CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210598Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119840

MEETING MINUTES

Theravance Biopharma R&D, Inc.
C/O Theravance Biopharma US, Inc.
901 Gateway Boulevard
South San Francisco, CA 94080

Attention: Daven Mody, PharmD, MBA
Senior Director, Regulatory Affairs

Dear Dr. Mody:

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

We also refer to the meeting between representatives of your firm and the FDA on March 16, 2017. The purpose of the meeting was to discuss the content of the proposed New Drug Application for revefenacin for the indication of chronic obstructive pulmonary disease, (b) (4).

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 me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Reference ID: 4348407

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:	March 16, 2017; 12:00 – 1:00 PM
Meeting Location:	White Oak Building 22, Conference Room 1415
Application Number:	IND 119840
Product Name:	Revefenacin
Indication:	Chronic obstructive pulmonary disease (COPD)
Sponsor Name:	Theravance Biopharma R&D, Inc.
Meeting Chair:	Badrul Chowdhury
Meeting Recorder:	Nina Ton

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Lydia Gilbert-McClain, MD, Deputy Director, DPARP
Tony Durmowicz, MD, Clinical Team Leader, DPARP
Robert Lim, MD, Clinical Reviewer, DPARP
Eleni Salicru, PhD, Pharmacology/Toxicology Reviewer, DPARP
Ijeoma Uzoma, PhD, Pharmacology/Toxicology Reviewer, DPARP
Shanti Gomatam, PhD, Acting Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
Mingyu Xi, PhD, Biostatistics Reviewer, Division of Biometrics II, OB
Craig Bertha, PhD, CMC Lead, Division of New Drug Products II Branch IV, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Bhawana Saluja, PhD, Acting Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Mohammad (Abir) Absar, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
Sarah Vee, PharmD, Team Leader, Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)
Shirley Abraham, PharmD, Safety Evaluator, DMEPA, OSE
Jasmeen Abou-Sayed, PharmD, Risk Management Analyst, Division of Risk Management, OSE
Nina Ton, PharmD, Senior Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Theravance Biopharma
Brett Haumann, MD, Senior Vice President, Clinical Development and Chief Medical Officer
Rebecca Coleman, PharmD, Vice President, Regulatory Affairs
Ed Moran, PhD, Vice President, R&D Program Leader
Glenn Crater, MD, Head of Clinical Development & Medical Affairs
Marie Borin, PhD, Clinical Pharmacology Lead
Chris Barnes, PhD, Senior Director, Biostatistics
Daven Mody, PharmD, MBA, Senior Director, Regulatory Affairs

Mylan
Jonathan Ward, MD, Vice President, Head of Global Clinical Respiratory (via teleconference)
Michelle Lee-Bourner, Head Respiratory Regulatory (via teleconference)

1. BACKGROUND

Theravance submitted a Pre-NDA meeting request dated January 6, 2017, to the Division of Pulmonary, Allergy, and Rheumatology Products and the Division granted the meeting on January 17, 2017. The purpose of the meeting was to discuss the content of the proposed New Drug Application for revefenacin for the indication of chronic obstructive pulmonary disease, (b) (4). Upon review of the meeting package, the Division provided preliminary comments to the Sponsor's questions via electronic correspondence dated March 10, 2017. Daven Mody, Theravance Biopharma's Senior Director, communicated to the Division via email dated March 13, 2017, that the Sponsor requested to focus the meeting discussion on Questions 3, 5a, 7, 8, and 16. The Sponsor's questions are in *italics*, FDA's responses are in normal font, and the meeting discussion is in **bold**.

2. DISCUSSION

Nonclinical

Question 1
Does the Agency agree that the nonclinical program meets the Agency's requirements for a 505(b)(1) filing and appears adequate to support approval of an NDA for revefenacin? (Section 6)

FDA Response
We note that the in-life portion of the two-year inhalation carcinogenicity studies in mice and rats have been completed and the results are under evaluation. The nonclinical program appears potentially adequate to support NDA filing. The adequacy of the data from the nonclinical studies will be a review issue.

Meeting Discussion
This question was not discussed.

Question 2
Does the Agency agree that the nonclinical program supports the proposed labeling for revefenacin? (Appendix 1)

FDA Response
The nonclinical program appears sufficient to support the proposed labeling. The final wording of the label will be determined upon review of the NDA. We note that the indications and usage statement in the Highlights section should identify the established pharmacological classification (i.e., anticholinergic).

Meeting Discussion
This question was not discussed.

Additional Nonclinical Comment
For an NDA, provide safety qualification for leachables (and extractables, as appropriate) from the container closure system. For further information, see USP 1663, *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems*, and USP 1664, *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems*.

Post-Meeting Comment
To facilitate the statistical review of carcinogenicity studies, to be provided in your future NDA, submit the tumor data set for each study in conformance to the electronic format specified in Study Data Specifications, Version 2.0 (July 18, 2012). This document is available at:
http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf.

Clinical Pharmacology

Question 3
Does the Agency agree that dedicated clinical drug-drug interaction studies are not needed based on the results from the human ADME study and nonclinical data? (Section 7.1)

FDA Response
Based on the summary of the *in vitro* cytochrome P450 isozymes drug-drug interaction (DDI) potential studies for revefenacin, your proposal of not conducting cytochrome P450-based DDI interaction studies for revefenacin in humans appears reasonable. However, we note that you have not provided study results to identify the metabolic pathway for the primary active metabolite, i.e., THRX-195518. In your NDA submission, include study results and data to identify the metabolic pathway for THRX-195518. The adequacy of the data will be a review issue.

We note that revefenacin is a substrate for P-gp and BCRP. In addition, THRX-195518 is a substrate for both OATP1B1 and OATP1B3. Address the likely impact of these findings in a clinical setting in the NDA submission. The adequacy of the data and justification will be a review issue.

Meeting Discussion
Theravance asked FDA to elaborate on the study results and data needed to identify the metabolic pathway for THRX-195518. FDA responded that the sponsor should provide in vitro study results and data to identify the metabolic pathway for THRX-195518. Theravance noted that they will evaluate the phase 3 data for over 100 subjects to show that concomitant medications did not affect the systemic exposure of revefenacin and THRX-195518.

FDA reiterated that the sponsor should also address the impact of the findings related to revefenacin being a substrate of P-gp and BCRP, and the primary metabolite being a substrate of OATP1B1 and OATP1B3 in a clinical setting. Theravance commented that phase 3 data for over 40 patients showed no impact on the parent drug and metabolites.

Question 4
Does the Agency agree that the clinical pharmacology and biopharmaceutical program meet the Agency's requirements for a 505(b)(1) filing and are adequate to support approval of an NDA for revefenacin? (Section 7.1)

FDA Response
In general, the clinical pharmacology program appears to be acceptable for filing of a 505(b)(1) application for revefenacin inhalation solution. The adequacy of the data submitted will be a review issue.

Meeting Discussion
This question was not discussed.

Question 5
Does the Agency agree that the clinical pharmacology program supports the proposed labeling for revefenacin? (Appendix 1) In particular,

(b) (4)

b) Does the Agency agree that no dose adjustment is needed in patients with renal impairment? (Section 7.1.2.13)

FDA Response

(b) (4)

Meeting Discussion
Theravance asked whether the Agency agrees (b) (4) **. FDA responded that the Agency will rely on the totality of evidence and this**

will be a review issue. The sponsor asked if predicted data for exposure of revefenacin and THRX-195518 would be acceptable to address (b) (4) **FDA noted that the approach appears reasonable; however, the adequacy of the data will be a review issue.**

b) It is premature to provide specific comments on labeling recommendations for revefenacin in patients with renal impairment. We note that the exposure of revefenacin and THRX-195518 was increased by 3.37-fold and 2.06-fold, respectively, in subjects with severe renal impairment. We agree with your proposal of evaluating the impact of renal function using population PK analysis of the phase 3 studies.

Meeting Discussion
This question was not discussed.

Clinical

Question 6
Does the Agency agree that given supportive results from the CV (Holter) monitoring during the long-term safety study (Study 0128), the use of a Clinical Events Committee to adjudicate cardiovascular events during the replicate Phase 3 studies (Study 0126 and Study 0127) are adequate to support approval of an NDA for revefenacin? (Section 7.3)

FDA Response
The CV safety data generated from trials 0126, 0127, and 0128 are adequate to support review of the CV safety of your product. Whether these data are sufficient to support approval is a review issue.

Meeting Discussion
This question was not discussed.

Question 7
Given the data from the replicate Phase 3 studies (Study 0126 and Study 0127) completed to date and assuming consistent results from the long-term safety study (Study 0128), does the Agency agree an NDA should be submitted with the 175 mcg dose as an appropriate dose on the basis of its reproducible benefits across the ITT population analysis sets and subgroups of patients within the replicate efficacy studies? (Section 7.2.1)

FDA Response
The proposed revefenacin dose included in your NDA is at your discretion. Whether we agree with your proposed dose will be a review issue. Additionally, note that safety data from Study 0128 will be a key factor in the review of revefenacin.

Meeting Discussion
Theravance commented that doses ranging from 44 mcg to 350 mcg were evaluated. Based on the dose-response curve and data from 3-month studies, the 175 mcg dose showed benefit over the 88 mcg dose. As such, while Study 0128 is ongoing, based on the data from

the 3 month studies, Theravance plans to seek approval only for the 175 mcg dose. The sponsor asked whether the Division agrees with the dose selection, has any concerns with the analyses already conducted, or has any requirements or additional requests for analyses. FDA state that the sponsor may propose a dose at their discretion, but whether or not the FDA agrees is a review issue. However, FDA added that it is not clear that the 175 mcg dose provides a greater benefit than 88 mcg dose and that data from the safety study (0128) will be important in dosing determination. FDA also stated that the Agency had no specific concerns with the subgroup analyses already conducted and, at this time, had no specific requests/requirements for additional analyses. Theravance noted that a lower dose of an anticholinergic may not be as effective in severe COPD patients and that they believed the higher revefenacin dose had a more consistent effect in the more severe COPD patients and was part of the reason the higher dose was proposed. FDA advised that the sponsor should include this in their justification for proposing the higher dose (175 mcg) in the NDA submission. FDA concluded the discussion of dosing by stating that the determination of dosing could not be made until all data from the revefenacin program has been reviewed. Theravance asked whether a teleconference to discuss study 0128 safety data would be needed when data became available. FDA responded that a need for discussion is not anticipated. The sponsor asked if exploratory efficacy data comparing tiotropium would be helpful in dose selection. FDA replied that the Agency would be willing to review such data if submitted.

Question 8

Does the Agency agree that the efficacy data from the replicate Phase 3 studies (Study 0126 and Study 0127), and assuming consistent results from the long-term safety study (Study 0128), support approval of revefenacin for the proposed indication? (Section 7.2)

FDA Response

This is a review issue.

Meeting Discussion

Theravance proposed [redacted] (b) (4) **FDA noted that many COPD patients are on multiple concurrent COPD medications and that the choice of which medication is a matter of clinical practice.** [redacted] (b) (4) **Section 14 of the label may contain a description of the background medications used by patients in the clinical studies.**

Question 9

Does the Agency agree that the overall clinical program meet the Agency's requirements for a 505(b)(1) filing and appear adequate to support approval of an NDA for revefenacin? (Section 7)

FDA Response

Based on the information provided, the overall clinical program appears adequate to support filing and review of your NDA.

Meeting Discussion
This question was not discussed.

Question 10
Does the Agency agree that the clinical program supports the proposed labeling for revefenacin? (Section 4)

FDA Response
The clinical program appears sufficient to support the review of the proposed revefenacin labeling. Whether or not we agree with your proposed labeling is a review issue. We refer you to recently approved labels for anticholinergic products.

Meeting Discussion
This question was not discussed.

Regulatory/Administrative

Question 11
Does the Agency agree with the proposed NDA Content Plan? (Appendix 2)

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 12
Does the Agency agree that preparation of an environmental assessment for revefenacin is not required to be included in the NDA for revefenacin? (Section 9.3)

FDA Response
Adequacy of the environmental assessment information will be determined at the time of NDA review. We encourage you to follow our recommendations in our related guidance at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm070561.pdf.

Meeting Discussion
This question was not discussed.

Question 13
Does the Agency agree that a Risk Evaluation and Mitigation Strategies (REMS) is not warranted based on the results obtained to date of the replicate Phase 3 studies (Study 0126 and Study 0127) and assuming consistent results from the long-term safety study (Study 0128) for revefenacin? (Section 9.4)

FDA Response
At this time, we have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Meeting Discussion
This question was not discussed.

Question 14
Does the Agency agree that the proposed Drug Abuse Assessment is adequate to satisfy the requirements provided in FDA Guidance for Industry - Assessment of Abuse Potential of Drugs (January 2017) for approval of revefenacin? (Section 9.5)

FDA Response
Based on the nonclinical information provided in the IND submission and meeting package, it appears that the abuse potential for revefenacin is low (e.g., unlikely to cross the blood-brain barrier, negative Irwin test with rats). Further, based on previous nonclinical and clinical experience with approved drugs of this class (see drugs@fda), the abuse potential for an anti-cholinergic is considered low. A final assessment will be an NDA review issue (Refer to the recently published Guidance for Industry: *Assessment of Abuse Potential of Drugs* [January 2017]).

Meeting Discussion
This question was not discussed.

Question 15
To avoid repetitive submission of reports to the FDA, the Sponsor proposes to hyperlink references in the NDA to reports already submitted to the IND for revefenacin. Does the Agency agree with this proposal? (Section 9.1)

FDA Response
No, we do not agree. The NDA submission package should be complete and contain all information required for review.

Meeting Discussion
This question was not discussed.

Question 16
Given the brevity of the clinical development program, the Sponsor has provided the outline and organization of an integrated summary of safety and integrated summary of efficacy in Section 7.3.7 and Section 7.3.8, respectively, and requests the Agency allow the Sponsor to include these discussions in Module 2.7.3 and Module 2.7.4, respectively, in lieu of separate Integrated Summary of Efficacy and Integrated Summary of Safety documents in Module 5. Does the Agency agree to this request? (Section 8.1)

FDA Response
No, we do not agree. We expect that module 5 of the NDA submission will be fully populated and contain all the requisite safety and efficacy information.

Meeting Discussion
Theravance asked whether all studies should be included in the ISS. FDA responded that all studies needed to support the NDA should be included and full tables with the required subgroup analyses should be included in Module 5. Theravance proposed to include a full ISS with complete tables for all the required analyses in Module 5 except text will not be included. FDA responded that the key pieces can be contextualized sections 2.7.3 and 2.7.4, but the full tables are expected in Module 5.

Question 17
The Sponsor proposes to submit only those Case Report Forms for subjects who experienced serious or "of interest" adverse events. Does the Agency agree with this proposal? (Section 5.6)

FDA Response
In addition to Case Report Forms (CRF) for subjects who have experienced serious or "of interest" adverse events, also include CRFs for adverse events which resulted in discontinuation and those that were adjudicated as cardiovascular events. Note that additional Case Report Forms may be requested pending review of the NDA submission.

Meeting Discussion
This question was not discussed.

Question 18
As the results of the long-term safety study will not be available until mid-July, the Sponsor requests the Agency allow a follow-up Safety Pre-NDA meeting in mid-August to discuss these results as they relate to the potential approved dose for revefenacin. Does the Agency agree to this request? (Section 9.6)

FDA Response
No, we do not agree. Such a meeting would not be productive as how Study 0128 results affect dosing, and approval decisions would be a review issue.

Meeting Discussion
This question was not discussed.

3. ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. FDA advised the sponsor to submit a complete NDA application.

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.

In addition, we note that a chemistry pre-submission meeting is scheduled for May 9, 2017. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PREA REQUIREMENTS

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

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.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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.

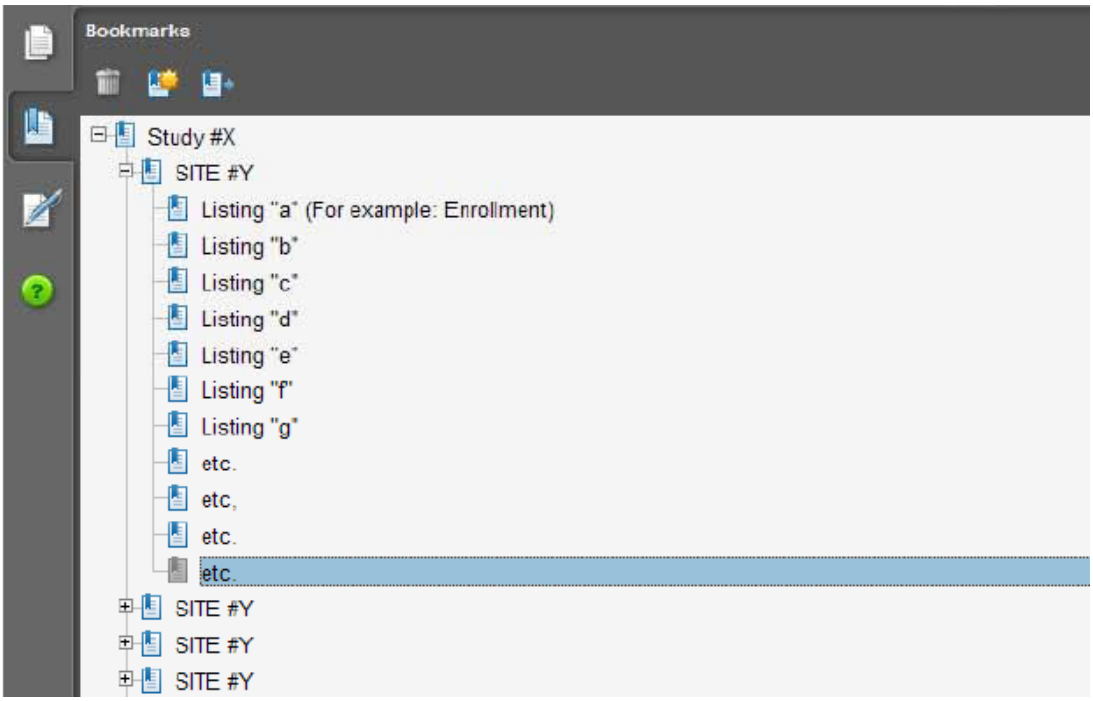
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere 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. ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

5. ACTION ITEMS
There were no action items.

6. ATTACHMENTS AND HANDOUTS
There were no attachments or handouts for the meeting minutes.

Reference ID: 4348407

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

/s/

PHUONG N TON
04/12/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119840

MEETING MINUTES

Theravance Biopharma R&D, Inc.
c/o Theravance Biopharma US, Inc.
901 Gateway Boulevard
South San Francisco, CA 94080

Attention: Dara Wambach, MA
Director, Regulatory Affairs

Dear Ms. Wambach:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TD-4208.

We also refer to the meeting between representatives of your firm and the FDA on December 8, 2014. The purpose of the meeting was to discuss the proposed phase 3 development 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 me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
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:	December 8, 2014; 2:00 – 3:00 PM EST
Meeting Location:	White Oak Building 22, Conference Room 1309
Application Number:	IND 119840
Product Name:	TD-4208
Indication:	Chronic Obstructive Pulmonary Disease (COPD)
Sponsor Name:	Theravance Biopharma R&D, Inc.
Meeting Chair:	Badrul A. Chowdhury
Meeting Recorder:	Nina Ton

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sally Seymour, MD, Deputy Director for Safety, DPARP, ODEII
Banu Karimi-Shah, MD, Clinical Team Leader, DPARP
Peter Starke, MD, Acting Associate Director for Labeling, DPARP
Tony Durmowicz, MD, Clinical Team Leader, DPARP
Robert Lim, MD, Clinical Reviewer, DPARP
Marcie Wood, PhD, Pharmacology/Toxicology Team Leader, DPARP
Nikunj S. Patel, PhD, Pharmacology/Toxicology Reviewer, DPARP
Satjit Brar, PhD, PharmD, BS, Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Yunzhao Ren, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
David Petullo, MS, Biostatistics Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
Robert Abugov, PhD, Biostatistics Reviewer, Division of Biometrics II, OB
Craig Bertha, PhD, Acting Team Leader, Division of New Drug Quality Assessment III, Office of New Drug Quality Assessment (ONDQA)
Robert Pratt, PharmD, Risk Management Analysts, Division of Risk Management, Office of Surveillance and Epidemiology
Nina Ton, PharmD, Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Theravance Biopharma US, Inc.
Brett Haumann, MD, MBA, Senior Vice President, Clinical Development
Rebecca Coleman, PharmD, Vice President, Regulatory and Quality
Michael Conner, DVM, Vice President, Nonclinical Safety Assessment
Edmund Moran, PhD, Vice President, Research and Development Project Leader
Christopher Barnes, PhD, Director, Biometrics
David Bourdet, PhD, Director, Clinical Pharmacology and DMPK
Dara Wambach, MA, Director, Regulatory Affairs

Mylan
Jon Ward, Vice President, Global Clinical Development Leader, Mylan Global Respiratory Group
Andrea Miller, SVP and Head, Global Complex Products Operations
Michelle Lee-Bourner, Senior Director, Global Respiratory Regulatory Lead

1. BACKGROUND

Theravance submitted an End of Phase 2 meeting request dated October 1, 2014, to the Division of Pulmonary, Allergy, and Rheumatology Products. The purpose of the meeting is to discuss the proposed phase 3 development program for TD-4208, a long-acting, antimuscarinic agent (LAMA) indicated for maintenance treatment of bronchoconstriction associated with chronic obstructive pulmonary disease (COPD), (b) (4) Upon review of the meeting package, FDA provided preliminary responses to Theravance's questions on December 3, 2014. Dara Wambach, Theravance's Director, Regulatory Affairs, communicated to the Division via email dated December 5, 2014, that the Sponsor requested to focus the meeting discussion to Questions 4, 5, and 7, and also seek clarification on Questions 6, 2, 9, and 10. The Sponsor's questions are in *italics*, the FDA's responses are in normal font, and the meeting discussion is in **bold**.

2. DISCUSSION

Question 1
Does the package of completed and proposed nonclinical studies support the marketing application for TD-4208?

FDA Response
The scope of the completed and proposed nonclinical studies appears generally adequate to support a marketing application for TD-4208; however, we have the following comments regarding your reproductive toxicology studies:

Results of fertility studies should be submitted before the initiation of large scale or long duration trials (Phase 3). Refer to ICH M3(R2) Guidance for the requirement and timing of fertility and reproductive toxicology studies.

Determination of the adequacy of reproductive toxicology studies conducted by the inhalation route will be a review issue. Specifically, if sufficient systemic exposure is not achieved via the inhalation route, to ensure proper characterization of reproductive risk, studies by an alternate route of administration (e.g., subcutaneous) may be requested.

Meeting Discussion
This question was not discussed.

Question 2
Does the Agency agree with the outlined Clinical Pharmacology Studies Plan?

FDA Response
Your proposed clinical pharmacology plan is reasonable. However, you are encouraged to conduct the thorough QT study prior to the initiation of the phase 3 study. In addition, drug-drug interaction studies may be needed once the metabolizing enzyme(s) of TD-4208 are elucidated.

Meeting Discussion
Theravance asked FDA to clarify the timing of the QT study. FDA responded that QT study is usually recommended prior to Phase 3. The Sponsor commented that TD-4208 demonstrated a low potential for hERG channel inhibition. Moreover, there was absence of cardiac effects in dogs given TD-4208 intravenously at doses up to 10 µg/kg and there were no remarkable ECG changes from the Holter data collected from 334 subjects from study 0117. Therefore, Theravance plans to conduct the thorough QT study in parallel to phase 3 studies, which also include Holter monitoring.

FDA commented that the Sponsor's approach does not appear unreasonable and it is at their own risk to conduct the thorough QT study in parallel to the phase 3 studies.

Question 3
Does the Agency agree with the proposed dose selection and dose interval for the Phase 3 studies?

FDA Response
Your proposal to carry the 88mcg and 175mcg once daily doses to Phase 3 appears reasonable.

Meeting Discussion
This question was not discussed.

Question 4
Does the Agency agree that the proposed study population, study design and study endpoints for the replicate Phase 3 12-week Efficacy Studies (Studies 0126 and 0127) are supportive of an NDA application?

FDA Response

No, we do not necessarily agree. We have the following comments regarding your phase 3 program:

- To support efficacy and safety, the study population in your phase 3 trials should be reflective of the target population. Given the characteristics of this product, it is likely that the target population would be older, have multiple co-morbidities, and be on standard of care COPD medications [e.g., long-acting beta-agonists (LABA) and LABA/inhaled corticosteroids (ICS)]. (b) (4)

- Given the immediate decrease in FEV_1 following administration, we recommend in your phase 3 trials that TD-4208 be dosed in the morning.

- For labeling purposes, include in your 12-week phase 3 trials, 24-hour serial spirometry measurements in a subset of patients.

- We note that you have included the SGRQ-C and EXACT scores as secondary endpoints. While the choice of secondary endpoints is at your discretion, (b) (4) Also note that while SGRQ has been used in product labeling, (b) (4) Consider including SGRQ and clinically defined exacerbations as secondary endpoints.

- We recommend that the phase 3 studies include a specific safety analysis for administration related bronchospasm.

Meeting Discussion

(b) (4)

(b) (4)

Question 5

Does the Agency agree that the proposed study population, study design and study endpoints for the Phase 3 52-week Safety Study (Study 0128) are supportive of an NDA application?

FDA Response

No, we do not agree for the following reasons:

- Study 128 includes a (b) (4)
- (b) (4)
- Note that this study would only support long-term safety for the 88mcg dose if no safety signal were identified for the 175mcg dose.

Meeting Discussion

Theravance proposed (b) (4) **and to include 1500 patients in the safety trial in order to retain 450-500 patients on active treatment at month 12. FDA**

agreed to this proposal provided that the Sponsor included the appropriate patient population (see Question 4 response and discussion). The Sponsor also proposed to add 88mcg as a third arm and use tiotropium Handihaler as a comparator. Theravance added that there will be 250 patients in each group of the 88mcg and 175 doses and that the study will be open-label. The Sponsor asked if the open-label approach was acceptable. FDA stated that it was.

Question 6
Does the Agency concur with the proposed CV monitoring plans presented in the protocol synopses?

FDA Response
While study 117 included Holter monitoring in a subset of patients, Holter monitoring was performed in a population which does not reflect the target population, i.e., those who would also be receiving other drugs with cardiac effects (see responses to Questions 4 and 5 above). As such, we recommend performing Holter monitoring in a subset of patients in your phase 3 program.

Meeting Discussion
Theravance proposed to include Holter monitoring (b) (4) in the safety study. FDA did not comment on the specific numbers needed, but referred the Sponsor to recent drug approvals with regards to the numbers and time-points for Holter monitoring in phase 3 studies.

Question 7
Does the Agency agree that the size and nature of the overall patient safety database for TD-4208 is supportive of an NDA application?

FDA Response
No, we do not agree. See our response to Question 5 above.

Meeting Discussion
See Questions 4 and 5 meeting discussion.

Question 8
Does the Agency agree with the statistical testing hierarchy of the study endpoints in Studies 0126 and 0127?

FDA Response
You propose an ordered hierarchy to control Type I error using the truncated Hochberg procedure. However, the Hochberg procedure may be sensitive to lack of independence between endpoints. Instead, use a truncated Holm or Bonferroni procedure.

Meeting Discussion
This question was not discussed.

Question 9
Does the Agency agree with the method of handling missing data for the primary endpoint in Studies 0126 and 0127?

FDA Response
We disagree. (b) (4) Instead, primary analyses for all endpoints should incorporate data collected from all randomized patients, regardless of whether they discontinue initially assigned randomized treatment and regardless of whether or not they actively maintain contact with their investigational site. To ensure unbiased estimates of treatment efficacy, establish consistent and effective data collection from patients who withdraw from treatment or who fail to actively maintain contact with the investigator. Specify in your protocol plans to contact withdrawn or missing patients, e.g., number of telephone calls, day of week and time of such calls, which calls will be made to work, home, or cell phone, offers for transportation to clinic for spirometry evaluations if patient is unable to drive, etc., and enlist continued participation by including on the patient consent form information concerning the importance of continued data collection after withdrawal from randomized treatment.

Presentation of results with missing data will be a review issue. Your sensitivity analyses should include "tipping point" multiple imputation analyses which include the possibility that patients randomized to TD-4208 with missing data have worse outcomes than patients on placebo while patients randomized to placebo with missing data have better outcomes than patients on TD-4208.

Ensure that your analysis datasets include a column or columns which clearly indicate whether each observation was imputed, missing, observed while the patient was on randomized treatment, or observed after the patient discontinued randomized treatment.

Meeting Discussion
Theravance confirmed that their sensitivity analyses will include tipping point analyses but asked FDA to clarify a clinically reasonable tipping point. FDA did not identify an unacceptable tipping point and advised the Sponsor that if missing data is minimized, the tipping point analysis, while still recommended, would be unlikely to substantially impact the review.

Post-meeting Addendum
If only a small percentage data is missing, the tipping point will be so large as to be considered implausible.

Question 10

(b) (4)

FDA Response

(b) (4)

Meeting Discussion

(b) (4)

Question 11

Does the Division have any comment or preliminary advice regarding the Sponsor's plan to propose in its PSP that the PREA requirements for pediatric studies be waived for the COPD indication for TD-4208?

FDA Response

This approach is acceptable. Also refer to PREA Requirements below.

Meeting Discussion

This question was not discussed.

3. ADDITIONAL INFORMATION

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

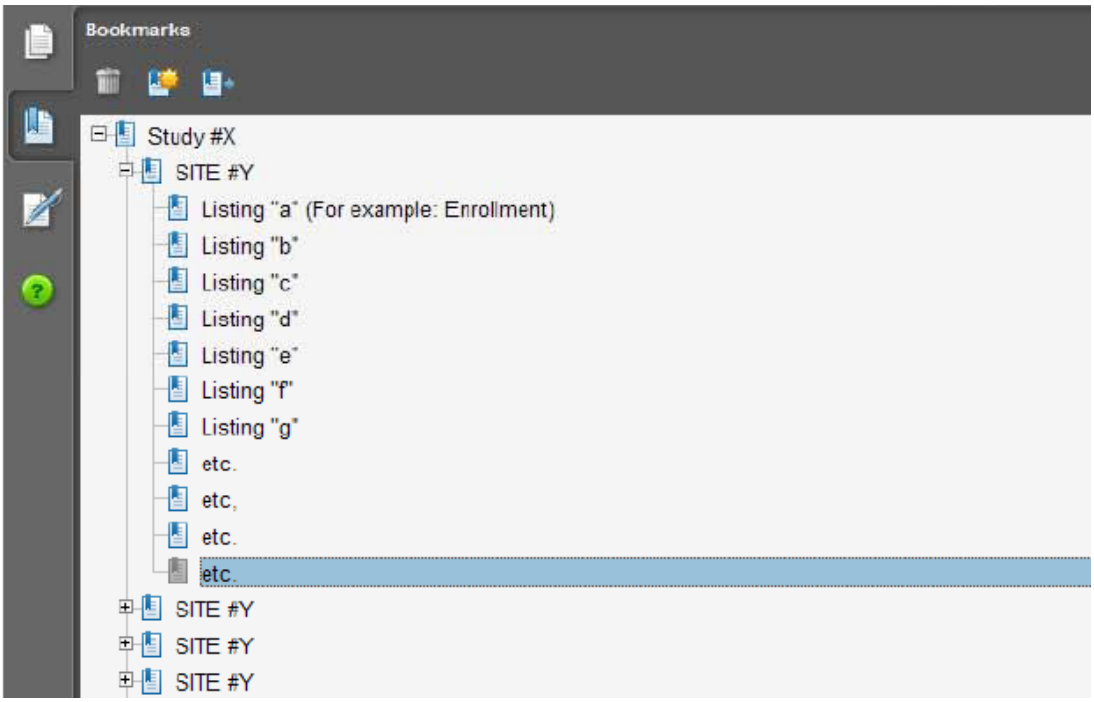
maintained. As above, this is the actual physical site where documents would be available for inspection.

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

4. ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

5. ACTION ITEMS
There were no action items.

6. ATTACHMENTS AND HANDOUTS
There were no attachments or handouts for the meeting minutes.

Reference ID: 4348407

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

/s/

PHUONG N TON
12/24/2014