mixture model. ***Can the Division confirm that our understanding is correct?*** In addition, Eisai references recently-submitted Sequence 0169 submitted on 08 June 2018 where we provided follow-up to

the Division regarding sensible sensitivity analysis for Study 303. ***Can the Division confirm that the approach outlined in Sequence 0169 is acceptable or provide additional clarification?***

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

/s/

MITCHELL V Mathis
06/25/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND111871

MEETING MINUTES

Eisai Inc.
Attention: Carlos Langezaal, PhD
Director, Global Regulatory Affairs
155 Tice Boulevard
Woodcliff Lake NJ, 07677

Dear Dr. Langezaal:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for E2006.

We also refer to the meeting between representatives of your firm and the FDA on November 19, 2014. The purpose of the meeting was to obtain advice from the Division on your planned Phase 3 program and to gain agreement that the clinical, nonclinical, and CMC components of the development program will be sufficient for the filing of a New Drug Application (NDA). An additional objective of this meeting was to obtain input from the Controlled Substances Staff on your proposed Drug Abuse Liability Assessment program.

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

If you have any questions, call Dr. Brendan Muoio, Regulatory Project Manager at (240) 402-4518.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
CAPT, USPHS
Director
Division of Psychiatry 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:	End of Phase 2
Meeting Date and Time:	November 19, 2014 from 2:00 to 3:30 PM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	111871
Product Name:	E2006
Indication:	Treatment of insomnia
Sponsor/Applicant Name:	Eisai
Meeting Chair:	Mitchell V. Mathis, MD Director, Division of Psychiatry Products
Meeting Recorder:	Brendan Muoio, PharmD Regulatory Project Manager

FDA ATTENDEES

Mitchell Mathis, MD	Director, Division of Psychiatry Products
Tiffany Farchione, MD	Deputy Division Director (acting)
Jing Zhang, MD	Clinical Team Lead
Greg Dubitsky, MD	Clinical Reviewer
Kofi Kumi, PhD	Clinical Pharmacology Reviewer
Praveen Balimane, PhD	Clinical Pharmacology Reviewer
Kevin Krudys, PhD	Clinical Pharmacology Reviewer
Aisar Atrakchi, PhD	Pharmacology/Toxicology Team Lead
Amy Avila, PhD	Pharmacology/Toxicology Reviewer
Kara Schmid, PhD	Pharmacology/Toxicology Fellow
Peiling Yang, PhD	Biometrics Team Lead
Eiji Ishida, PhD	Biometrics Reviewer
Ron Farkas, MD	Medical Team Lead, Division of Neurology Products
Stephen Voss, MD	Medical Reviewer, Division of Bone, Reproductive and Urologic Products
Katherine Bonson, PhD	Controlled Substance Staff
Colin Vechery	Pharmacy Student
Brendan Muoio, PharmD	Regulatory Project Manager

EISAI ATTENDEES

Shoji Asakura, PhD, DABT	Senior Director, Biopharmaceutical Assessment Core Function Unit, Eisai Co Ltd, Japan
Nancy Bower, MS, DABT	Senior Director, Global Regulatory Affairs - Nonclinical, Eisai Inc. US
Shobha Dhadda, PhD	Senior Director, Biostatistics, Neuroscience, Eisai Inc. US
Jim Ferry, PhD	Vice-President, Head of Clinical Pharmacology, Eisai Inc. US
Quan Hong, PhD	Director, Biostatistics, Neuroscience, Eisai Inc. US
Carlos Langezaal, PhD	Director, Global Regulatory Affairs, Eisai Inc. US
Margaret Moline, PhD	Neuroscience and General Medicine Product Creation Unit (PCU), Eisai Inc. US
Patricia Murphy, PhD	Associate Director, Clinical Research, Neuroscience and General Medicine PCU, Eisai Inc. US
Gina Pastino, PhD, DABT	Associate Director, Clinical Pharmacology, Neuroscience, Eisai Inc. US
Richard Plumb, MSc	Associate Director, Global Regulatory Affairs – CMC, Eisai Limited, UK
Martin Rabe, MSc	Senior Director, Global Regulatory Affairs - Eisai Inc. US
Andrew Satlin, MD	Executive Vice-President, Neuroscience and General Medicine PCU, Eisai Inc. US
Martina Struck, PhD	President, Global Regulatory Affairs, Eisai Inc. US

1.0 BACKGROUND

E2006 is an orexin receptor antagonist that is being developed under IND 111871 for the treatment of DSM-5 Insomnia Disorder. The dosing regimen will be (b) (4) 5, or 10mg just before bedtime.

Several clinical studies have been completed to date, including the following:

- E2006-A001-001 - a single morning dose study in healthy adults over the range 1-200mg and a study of 2.5, 10, and 25mg evening doses in adults with insomnia.
- E2006-A001-002 - a multiple ascending dose study in healthy adults (ages 18-55) and healthy elderly subjects (ages 65-80) using evening doses from 2.5 to 75mg.
- E2006-A001-003 - a multiple dose study in healthy white males (10mg x14 days) and Japanese males (2.5, 10, and 25mg x14 days).
- E2006-A001-004 - a drug-drug interaction study of itraconazole and rifampin on E2006 PK and of E2006 on midazolam and bupropion PK.
- E2006-A001-005 - a relative bioavailability study in healthy adults comparing tablet versus capsule formulations of 2.5, 10, and 25mg morning doses.
- E2006-A001-007 - a human mass balance study using [^{14}C]E2006.
- E2006-A001-008 - a study of the effect of a high-fat meal on the rate and extent of absorption of E2006.

- EE2006-G000-201 - a randomized, double-blind, placebo-controlled, Bayesian adaptive, dose response study in 235 adult subjects with insomnia using doses of 1, 2.5, 5, 10, 15, and 25mg for 2 weeks.

During preclinical development, a 26-week oral toxicity study in the rat identified bone and dental abnormalities, which were reported to the Agency on June 12, 2013. Bone fracture was seen in one male and 2 female rats at the highest dose (1,000 mg/kg). Histologic bone structural changes or decreased bone density, accompanied by increases in serum calcium and decreases in serum iron, were observed at the mid (100 mg/kg) and high doses in females and at the high dose in males. Also, adverse histologic changes in the incisors were seen at these doses. Some low dose (30 mg/kg) animals showed bone pigmentation or whitish or banded discoloration of the teeth. Three completed or ongoing human studies at that time were reviewed for relevant findings in serum chemistry and hematology parameters (calcium, hemoglobin, and red blood cells) as well as pertinent treatment-emergent adverse events. No such findings were identified. Nonetheless, the IND was placed on partial clinical hold on June 19, 2013, because of these findings. Eisai responded to the hold action on September 12, 2014. Their response indicated that they believe that the mechanism for bone toxicity in the rat has been explained by the release of fluoride during the metabolism of E2006, which, with chronic administration, produces clinical, mechanical, and histological changes associated with fluorosis. Urinary fluoride measurements and metabolism studies in rats and monkeys have demonstrated a 4-fold lower exposure to fluoride in monkeys compared to rats, suggesting that this concern is species-dependent. Defluorinated metabolites of E2006 have not been detected in human trials with single doses to 200mg. This will be confirmed using samples from the human mass balance study. The risk in humans is felt to be negligible even with chronic dosing at the highest planned dose (10 mg/day for up to one year). On October 10, 2014, the Agency lifted the partial clinical hold for a Phase 3 trial with a maximum dose of 10 mg/day and conveyed the following requests to the sponsor: 1) assessments for bone toxicity in the pre-post-natal development study in the rat, 2) proposal for the monitoring of bone toxicity in clinical trials, and 3) submission of defluorinated metabolite levels from the mass balance study as soon as available. The monitoring for bone toxicity in the Phase 3 program will consist of measuring serum ferritin in addition to routine surveillance of iron, calcium, hemoglobin, and red blood cells. In addition, adverse events possibly related to bone toxicity, such as falls and fractures, will be routinely assessed.

Several additional Phase 1 clinical studies are part of the development program, including (but not limited to) an alcohol interaction study, a driving study, studies in subjects with hepatic impairment and renal impairment, a safety study in obstructive sleep apnea, and a human abuse liability study.

The following Phase 3 trials are planned to provide key safety and efficacy data to support a marketing application:

- E2006-G000-301 - This trial will be a one-month, randomized, double-blind, placebo-controlled, parallel group trial to confirm efficacy on objective sleep onset (latency to persistent sleep or LPS) and sleep maintenance (wake after sleep onset or WASO) based on polysomnography (PSG) in 900 randomized adult subjects meeting DSM-5 criteria for Insomnia Disorder. Subjects will be randomized in a 1:1:1:1 ratio to E2006 2.5, 5, or

10mg or placebo. The primary efficacy endpoints will be the changes from baseline in LPS and WASO at Month 1 (mean of days 29 and 30). Morning residual sleepiness will be assessed using a Visual Analog Scale in the sleep diary, withdrawal symptoms will be evaluated using the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire, suicidality will be assessed with the C-SSRS, and rebound insomnia will be monitored by comparing sleep diary data from the 2-week follow-up period with data from the screening period.

- E2006-G000-302 - This trial will be a 3-month, randomized, double-blind, placebo-controlled, parallel group trial to confirm efficacy on subjective sleep onset as measured by subjective sleep onset latency (sSOL) and subjective sleep maintenance as measured by subjective wake after sleep onset (sWASO) in 900 randomized adult subjects (at least 20% ≥age 65 years) meeting DSM-5 criteria for Insomnia Disorder. Subjects will be randomized in a 1:1:1 ratio to E2006 2.5 or 10mg, or placebo. A Sleep Diary will be completed within an hour of morning waketime daily and provide data to measure sSOL (estimated minutes from the time that sleep is attempted until sleep onset) and sWASO (estimated minutes of wakefulness during the night after initial sleep onset), which are the primary efficacy endpoints. Morning residual sleepiness, withdrawal symptoms, suicidality, and rebound insomnia will be evaluated as in study E2006-G000-301.

- E2006-G000-303 - This will be a 6-month, randomized, double-blind, placebo-controlled, parallel group trial to confirm efficacy on subjective sleep onset and subjective sleep maintenance in 900 randomized adult subjects (at least 20% age 65 or older) with DSM-5 Insomnia Disorder. Subjects will be randomized in a 1:1:1 ratio to E2006 5 or 10mg or placebo. A Sleep Diary will be completed within an hour of morning waketime daily and provide data to measure sSOL and sWASO (defined as above), which will be the primary efficacy endpoints. Morning residual sleepiness, withdrawal symptoms, suicidality, and rebound insomnia will be evaluated as in study E2006-G000-301.

- E2006-G000-307 - This will be a 12-month, randomized, blinded, parallel group study of the long-term safety and tolerability of E2006 in 480 adult subjects with DSM-5 Insomnia Disorder. Subjects will be randomized to E2006 2.5, 5, or 10mg in approximately equal proportions. Safety assessments will consist of adverse events, laboratory testing, vital signs, weight, ECGs, and evaluation of morning residual sleepiness, withdrawal symptoms, suicidality, and rebound insomnia. Efficacy measures will include sSOL and sWASO based on data from a Sleep Diary as general secondary endpoints.

Projected exposure in the Phase 3 trials is a total of 2,355 subjects treated with one of three doses of E2006 (2.5, 5, or 10mg) for at least one month, with 1,740 in the age range 18 to 64 years and 615 age 65 and older. Of the total, 1,080 will be exposed for at least 6 months and 480 for at least 12 months.

The purpose of this meeting is to obtain advice from the Agency on the planned Phase 3 program and to gain agreement that the development program from a clinical, nonclinical, and CMC perspective is sufficient for filing an NDA.

2. DISCUSSION

2.1. Clinical

Question 1: Does the Division agree that the studies described below will provide replicate evidence of efficacy and other design features to support the proposed indication of the treatment of insomnia disorder characterized by sleep onset and/or sleep maintenance difficulties?

a. Does the Division agree that the proposed efficacy variables will support the proposed indication?
b. Does the Division agree the durations of treatment are sufficient for registration?
c. Does the Division agree that administration of study drug within a few minutes of bedtime can be applied across all Phase 3 studies?
d. Does the Division agree that the proposed dosage-strength strategy is acceptable for study in the Phase 3 clinical program?

FDA Response to Question 1: *Yes. Please note that "co-primary" endpoints refer to the scenario where simultaneous winning on both endpoints is required to demonstrate efficacy. If you intend to use either of the two endpoints to support efficacy, they would be referred to as "primary endpoints".*

Discussion: *There was no further discussion.*

Question 2: Does the Division agree that the proposed approach to the determination of rebound insomnia is acceptable?

FDA Response to Question 2: *Yes.*

Discussion: *There was no further discussion.*

Question 3: In the case that (b) (4) clearly differentiate among doses in Phase 3, does the Division agree that (b) (4) can be presented in the Prescribing Information?

FDA Response to Question 3: *No. The Agency has not reached agreement on an acceptable definition for* (b) (4) *in Insomnia Disorder.*

Discussion: *The sponsor asked whether DPP would be open to the idea of considering* (b) (4) *for inclusion in labeling because they felt that this information might be useful to prescribers in deciding on an appropriate dose. DPP responded that they were open to this concept and agreed to consider it further after reviewing the clinical data.*

Question 4: Does the Division agree that the planned total subject exposures are adequate to provide the safety database for registration?

FDA Response to Question 4: *Yes.*

Discussion: *There was no further discussion.*

Question 5: Does the Division agree that dosing at 10 mg/day for up to 1 year is permissible?

FDA Response to Question 5: *Yes.*

Discussion: *There was no further discussion.*

Question 6: Does the Division agree that the number of elderly subjects proposed for the clinical trial program is sufficient for demonstrating the efficacy and safety of E2006 in elderly subjects with insomnia?

FDA Response to Question 6: *No, we recommend that the clinical trials enroll approximately 50% elderly subjects instead of 20%.*

Discussion: *The Division of Neurology Products consultant explained that enrolling 50% elderly patients would provide adequate statistical power to evaluate differences between the elderly and younger patient subgroups. After considerable discussion, the sponsor agreed to enroll approximately 40% elderly patients into their clinical trials.*

Question 7: Does the Division agree that no dose adjustments based on age, sex, or body mass index (BMI) are required in the Phase 3 studies?

FDA Response to Question 7: *Based on the current information we agree that dose adjustments for age, sex or BMI are not required in the Phase 3 studies. The results of the Phase 3 studies should be used to update the PK/PD model and to re-evaluate the need for dose adjustment in these populations.*

Discussion: *There was no further discussion.*

Question 8: Does the Division agree with the inclusion and exclusion criteria as outlined in the Phase 3 synopses for Studies 301, 302, 303, and 307?

a. Does the Division agree that the DSM-5-defined insomnia population is appropriate for the intended indication?
b. Does the Division agree with the proposed use of the following instruments to exclude subjects with sleep disorders other than insomnia: StopBANG score >5, International Restless Legs Scale score >16, Epworth Sleepiness Scale score >5, Narcolepsy Self-test "Yes" response to 2 or more questions?

c. Does the Division agree with the proposed approach to screening for and excluding parasomnias in the Phase 3 studies: Munich Parasomnia Scale (MUPS) to exclude subjects with sleep terrors, confusional arousals, REM behavior disorder, and sleep-related violent behavior; subjects with a history of sleep driving or sleep eating at any time will also be excluded?
d. Does the Division agree with the strategy of enrolling patients with different chief complaints (verified by sleep diary) across the placebo-controlled Phase 3 program? All subjects must report sSOL >30 minutes and have this complaint confirmed by sleep diary during Screening; in Study 301, subjects must also demonstrate LPS >30 minutes. In Studies 301, 303, and 307, subjects must also meet criteria for difficulties with sleep maintenance (report sWASO >60 minutes confirmed by sleep diary at Screening) and in Study 301 must also demonstrate objective WASO >30 minutes. However, in Study 302, subjects may enroll with either both chief complaints or with sleep onset difficulties alone.

FDA Response to Question 8: *Yes, except that an Epworth Sleepiness Scale score >5 appears to be a low cutoff for screening subjects with sleep disorders other than insomnia. For example, in one study, the modal and mean ESS score among a control group with normal sleeping habits and no snoring was about 6 (Johns MW. A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale. Sleep 1991;14(6):540-545.)*

Discussion: *Regarding the cutoff score of >5 on the Epworth Sleepiness Scale, the sponsor explained that this score was intended to be conservative in excluding patients with other sleep disorders. The Division of Neurology Products consultant explained that there is an effort to expand enrollment criteria in order to study a wide variety of patients in clinical trials. The sponsor agreed to provide further references to support their choice of this cutoff value.*

Question 9: Does the Division agree that the proposed (b) (4) is appropriate to adjust for multiplicity of the co-primary endpoints and 2 (or 3) doses and maintain the overall type I error under 5%?

FDA Response to Question 9: *No, if you intend to use either one of the two endpoints to support efficacy. The proposed* (b) (4) *may inflate the overall type I error rate depending on the underlying distributions of the test statistics.* (b) (4) (b) (4)

Discussion: *The sponsor agreed to a concern about the proposed multiplicity adjustment method addressed in the preliminary response, and stated that they would propose a gatekeeping strategy. Division of Biometrics I stated that they would review a revised proposal when submitted.*

Question 10: Does the Division agree with the proposed sample size for each placebo-controlled study for the purpose of efficacy evaluation?

FDA Response to Question 10: *We cannot respond to this question. The sample size calculation depends on unverifiable assumptions as well as the planned multiple testing procedure (refer to preliminary response to Question 9). In addition, no details of the calculation are provided.*

Discussion: *There was no further discussion.*

Question 11: With respect to the Driving Study (E2006-E044-106; Study 106), does the Division agree that the subject population, study design, choice of primary endpoint, and statistical approach are appropriate for the analysis of potential effects of E2006 on morning driving? Eisai intends to employ a 4-period, randomized cross-over study design in the on-road driving study to study 2 doses of E2006, 5 mg and 10 mg, controlled both by an active comparator (zopiclone 7.5 mg) and by placebo in a total of 48 healthy subjects, stratified in a 1:1 ratio by age group (ages 21-64 and ≥65). Driving tests will be conducted following single dose (acute administration) and at steady state for E2006. During the zopiclone treatment period, zopiclone will be administered only on the nights before the driving test; the rest of that treatment period will be comprised of placebo. As the primary endpoint, the study will measure the standard deviation of lateral position (SDLP) to determine the differences, if any, between each dose of E2006 and placebo both acutely and at steady state. Eisai proposes not to conduct a symmetry analysis as the primary analysis; rather this analysis will be a comparison of mean SDLP following active treatment with mean SDLP following placebo treatment. Additional endpoints and analyses include the number of lapses, defined as continuous change in lateral position of greater than 100 cm lasting for at least 8 seconds; number of subjects who cannot begin the driving test or were stopped during the on-road driving test; the proportion of subjects in each treatment condition with SDLP >2.4 cm and/or lapses >5; and symmetry analyses of SDLP. The impact of intrinsic factors on the results will also be determined.

FDA Response to Question 11: *The proposed study is acceptable, but in this type of safety study there is less distinction between primary and secondary endpoints than in an efficacy study; if, for example, the symmetry analysis was statistically positive, but the mean change in SDLP was not, we would likely still be concerned about safety. Similarly, it appears that your primary analysis will be based on combined adult and elderly patients, but it will be important to do each of your proposed analyses separately for adult and elderly patients, as we are typically concerned that elderly patients can respond differently to this type of drug than younger patients.*

Discussion: *There was no further discussion.*

Question 12: Does the Division consider that the proposed measures to assess residual sleepiness are sufficient?

FDA Response to Question 12: *Yes.*

Discussion: *There was no further discussion.*

Question 13: Does the Division agree with the plan to provide thorough analysis of cataplexy and cataplexy-like events by an independent Adjudication Committee? For the Phase 3 program, an independent Adjudication Committee will be employed at regular intervals to review, in a blinded manner, adverse events that could potentially be associated with cataplexy. A set of preferred terms constituting a customized MedDRA query will be defined (including: cataplexy, muscle weakness, muscle fatigue, muscle tone disorder, hypotonia, drop attack, double vision, slurred speech and fall) to identify all potential cases; these will then be flagged for review by the Adjudication Committee. The results of the adjudication process would be reported in addition to the coded terms from the clinical trial database.

FDA Response to Question 13: *In addition, we request that detailed descriptions of all cataplexy and cataplexy-related events be documented and considered by the Adjudication Committee and for inclusion in any future NDA submission, for example, "The patient experienced sudden severe weakness in her thigh muscles while walking down the street and fell to the ground without dizziness or loss of consciousness. She was unable to stand back up for 5 minutes. The weakness gradually resolved over the next 2 hours. There was no recurrence."*

Discussion: *There was no further discussion.*

Question 14: Does the Division agree that it is not necessary to adjudicate adverse events of sleep paralysis? Eisai has collected detailed information on events of sleep paralysis in the Phase 1 and Phase 2 studies. A majority of the events occurred during times when sleep was not permitted (i.e., in the clinic between dosing 30 minutes prior to lights out and lights out/bedtime) or was interrupted (e.g., in PK studies with morning dosing when the blood sampling procedure was initiated). In the Phase 2 study, the events of sleep paralysis in 10 subjects typically were single episodes and occurred after the first dose within 30 min to 2 hours post dose. Most were rated mild in severity, and no subject discontinued due to sleep paralysis. Since Eisai believes that adjudication of such events is not necessary, Eisai does not intend to require an Adjudication Committee to further evaluate any such events. However, if sleep paralysis is reported as an adverse event, Eisai will collect additional information on specific case report forms.

FDA Response to Question 14: *We request that detailed descriptions of all sleep paralysis events be recorded and submitted in any future NDA submission for our review. Please see our response to the previous question for an example.*

Discussion: *There was no further discussion.*

Question 15: Does the Division agree that Eisai will not be required to conduct a pediatric program under the Pediatric Research Equity Act (PREA) (21 USC 355c)?

FDA Response to Question 15: *Under FDASIA, an initial Pediatric Study Plan (iPSP) must be submitted to the Agency within 60 calendar days after the date of this meeting. The iPSP should convey your intention to request a full waiver of PREA requirements and describe the basis for your request. A decision on whether your waiver will be granted will be made by the FDA Pediatric Review Committee (PeRC). Please see "PREA Requirements" in Section 3.0 below for further information.*

Discussion: *The sponsor stated that they will submit an iPSP by January 19, 2015, and this will include a formal request for a waiver of PREA requirements. There was no further discussion.*

Question 16: Does the Division agree that the overall proposed clinical program is adequate to support registration?

FDA Response to Question 16: *From a clinical standpoint, yes.*

Discussion: *There was no further discussion.*

2.2. Clinical Pharmacology

Question 17: Population PK and PK/PD analyses are planned to support assessment of intrinsic and extrinsic factors in PK and to assess pertinent concentration–efficacy and concentration-response relationships to support labeling. Does the Division agree with the population modeling plan? Can the Division comment on whether additional analyses other than those already planned would be expected?

FDA Response to Question 17: *Your population modeling plan is reasonable. We do not expect additional analyses at this time.*

Discussion: *There was no further discussion.*

2.3. Nonclinical

Question 18: Does the Division agree that the nonclinical studies conducted with E2006 are sufficient to support the proposed Phase 3 clinical trials?

FDA Response to Question 18: *No. An adequate assessment of E2006's effects on male fertility was not conducted in the male fertility study (study no. K13078). Reproductive performance and macroscopic examination of male reproductive organs alone is an insensitive means of detecting effects on spermatogenesis. Histopathology of the testes and male reproductive organs is the most sensitive means of detecting toxic effects. The reproductive organs from the male fertility study (K13078) need to be examined microscopically (at minimum the control and high dose animals). Depending on findings from those tissues, additional assessments may be needed. Refer to guideline for industry*

ICH-S5B and ICH-S5(R2). Also, please provide a table comparing exposure levels (AUC values) of all major(>10% of total drug-related material) and human specific metabolites at the maximum recommended human dose of 10 mg at steady state compared to exposure levels (AUC values) in rats and monkeys. Additional nonclinical studies with major human metabolites may be required if there is not adequate coverage in nonclinical species.

Discussion: *The sponsor stated that male reproductive organs, including testes and epididymides, were evaluated microscopically in general toxicity studies in rats and monkeys up to 6-months and 9-months in duration without any signs of toxicity. They asked if this was sufficient for evaluation of male reproductive organs and that tissues from the male fertility study did not need to be evaluated microscopically. The Division considered this acceptable, but the final assessment will be a matter of review. The sponsor referred to a study comparing plasma exposure of E2006 metabolites between humans and animals. However, the Division pointed out that only exposure ratios were provided in that study report, and that tables containing plasma AUC values of metabolites in animals compared to those in humans at steady state are needed. The sponsor stated they will provide those data.*

Question 19: Does the Division agree that the nonclinical program as described, plus the additional ongoing and planned nonclinical studies, is sufficient to support the filing of a new drug application for E2006 for the treatment of patients with insomnia disorder?

FDA Response to Question 19: *On face the nonclinical program appears sufficient for NDA filing. We remind you from the remove partial hold letter dated October 10, 2014 that "Assessments for bone toxicity should be incorporated into the pre-post-natal development study in the rat in order to determine the effects of E2006 on the developing bone. Appropriate parameters should be studied such as bone density, biomarker measurements, iron metabolism, and fluoride measurements." If any new impurities, potentially genotoxic impurities, or levels of existing impurities increase during clinical development, they may require qualification in nonclinical studies. The major human metabolites (M4, M9, and M10) should be measured in the dose range-finding study for the 26-week mouse carcinogenicity bioassay in Tg rasH2 mice. Additional nonclinical studies may be necessary if any safety concerns arise during the course of clinical development or in any ongoing or planned nonclinical studies.*

Discussion: *The sponsor confirmed that they will be incorporating an assessment of bone toxicity in the pre-post-natal development study in the rat including calcium, phosphorus, iron, histopathology and bone length, but that bone density assessments using DXA and pQCT will not be conducted due to high variability in young rats and limited historical control data. The division stated that their proposal is acceptable. The sponsor informed the division that, to date, all impurities and potentially genotoxic impurities have been addressed, but that they will consider additional assessments if anything new arises in the future. The sponsor also informed the division that plasma samples for metabolite evaluation have been taken from the dose range-finding study in Tg rasH2 mice. The division informed the sponsor that all data on metabolites should be submitted with the special protocol assessment.*

2.4. Drug Liability Assessment

Question 20: Do the Division and Controlled Substances Staff (CSS) agree that the totality of the data package is adequate to fully assess the abuse liability of E2006 and to perform a full 8-factor analysis for inclusion in the submission as outlined in the FDA Guidance of the Assessment of Abuse Potential of Drug (2010), and that no other clinical studies will be required other than the human abuse liability study and the ethanol interaction study?

FDA Response to Question 20: *The list you provided in Table 14 ("E2006 Drug Abuse and Liability Testing Program") of the meeting package appears to be comprehensive in assessing the abuse potential of E2006. However, since all of the preclinical abuse-related studies have already been conducted, their adequacy is a review issue that will be determined after the NDA has been submitted.*

As addressed below in Question 23, it will be necessary for you to conduct a drug discrimination study with E2006 using animals that have been trained to discriminate between the Schedule IV orexin antagonist, suvorexant, and saline.

Discussion: *There was no further discussion.*

Question 21: Do the Division and CSS agree with the designs of the 2 human abuse liability studies?

FDA Response to Question 21: *Although we generally agree with the design of the human abuse potential study (E2006-A001-103), there should be two positive controls in the Randomization Phase: a single dose of the Schedule IV sedative, zolpidem (40 mg), and a single dose of the Schedule IV dual orexin receptor antagonist, suvorexant (40 mg).*

We also generally agree with the design of the alcohol interaction study (E2006-A001-009). However, we recommend that subjects remained in the clinic research unit for 72 hours after the last administered drug dose, instead of the 48 hours stated in the protocol. This is the amount of time used in the human abuse potential study and is appropriate for a drug with such a long half-life.

Finally, safety procedures during the studies are not described. This includes details of procedures in the event of serious adverse events or drug overdose. You should also provide details regarding how subjects will be evaluated for release from the research unit at the end of test sessions. This information should include a description of the transportation arrangements for subjects to return home. Due to the long half-life of the drug, subjects should not be allowed to drive themselves home (i.e., they should be driven home via a friend, family member, or taxi service).

Discussion: *The sponsor agreed to use suvorexant as a positive control, but suggested that the dose should be greater than 40 mg, given that the 40 mg dose only represented a 2-fold increase over the recommended therapeutic dose. CSS explained that, in a previous human abuse potential study conducted with suvorexant, there was no significant difference in*

responses on positive subjective measures (such as "Drug Liking" or "High") between 40, 80 and 150 mg of suvorexant. Additionally, the highest incidence of the AE "euphoria" was reported with the 40 mg dose, and there was an increase in non-abuse-related AEs at the 80 and 150 mg doses. Thus, 40 mg is the most appropriate dose of suvorexant for a human abuse potential study with E2006 because this dose would produce adequate abuse-related responses without exposing subjects to unwanted AEs.

The sponsor then inquired whether they could revise their protocol such that the highest dose of E2006 tested was lower than 50 mg (a 5 fold increase over the proposed therapeutic dose). CSS noted that the Guidance for Industry: Assessment of the Abuse Potential of Drugs (2010) did not require such a high multiple of the therapeutic dose. Thus, the sponsor could provide a justification for lowering the doses of E2006 tested in the human abuse potential study.

The sponsor stated they would submit a justification to account for the difference in the amount of time subjects stayed in the research unit after the last dose of the drug between the human abuse potential study and the alcohol interaction study.

Question 22: Do the Division and CSS agree with the approach to analyze adverse events related to drug abuse liability and with the proposed customized MedDRA queries?

FDA Response to Question 22: *The extensive list of abuse-related AE terms that you provided appears adequate because they are consistent with the evaluation of AEs as described in the Guidance for Industry: Assessment of the Abuse Potential of Drugs (2010). Narratives must be available for all AE terms.*

Discussion: *There was no further discussion.*

Question 23: Do the Division and CSS agree that the nonclinical program conducted to assess the abuse liability associated with the use of E2006 is adequate and that the conduct of a drug discrimination study is not warranted?

FDA Response to Question 23: *No. A drug discrimination study will be necessary, given that E2006 has the same mechanism of action as suvorexant, an orexin antagonist that is a Schedule IV drug under the Controlled Substances Act. The training drug in the drug discrimination study should be suvorexant. CSS will review the revision of the protocol for this study prior to study initiation, if desired.*

All other nonclinical abuse-related assessments of E2006 have already been completed, so the adequacy of these studies is a review issue that will be determined after the NDA is submitted.

Discussion: *The sponsor suggested using zolpidem as the training drug (as proposed in their protocol) because it is known to produce stimulus control, while it is not clear suvorexant can serve in this capacity. CSS explained that the drug discrimination procedure is highly reliant on mechanism of action, so that drugs with different mechanisms will not*

generalize to each other. Thus, it can be predicted with certainty that E2006 (an orexin antagonist) will not generalize to zolpidem (a GABA agonist), so there is no reason to perform this study. The sponsor also suggested using an opioid as the training drug (as proposed in their protocol), but CSS rejected this drug for the same reason. CSS suggested that the sponsor test various doses of suvorexant (an orexin antagonist) as the training drug and, if it did not work, the sponsor could provide a justification for not conducting a drug discrimination study. However, because suvorexant is the only drug scheduled under the Controlled Substances Act that has the same mechanism of action as E2006, it is the only appropriate training drug for a drug discrimination study.

2.5. Chemistry

Question 24: Does the Division concur with the proposed (b) (4) regulatory GMP starting materials (b) (4) for E2006 drug substance synthesis?

FDA Response to Question 24: *On its face the choice of starting materials appears appropriate. A final determination will be made after NDA submission where, as per ICH Q11, enough of the drug substance manufacturing process should be described for the Agency to understand how impurities are formed; how changes in the process could affect the formation, fate, and purge of impurities; and why the proposed control strategy is suitable for the drug substance manufacturing process.*

Discussion: *There was no further discussion.*

3. ADDITIONAL COMMENTS

Division of Bone, Reproductive and Urologic Products

1. Due to potential secondary hyperparathyroidism associated with fluoride exposure, we recommend also monitoring serum PTH in a subset of subjects.
2. We do not recommend other specific monitoring for skeletal toxicity e.g. X-rays, DXA or markers of bone turnover.
3. We agree with the proposed plan to monitor fractures and falls, and would advise further evaluation of subjects with low-trauma fractures as clinically indicated.
4. If the mass balance study indicates substantial metabolism of E2006 with systemic release of fluoride, monitoring fluoride levels in plasma and/or urine could be considered.

Discussion: *The sponsor did not agree that monitoring serum PTH in the phase 3 trials would be warranted unless additional data suggest the potential for higher than expected metabolism of E2006 with fluoride release. DBRUP agreed with this plan.*

4. GENERAL GUIDANCE

PREA REQUIREMENTS

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

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

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

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product

registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

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

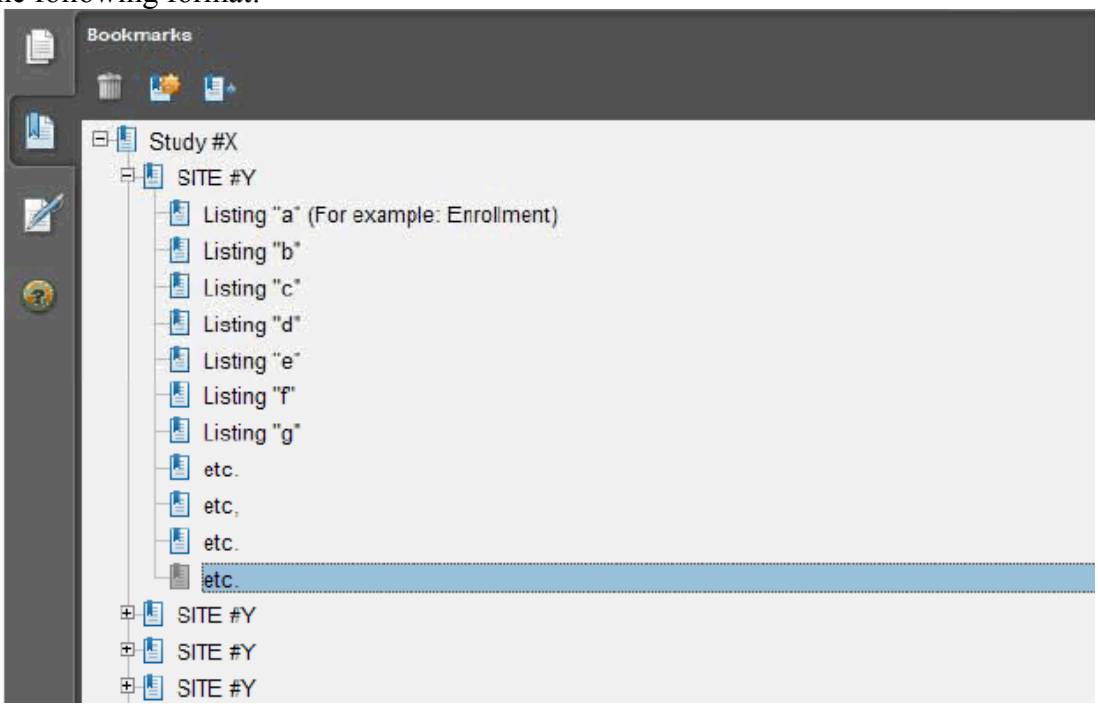
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,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

5. ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

MITCHELL V Mathis
12/03/2014