CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210238Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 076680

MEETING MINUTES

Eisai Inc.
Attention: Stacie P. O'Sullivan,
Associate Director, Global Regulatory Affairs
155 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. O'Sullivan:

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

We also refer to the meeting between representatives of your firm and the FDA on May 10, 2017. The purpose of the meeting was to discuss the top-line safety and efficacy data from the two Phase 3 Studies E5501-G000-310 (Study 310) and E5501-G000-311 (Study 311) which will constitute primary support for a marketing application. Additionally, Eisai is seeking agreement on the content and format of the proposed NDA.

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 Rachel McMullen, Senior Regulatory Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
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:	May 10, 2017; 3:00-4:00 PM (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	IND 076680
Product Name:	Avatrombopag maleate
Indication:	Treatment of thrombocytopenia in patients with chronic liver disease undergoing (b) (4) procedure.
Sponsor/Applicant Name:	Eisai Inc.
Meeting Chair:	Kathy Robie Suh, MD, PhD
Meeting Recorder:	Rachel McMullen, MPH, MHA

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Albert Deisseroth, MD, PhD, Supervisory Associate Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Andrew Dmytrijuk, MD, Medical Officer
Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Brenda Gehrke, PhD, Pharmacology/Toxicology Reviewer

Office of Biostatistics/Division of Biometrics V
Yuan Li Shen, DrPH, Statistical Team Leader
Che Smith, PhD, Statistical Reviewer

Office of Product Quality
Sherita McLamore-Hines, PhD, Team Leader
Amit Mitra, PhD, Product Quality Reviewer

SPONSOR ATTENDEES

Eisai Inc.
Francesco Bibbiani, Sr. Director, Clinical Development
Thomas Broadbent, PhD, Associate Director, Regulatory Affairs (CMC)
Connie Chou, Director, Biostatistics
Shobha Dhadda, Executive Director, Head of Project Operations
Lynn Kramer, MD, FAAN, President of Business Group
Stacie P. O'Sullivan, Associate Director, Global Regulatory Strategy
Bhaskar Rege, Executive Director, Clinical Pharmacology

AkaRx Inc.
Jayson Rieger, PhD, EVP, Regulatory & Development
Alex Sapir, Chief Executive Officer
Lee Allen, MD, Chief Medical Officer
Caroline Diaz, Director, Regulatory Affairs

(b) (4)
(b) (4) Chief Regulatory Officer

1.0 BACKGROUND

Eisai Inc. is developing Avatrombopag maleate for the treatment of thrombocytopenia in patients with chronic liver disease undergoing (b) (4) procedure. The sponsor proposes to submit a New Drug Application (NDA) for avatrombopag in June/July 2017. The purpose of this pre-NDA meeting is to present the top-line safety and efficacy data from the two Phase 3 Studies E5501-G000-310 (Study 310) and E5501-G000-311 (Study 311), which will constitute primary support for a marketing application.

This product currently does not have an orphan status but the sponsor has submitted a request for Orphan Designation to the Agency for review.

FDA sent Preliminary Comments to Eisai Inc. on May 5, 2017.

2. DISCUSSION

Final Clinical Questions

Question 1: *Top-line results from Studies 310 and 311 demonstrate that avatrombopag provides statistically significant and clinically meaningful benefit to this population. Also, the observed AEs and SAEs demonstrate a favorable safety profile in the avatrombopag group compared to placebo. 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 and indication statement as written "Avatrombopag is indicated for the* (b) (4) *treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure?*

FDA RESPONSE: The wording of the indication and the labeling will be a review issue.

DISCUSSION: There was no discussion.

Final Clinical Pharmacology Questions

Question 2: *Does the Division agree with the proposed Population Pharmacokinetic (PPK) and Pharmacokinetic/Pharmacodynamic (PK/PD) analysis plan?*

FDA RESPONSE: Yes, the proposed PPK and PK/PD analysis plan appears reasonable; however, the ability of the PPK and PK/PD modeling results to support the approval or labeling decisions will be a review issue.

DISCUSSION: There was no discussion.

Final Regulatory Questions Related to the Data Submission Plan

Question 3: *Does the Division agree with the Table of Contents for the proposed NDA?*

FDA RESPONSE: From a technical standpoint (not content related) yes, the structure and eCTD format for the planned NDA is generally acceptable. However, sponsors should not create additional nodes beyond what is in the specifications, it is likely that the information will not display properly. Please use leaf titles to differentiate between studies in module 4.

Also, please see additional comments below.

i. For ease of review, all pdf documents more than 5 pages long should have a table of contents (TOC), proper and clear bookmarks and hyperlinks (including the Briefing Package, which was not bookmarked). For more information on submitting pdf files, please refer to the PDF Specifications located here: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf
ii. Make sure leaf titles of documents are clear and indicative of the content
iii. All module 5 literature reference should reside in m5.4 only
iv. Please note that Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in 5 with the exception of module 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study's STF, including case report forms (crfs). Case Report Forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Subject Data Listings (16.4) should be file tagged as "data-listing-dataset". For documents with no specific file tags, "study-report-body" or "legacy-clinical-study-report" file tag can be applied. Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008) - http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf

DISCUSSION: There was no discussion.

Question 4: *In accordance with 21CFR54, the sponsor plans to include financial certification for all applicable investigators only from the adequate and well-controlled Phase 3 clinical studies, 310 and 311. Does the Division agree?*

FDA RESPONSE: Any studies that will be submitted to support a marketing approval require the submission of a financial certification or disclosure statement for all clinical investigators who participated in the covered clinical studies.

DISCUSSION: The Sponsor agreed for studies 202, 204, 310 and 311.

Question 5: *The sponsor proposes to provide defi, ne documents for SDTM datasets, with analysis datasets provided in .xml file format Version 2.0. Does the Division agree?*

FDA RESPONSE: Your approaches are acceptable.

DISCUSSION: There was no discussion.

Final Regulatory Questions

Question 6: *The sponsor will be requesting Priority Review of the avatrombopag marketing application due to the safety and efficacy demonstrated for avatrombopag and the unmet medical need addressed by the product. After review of the information that will be provided in the Briefing Document, does the Division have any additional questions related to this Priority Review so the sponsor may be best prepared to support an expedited review?*

FDA RESPONSE: You should submit additional rationale to support a request for Priority Review. Platelet transfusions are generally considered safe and effective therapy for the patient population for which Avatrombopag is to be indicated, i.e., patients with thrombocytopenia associated with chronic liver disease who are scheduled to undergo a procedure. It does not appear that Avatrombopag meets an unmet medical need or provide a significant improvement in safety and effectiveness. Based on the information provided in the Meeting Package it does not appear that Priority Review would be granted. See also the Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf)

DISCUSSION: The Sponsor summarized their argument for priority review of the application. The Agency agreed with the Sponsor on the desirability of therapeutic options for the indication. However, the Agency commented that the support for priority review will need to be reviewed within the context of the full application and the Agency looks forward to considering the submission.

Final CMC Questions

Question 7a: *Do the Division of Hematology Products (DHP) and the Office of Pharmaceutical Quality/Office of New Drug Products (OPQ/ONDP) agree that the sponsor may amend Section 3.2.P.7 Container Closure System* (b) (4) *for the commercial product no later than 3 months after the initial NDA submission?*

FDA RESPONSE: No, we recommend that all CMC information including the 3.2.P.7 be included in the proposed NDA within 30 days of initial submission. Information submitted after 30 days may or may not be reviewed during the review cycle.

DISCUSSION: There was no discussion.

Question 7b*: Do DHP and OPQ/ONDP agree that the sponsor may amend Section 1.14.2.1 Final carton or container labels* (b) (4) *for the commercial product, after finalization of the labeling* (b) (4)*, no later than 3 months after the initial NDA submission?*

FDA RESPONSE: No, we recommend that all CMC information including the 1.14.2.1 be included in the proposed NDA within 30 days of initial submission. Information submitted after 30 days may or may not be reviewed during the review cycle.

DISCUSSION for 7b: The Agency indicated that this will be a review issue.

Also, there is inadequate information in the meeting package to provide an answer with regard to acceptability of the stability data (b) (4) . Therefore, we recommend that Eisai provide adequate evidence in the NDA (b) (4)

DISCUSSION for 7b: The Sponsor presented their perspective on why the primary packaging should provide adequate stability for the drug product. The Agency indicated that this would be a review issue.

Additional Statistical Comments:
Please include the SAS programs used to derive the primary and key secondary efficacy endpoints from SDTM datasets and the programs used to perform the primary and key secondary efficacy analyses.

Additional Clinical Pharmacology Comments:
Address the following questions in the Summary of Clinical Pharmacology:

1. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications,

and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

2. What are the exposure-response relationships for efficacy, safety and biomarkers?
3. What is the effect of avatrombopag on the QT/QTc interval?
4. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
5. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
6. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

1. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

2. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.

3. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

    a. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    b. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

4. Submit the following for the population pharmacokinetic analysis reports:
    a. Standard model diagnostic plots
    b. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
    c. Model parameter names and units in tables.
    d. Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

5. Submit the following information and data to support the population pharmacokinetic analysis:
    a. SAS transport files (*.xpt) for all datasets used for model development and validation
    b. A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
    c. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

6. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships.

DISCUSSION: There was no discussion.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

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

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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 pdit@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.

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

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

SUBMISSION FORMAT REQUIREMENTS

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

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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.

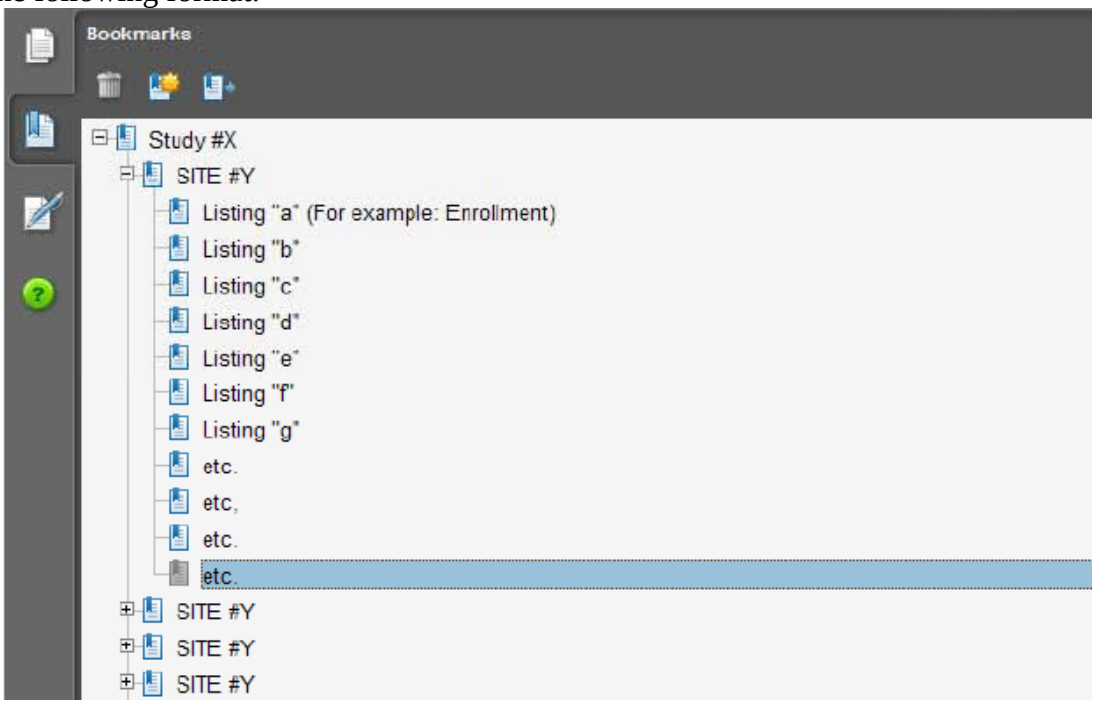
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

A copy of the Sponsor's response document is attached for reference.

Eisai Inc. IND 076680
Avatrombopag Pre-NDA Meeting
Clarification Questions/Comments
Division of Hematology Products
Meeting 10 May 2017

The sponsor would to like to thank the Division of Hematology for providing timely responses to the avatrombopag pre-NDA meeting questions and also for including Additional Comments and Other Important Meeting Information to guide our preparation of the avatrombopag NDA. Specifically, we look forward to discussing Question 6 and the paragraph following the FDA response to Question 7b in more detail at the meeting on Wednesday, 10 May 2017.

Please see sponsor confirmations or clarifications in *italics*.

Question 1: Top-line results from Studies 310 and 311 demonstrate that avatrombopag provides statistically significant and clinically meaningful benefit to this population. Also, the observed AEs and SAEs demonstrate a favorable safety profile in the avatrombopag group compared to placebo. 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 and indication statement as written "*Avatrombopag is indicated for the* (b) (4) *treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure?*

FDA RESPONSE: The wording of the indication and the labeling will be a review issue.

No further discussion needed.

Question 2: Does the Division agree with the proposed Population Pharmacokinetic (PPK) and Pharmacokinetic/Pharmacodynamic (PK/PD) analysis plan?

FDA RESPONSE: Yes the proposed PPK and PK/PD analysis plan appears reasonable; however, the ability of the PPK and PK/PD modeling results to support the approval or labeling decisions will be a review issue.

No further discussion needed.

Question 3: Does the Division agree with the Table of Contents for the proposed NDA?

FDA RESPONSE: From a technical standpoint (not content related) yes, the structure and eCTD format for the planned NDA is generally acceptable. However, sponsor should not create additional nodes beyond what is in the specifications, it is likely that the information will not display properly. Please use leaf titles to differentiate between studies in module 4.

Also, please see additional comments below.

No further discussion needed.

Question 4: In accordance with 21CFR54, the sponsor plans to include financial certification for all applicable investigators only from the adequate and well-controlled Phase 3 clinical studies, 310 and 311. Does the Division agree?

FDA RESPONSE: Any studies that will be submitted to support a marketing approval require the submission of a financial certification or disclosure statement for all clinical investigators who participated in the covered clinical studies.

Thank you for your response, the sponsor will include a financial certification or disclosure statement for investigators who participated in the covered clinical studies (Studies 202, 204, 310 and 311).

Question 5: The sponsor proposes to provide define documents for SDTM datasets, with analysis datasets provided in .xml file format Version 2.0. Does the Division agree?

FDA RESPONSE: Your approaches are acceptable.

No further discussion needed.

Question 6: The sponsor will be requesting Priority Review of the avatrombopag marketing application due to the safety and efficacy demonstrated for avatrombopag and the unmet medical need addressed by the product. After review of the information that will be provided in the Briefing Document, does the Division have any additional questions related to this Priority Review so the sponsor may be best prepared to support an expedited review?

FDA RESPONSE: You should submit additional rationale to support a request for Priority Review. Platelet transfusions are generally considered safe and effective therapy for the patient population for which Avatrombopag is to be indicated, i.e., patients with thrombocytopenia associated with chronic liver disease who are scheduled to undergo a procedure. It does not appear that Avatrombopag meets an unmet medical need or provide a significant improvement in safety and effectiveness. Based on the information provided in the Meeting Package it does not appear that Priority Review would be granted. See also the Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

(https://ww.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf)

The sponsor will provide additional rationale in the NDA to support our request for Priority Review. A summary of some of this information is below:

Thrombocytopenia is a frequent complication in patients with chronic liver disease, making the medical management of these patients challenging, often leading to delays in necessary

diagnostic and therapeutic procedures. Platelet transfusions are currently the only available therapeutic option for thrombocytopenia in patients with chronic liver disease undergoing a scheduled procedure. While often effective in transiently raising platelet count prior to a procedure, platelet transfusions are associated with significant limitations which are not seen with avatrombopag. Examples include, but are not limited to: refractoriness, supply issues, and infection risk.

Refractoriness: *Platelet refractoriness is defined as a post-transfusion increase in platelet count that is less than expected. It is estimated that up to 50% of subjects who are exposed to repeat transfusions will develop refractoriness. Given that avatrombopag stimulates the body's own megakaryocytes to produce platelets, there is no immune response and thus no risk of refractoriness. This has important implications in preserving the utilization of platelets for emergent or future needs of the patients, which may not be available if they become refractory.*

Supply Issues: *Every day, there are 7,000 units of platelets needed in the US. However, because of the time required to donate platelets (~3 hours) plus the short five day shelf life for platelets, they are often in short supply. As stated by the Red Cross, blood donations have fallen short of hospital needs, resulting in about 39,000 fewer donations than what's needed. Unavailability of platelet supply may lead to prolonged patient hospitalization if scheduled procedures have to be postponed in order to wait for an adequate platelet supply. As avatrombopag is a small molecule therapeutic that is stable and produced under well-controlled manufacturing processes, this eliminates supply chain constraints, reduces demand on donors, and makes this treatment option readily available to patients and medical providers.*

Infection Risk: *Platelet transfusions are associated with adverse transfusion reactions (including fever, acute hemolytic reactions and sepsis) that could result in prolonged hospitalization and potentially cancellation of scheduled procedures. In addition, platelet transfusions carry the risk of viral transmission, such as Zika, as cited in the New England Journal of Medicine (2016). Avatrombopag eliminates these potential problems as they are not inherent to a small molecule therapy.*

Given that there are no currently approved therapeutics for this indication, we believe that avatrombopag offers significant advantages over platelet transfusions in patients with chronic liver disease undergoing a procedure that warrants consideration for Priority Review.

Question 7a: Do the Division of Hematology Products (DHP) and the Office of Pharmaceutical Quality/Office of New Drug Products (OPQ/ONDP) agree that the sponsor may amend Section 3.2.P.7 *Container Closure System* (b) (4) for the commercial product no later than 3 months after the initial NDA submission?

FDA RESPONSE: No, we recommend that all CMC information including the 3.2.P.7 be included in the proposed NDA within 30 days of initial submission. Information submitted after 30 days may or may not be reviewed during the review cycle.

No further discussion needed.

Question 7b: Do DHP and OPQ/ONDP agree that the sponsor may amend Section 1.14.2.1 *Final carton or container labels* (b) (4) for the commercial product, after finalization of the labeling (b) (4) no later than 3 months after the initial NDA submission?

FDA RESPONSE: No, we recommend that all CMC information including the 1.14.2.1 be included in the proposed NDA within 30 days of initial submission. Information submitted after 30 days may or may not be reviewed during the review cycle.

No further discussion needed

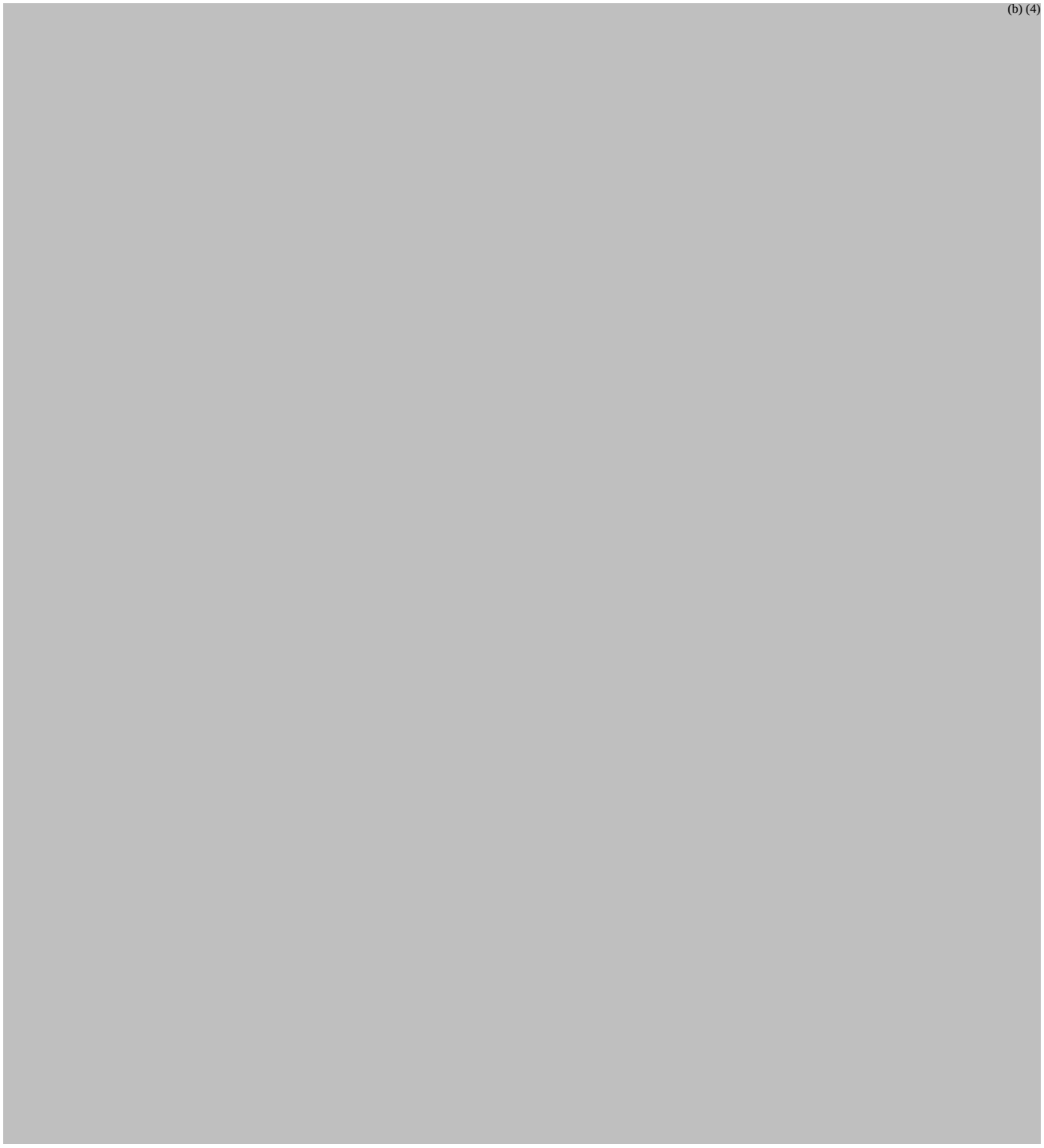
Also, there is inadequate information in the meeting package to provide an answer with regard to acceptability of the stability data (b) (4)

Therefore, we recommend that Eisai provide adequate evidence in the NDA (b) (4)

In response to the FDA's comments, the sponsor would like to provide the following clarification regarding the paragraph following the FDA response to Question 7b:

Sufficient data exist to support the adequacy of the planned primary packaging for avatrombopag, (b) (4) *and will be provided in the NDA. The design of the avatrombopag drug product primary packaging and available stability data will be presented in the NDA to support the packaging strategy.*

(b) (4)


(b) (4)

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

/s/

KATHY M ROBIE SUH
05/11/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 076680

MEETING MINUTES

Eisai Inc.
Attention: Jacqueline M. Kline, PhD, PMP
Manager, Regulatory Affairs
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Dr. Kline:

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

We also refer to the teleconference between representatives of your firm and the FDA on December 17, 2012. The purpose of the meeting was to discuss the design of the Phase 3 program.

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

If you have any questions, call Mara Miller, Regulatory Project Manager at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, M.D., Ph.D.
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	December 17, 2012 9:00 AM -10:00 AM
Meeting Location:	White Oak Building 22, Room 2201, Via Teleconference
Application Number:	IND 076680
Product Name:	Avatrombopag Maleate
Indication:	Treatment of thrombocytopenia in patients with chronic liver disease undergoing (b) (4) procedure (b) (4)
Sponsor/Applicant Name:	Eisai, Inc.
Meeting Chair:	Kathy Robie Suh, M.D., Ph.D.
Meeting Recorder:	Mara Miller, M.A.

FDA ATTENDEES

Division of Hematology Products
Edvardas Kaminskas, M.D., Deputy Division Director
Kathy Robie Suh, M.D., Ph.D., Clinical Team Lead
Andrew Dmytrijuk, M.D., Clinical Reviewer

Office of Biostatistics
Mark Rothmann, Ph.D., Statistical Team Lead
Qing Xu, Ph.D., Reviewer

Office of Clinical Pharmacology
Joseph Grillo, Pharm.D., Reviewer
Nitin Mehrotra, Ph.D., Pharmacometrics Team Lead
Jee Eun Lee, Ph.D., Pharmacometrics Reviewer

Office of New Drug Quality Assessment
Janice Brown, Ph.D., Team Lead
Zedong Dong, Ph.D., Biopharmaceutics Reviewer

SPONSOR ATTENDEES

Connie Chou, Ph.D., Director, Biostatistics
Shobha Dhadda, Ph.D., Senior Director, Biostatistics
Cindy Dobrinsky, M.D., Medical Director, Product Safety
Jim Ferry, Ph.D., Senior Director, Clinical Pharmacology
Tim Jenkins, Ph.D., Director, Clinical Development
Jacqueline Kline, Ph.D., Senior Director, Global Regulatory Affairs
Lynn D. Kramer, M.D., FAAN, President, Neuroscience Product Creation Unit
Alireza Manuchehri, M.D., MFPM, Director, Clinical Development
Joe McIntosh, M.D., Director, Clinical Development
Joanne Plumb, Senior Manager, Global Regulatory Affairs
Andrew Satlin, M.D., Senior Vice President, Neuroscience
Mark Taisey, President, Global Regulatory Affairs
Hironori Takayama, Global Regulatory Affairs

1.0 BACKGROUND

Eisai requested a Type B meeting to discuss the design of a Phase 3 clinical program to confirm the safety, tolerability, and efficacy of avatrombopag maleate for the treatment of thrombocytopenia in patients with chronic liver disease undergoing (b) (4) procedure (b) (4) The results from the proposed Phase 3 program will be used as the basis for a New Drug Application.

2. DISCUSSION

QUESTION 1

Does the Division agree with the sponsor's proposed (b) (4) *?*

FDA Response:

We generally agree with your proposal. However, we have the following additional comments for your proposed NDA.

(b) (4)

Discussion

No discussion occurred.

QUESTION 2

Does the Division agree that the nonclinical package is adequate to support the proposed clinical program and submission of a NDA for a five day dosing regimen of avatrombopag for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo (b) (4) *procedure?*

FDA Response:

We agree that the nonclinical package contains the studies needed to support a marketing application for the proposed indication. A decision on the adequacy of the studies will be made after review of the data.

Discussion

No discussion occurred.

QUESTION 3

The sponsor has identified reversible, dose-related changes in the stomach in repeated-dose nonclinical toxicity (6 weeks to 52 week) studies. Although this reversible safety signal has not been specifically studied in humans, the sponsor believes that the short duration of dosing (5 days) in Study E5501-G000-310 and Study E5501-G000-311 does not pose a significant gastric safety risk to study subjects and therefore, gastroduodenoscopic examination during the Phase 3 program is not necessary. Does the Division agree?

FDA Response:

Based on the summary information provided in the briefing package, we agree that the findings in the stomach of animals may not be a significant concern in patients for a 5 day-administration.

Discussion

No discussion occurred.

QUESTION 4

Does the Division agree that the proposed plan for the clinical pharmacology package is adequate to support registration for the proposed indication and the planned five day dosing regimen?

FDA Response:

Your clinical pharmacology development plan appears reasonable. However, the adequacy of dosing regimen will depend on the adequacy of the target platelet counts (See Response to Questions 6 and 9).

Discussion

No discussion occurred.

QUESTION 5

Given the lack of any QT interval corrected for heart rate (QTc) signal from nonclinical and clinical studies, and the exposure QTc relationship assessment, does the Division agree that the QT interval data compiled to date is adequate to support registration of avatrombopag for the proposed indication and five day dosing regimen?

FDA Response:

We cannot answer this question at this time. Submit the following for review by the QT-IRT team:

- **Compiled QT data**
- **A completed Highlights of Clinical Pharmacology Table (see attached).**

Discussion

No discussion occurred.

QUESTION 6

Does the Division agree that the planned population PK/PD dataset is sufficient to support registration for the proposed indication, including evaluation of effects of intrinsic and extrinsic factors on PK and PK/PD as described in Question 4?

FDA Response:

See question 4. In principle, your approach of using population method to evaluate the effect(s) of intrinsic/extrinsic factor(s) appears reasonable. However, evaluating the effect(s) of intrinsic/extrinsic factor(s) will be a review issue and it is possible that additional confirmatory dedicated clinical trials may be required if the results from your model are not deemed to be sufficiently robust. We have the following recommendations for you to consider:

- **To adequately assess the effect of renal impairment, a sufficient number of subjects and a sufficient representation of a range of renal or hepatic function should be included in the trials. Thereby the difference in PK/PD that warrant dosage adjustment can be effectively detected.**
- **For an adequate evaluation of DDI potential, you should prospectively design your study to be able to detect the difference in PK. Accurate dosing records including dosing time, amount, frequency and duration of dosing for the concomitant medication must be included. The information on relative timing of dosing of the concomitant medication relevant to PK sampling is important for an adequate DDI evaluation.**
- **Sparse PK sampling for all patients is recommended in protocol 310.**

Discussion

No discussion occurred.

QUESTION 7

Does the Division agree that the current evaluation of the potential of avatrombopag as a substrate or inhibitor of major drug transporters is sufficient and that no additional clinical evaluation is necessary for registration?

FDA Response:

Maybe. The overall the breadth of your in vitro assessment appears reasonable. We refer you to the newly released draft guidance Drug Interaction Studies regarding whether additional clinical trials are needed.

Discussion

No discussion occurred.

QUESTION 8

A bioequivalence (BE)-based analysis, i.e., comparison of 90% confidence interval (CI) for the log-transformed geometric mean ratios of Cmax and AUC values between test and reference, is often used in Phase 1 studies including relative BA, BE, food effect, and DDIs to conclude comparability between the two treatments. As avatrombopag is a Biopharmaceutics Classification System Class IV compound characterized by high intra- and inter-subject variability, does the Agency agree (b) (4) *?*

FDA Response:

No we do not agree. While we understand the issue, at this time we recommend the sponsor use a standard 90% confidence interval (CI) of 80% to 125% or consider a Reference-Scaled Average Bioequivalence (RSABE) approach (see Davit BM, et al. *The AAPS Journal* 2012;14:915-24). If you choose to pursue RSABE you should discuss your plan with the agency prior to initiation.

Discussion

The Sponsor inquired as to the use of a fed cohort for the bioequivalency trial as opposed the traditional fasted approach. The Agency responded that the Sponsor could provide a protocol and the Agency would review the information and discuss this further with the Sponsor. At this point, based on the PK variability provided by the Sponsor, a traditional limit of 90% CI of 80-125% should be considered. If the Sponsor chooses to do their BE study in a fed condition, this may be acceptable provided there is appropriate justification.

QUESTION 9

The sponsor has noted significant variability among treating clinicians in their target platelet count for a given patient and/or procedure. For this reason, the treating physician will be required to declare their target platelet count for a given patient at the time of screening. Based on the current guidelines and guidance from key opinion leaders, two target platelet counts of ≥50 x 109/L or ≥75 x 109/L have been considered for the Phase 3 studies, Study E5501-G000-310 and Study E5501-G000-311. Does the Division agree that treating to these platelet count targets is clinically justified and acceptable?

FDA Response:

No. These 2 target levels are essentially the same. There is only a 25,000 platelet count difference between these 2 target platelet count levels and bleeding risks that these 2 levels (≥50,000 and ≥75,000) represent can be expected to be similar. In order to achieve a broad indication for avatrombopag for the treatment thrombocytopenia in patients with CLD undergoing a (b) (4) **procedure where various procedures with widely differing risks for**

bleeding are represented the difference between the 2 target platelet counts should be larger (e.g., ≥50,000 and ≥100,000). Please provide additional justification for the target platelet counts you have proposed for the procedures you intend to study.

Discussion

The Sponsor discussed that they were concerned if the upper platelet target was set at 100,000 that more patients would exceed 200,000 possibly incurring a greater risk of thrombosis. The Sponsor asked if a single platelet target of 50,000 would be acceptable. The Agency commented that employing a second target level of platelets such as 100,000 would allow determination of whether there was a possible advantage in terms of less bleeding with that platelet count as compared to 50,000. Either of these approaches would be acceptable to the Agency.

QUESTION 10

The sponsor proposes to study a group of procedures that is diverse anatomically and also by specialty as listed below:

- *Dental procedures.*
- *Liver biopsy.*
- *Paracentesis.*
- *Gastrointestinal endoscopy with or without plans for biopsy, polypectomy, or variceal banding.*
- *Bronchoscopy with or without plans for biopsy.*
- *Transjugular intrahepatic portosystemic shunt.*
- *Ablation therapy for hepatocellular carcinoma (HCC) e.g., radiofrequency ablation,ethanol ablation or chemoembolization.*
- *Vascular Catheterization.*

Does the Division agree that the types of procedures to be studied are generalizable so as to allow for a label indication that is not procedure-specific?

FDA Response:

The types of procedures appear to be adequately diverse; however, there should be sufficient representation of patients in each risk category of low, moderate and high risk to assess clinical benefit in each risk category.

Discussion

The Sponsor indicated that they would stratify the enrollment by risk category. They proposed to include at least 10% of patients in the high risk category and not more than 60% of patients in the low risk category. The Agency commented that this seems reasonable. Adequacy of the data for the entire population would be a review issue.

QUESTION 11

Study subjects will be stratified by target platelet count (≥50 x 109/L or ≥75 x 109/L), HCC status (Yes or No), and baseline platelet count (<40 x 109/L or ≥40 x 109/L). Within each stratum, subjects will be randomized in a 1:1:1 ratio to receive avatrombopag (at one of two doses) or placebo. Does the Division agree with the proposed stratifications for Study E5501-G000-310 and Study E5501-G000-311?

FDA Response:

The proposed strata appear to be acceptable. See also response to question 9.

Discussion

Considering the discussion for question 9, the Sponsor proposes to use a platelet target of 50,000 and will stratify the randomization by baseline platelet count, procedure risk category and HCC status. The Agency agreed this is acceptable. Adequacy of the data for the entire population would be a review issue.

QUESTION 12

Based on data derived from Study E5501-G000-202 and modeling and simulation, the sponsor is proposing to study two dosing regimens. (b) (4) *Does the Division agree with these dosing regimens?*

FDA Response:

In principle, utilizing modeling and simulation for selection of Phase 3 dosing regimens appears reasonable. However, the adequacy of the proposed two dosing regimens will depend on the acceptable target platelet counts. Moreover, Figure 5 on page 76 of the briefing package shows that the mean platelet changes from baseline for 20 mg and 40 mg are similar while Figure 3 on page 32 (simulated mean platelet count profiles following 20 and 40 mg) show differentiation between the two dosing regimens. Please clarify. (See Response to Questions 6 and 9)

Discussion

No discussion occurred.

QUESTION 13

Does the Division agree with the proposed risk mitigation strategies for thromboembolism associated with TPO agonists?

FDA Response:

The proposed strategies are acceptable.

Discussion

No discussion occurred.

QUESTION 14

Does the Division agree with the proposed primary endpoint for the two pivotal studies, Study E5501-G000-310 and Study E5501-G000-311, i.e., "Proportion of subjects who do not require a procedure- (b) (4) following an elective procedure"?

FDA Response:

No. Platelet transfusions for any reason and any rescue procedure for bleeding should be considered as part of the primary endpoint. Also, patients receiving any rescue procedure for bleeding should be considered treatment failures. In addition, the evaluation period for the primary endpoint should be 7 days. "Proportion of subjects who do not require a procedure (b) (4) following an elective procedure" can be analyzed as a secondary endpoint.

Discussion

The Sponsor proposes the following revised wording for the primary endpoint-"Proportion of subjects who do not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure." The Agency agrees with this wording.

The Sponsor discussed that they plan to define rescue procedure for bleeding as receipt of fresh frozen plasma, cryoprecipitate, blood transfusions and asked if this would this be acceptable. The Agency commented that this definition seems narrow and other local interventions or aminocaproic acid may also be employed. More comment may be made on this point with review of the full protocol when it is submitted. The Sponsor will address this point in their SPA submission.

QUESTION 15

For Study E5501-G000-310 and Study E5501-G000-311, the sponsor plans to enroll a total of 300 subjects in each study (600 subjects total) randomized to receive either placebo or one of two active avatrombopag treatments at a 1:1:1 ratio. Does the Division agree with the proposed sample size for the purpose of efficacy evaluation?

FDA Response:

Yes. However you may want to consider anticipated number of dropouts in order to keep appropriate power.

Discussion

No discussion occurred.

QUESTION 16

Does the Division agree with the statistical methods proposed in the evaluation of the primary efficacy endpoint Study E5501-G000-310 and Study E5501-G000-311?

FDA Response:

Yes

Discussion

No discussion occurred.

QUESTION 17

Does the Division agree that the primary secondary efficacy endpoints from Study E5501-G000-310 and Study E5501-G000-311, if positive, can be included in the Package Insert Section 14 Clinical Studies (as noted in the Target Product Profile [TPP] [see Appendix 5]) and that the WHO bleeding scale is the most appropriate instrument for the assessment of bleeding?

FDA Response:

With regard to the WHO bleeding scale, small incremental changes in bleeding scale are of unclear clinical significance. Whether the results of secondary endpoints are included in the label will be a review issue.

Based on your primary analysis method, secondary efficacy endpoints can be tested for labeling claims only if both treatment arms provide statistically significant results compared with placebo for the primary efficacy endpoint.

Discussion

No discussion occurred.

Post Meeting Communication

Sponsor follow-up question:

Finally, recently the EMA have suggested the potential use of the BARC (Bleeding Academic Research Consortium) bleeding scale for assessment of bleeding. Would the FDA consider this bleeding scale to be appropriate for use in studies 310 & 311?

FDA Response:

You have not provided sufficient rationale to allow assessment of the applicability of this bleeding scale, which was developed primarily for cardiovascular trials, to chronic liver disease setting. You should provide the rationale for the clinical applicability of this bleeding scale.

QUESTION 18

Does the Division agree with the statistical methods proposed in the evaluation of the secondary efficacy endpoints in Study E5501-G000-310 and Study E5501-G000-311?

FDA Response:

No. We do not accept non-inferiority efficacy claims for comparisons with placebo.

Discussion

The Agency mentioned that they are not asking for a formal non-inferiority claim but they will be looking at this endpoint for risk benefit purposes.

Post Meeting Communication

Sponsor Follow up question:

The sponsor understands that the FDA does not accept non-inferiority efficacy claims for comparisons with placebo. However, in this particular situation the sponsor believes that the use

of a non-inferiority comparison between avatrombopag and 'standard of care' for the bleeding endpoint is reasonable, as this approach is clinically meaningful, because avatrombopag is intended to replace the current standard of care (platelet transfusion) to address the bleeding risk in this patient population. Note that in Study 310 and 311, the inclusion criteria will require that a subject's platelet count is less than 50 x 109/L. Therefore, the vast majority of subjects randomized to placebo are expected to receive a platelet transfusion in order to complete their procedure. While we think it may well be appropriate to compare the avatrombopag arms against the placebo arm - perhaps a more conservative approach, that also better reflects actual standard of care, would be a non-inferiority comparison between only those subjects in the placebo arm who receive a platelet transfusion and those who receive avatrombopag.

Does FDA agree with this approach to evaluate noninferiority?

FDA Response:

No, this is not acceptable. Any evaluation of the risk of bleeding should involve all randomized patients. We reiterate that we are not interested in a non-inferiority comparison to placebo on bleeding. We are interested in the comparison on bleeding for risk-benefit purposes.

Sponsor Follow up question:

If this more conservative approach is acceptable to the FDA and non-inferiority is observed in both studies (310 & 311) the sponsor would then plan to pool results of Study 310 and 311 to evaluate superiority of avatrombopag versus standard of care (platelet transfusion) for the bleeding endpoint. The sponsor believes this approach is an important comparison of this secondary endpoint, as it addresses the reason platelet transfusions are currently administered to this patient population.

Does FDA agree with this approach to evaluate superiority? If yes, does the FDA agree that the results from such an approach could support a labeling claim?

FDA Response

See response to above question. Proper alpha adjustment would be necessary to maintain the appropriate overall type I error rate for all labeling claims.

QUESTION 19

Does the Division agree that safety data from Study E5501-G000-310 and Study E5501-G000-311 combined with data from earlier phase studies and data obtained from avatrombopag clinical studies in other indications (b) (4) *) will adequately characterize the safety profile of avatrombopag in the proposed indication?*

FDA Response:

Whether or not the safety database adequately characterizes the safety profile for avatrombopag in the proposed indication will be a review issue.

Discussion

The Sponsor asked for clarification on the number of patients with long-term treatment with avatrombopag that would be needed in the safety database. They currently have about 150 patients treated for approximately 6 months. The Agency commented that they are not able to give a specific number, but the adequacy would be dependent upon safety results amongst the patients who had been studied.

QUESTION 20
The sponsor proposes to enroll 30% of patients from Study E5501-G000-310 and Study E5501-G000-311 at sites located in the US. Does the Division agree?

FDA Response:

Yes.

Discussion

No discussion occurred.

QUESTION 21
The sponsor requests a waiver of clinical studies (b) (4)
Does the Division agree?

FDA Response:

You should include your request for pediatric waiver with your NDA along with the rationale.

Discussion

No discussion occurred.

Additional Statistical Issues and Comments

The number of subjects not measured for the primary endpoint should be kept to a minimum. Too much missing data undermine the reliability and confidence of the results.

Please outline measures you plan to implement to minimize the amount of missing data. Please propose several sensitivity analyses to assess the limitation of the data and its impact on the results.

The randomization method (e.g., permutation blocks) should be included in the protocol.

Additional Biopharmaceutics Comments

Include the following information/data for the development of dissolution method and the establishment of the acceptance criteria in your future NDA submission.

a) **<u>Dissolution Test</u>: The dissolution method development report supporting the selection of the proposed dissolution test should be provided in the future NDA. The dissolution development report should include the following information:**

   i) **Solubility data for the drug substance covering the pH range;**

   ii) **Detailed description of the dissolution test being proposed for the evaluation of the proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (*i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.*). If a surfactant was used, the data supporting the selection of the type and amount of surfactant should be included. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (*i.e., 15, 20, 30, 45, & 60 minutes*) and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend that at least twelve samples be used per testing variable;**

   iii) **Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for the proposed drug product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and**

   iv) **Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).**

b) **<u>Dissolution Acceptance Criterion(a)</u>: For the setting of the dissolution acceptance criterion(a) of your proposed drug product, the following points should be considered:**

   i) **The dissolution profile data (*i.e., 15, 20, 30, 45, & 60 minutes*) from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your proposed drug product [i.e., specification-sampling time point and specification value].**

ii) The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.

iii) The selection of the specification time point should be where Q = 80% dissolution occurs.

iv) The dissolution acceptance criterion should be based on average in vitro dissolution data (n=12).

Note that the final determination on the acceptability of the proposed dissolution method and acceptance criterion for your proposed product will be made during the NDA review process based on the provided data.

Discussion

No discussion occurred.

3.0 OTHER IMPORTANT INFORMATION

PREA PEDIATRIC STUDY PLAN

Please be advised that you must submit a Pediatric Study Plan within 60 days of your scheduled end-of-Phase 2 meeting. 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. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

No action items were identified.

6.0 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/

KATHY M ROBIE SUH
12/28/2012