CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208855Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106100

**MEETING REQUEST-
WRITTEN RESPONSES**

Eli Lilly and Company
Attention: Guy C. Ruble, PharmD, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center, Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Ruble:

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

We also refer to your submission dated May 10, 2017, containing a Type B meeting request. The purpose of the requested meeting was to obtain feedback on the content and format of your proposed MONARCH 3 NDA.

Further reference is made to our Meeting Granted letter dated June 8, 2017, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your May 10, 2017 background package.

If you have any questions, call Janice Kim, Regulatory Project Manager at (301) 796-9628.

Sincerely,

{See appended electronic signature page}

Janice Kim, PharmD, MS
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Application Number:	IND 106100
Product Name:	abemaciclib
Indication:	hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer in combination with aromatase inhibitors as initial endocrine-based therapy in postmenopausal women
Sponsor/Applicant Name:	Eli Lilly and Company
Regulatory Pathway:	505(b)(1)

1.0 BACKGROUND

The purpose of this Type B Pre-NDA meeting request is to discuss the planned submission of the MONARCH 3 study interim progression free survival (PFS) results for review and approval of abemaciclib for patients with hormone receptor positive (HR+), HER2 negative advanced or metastatic breast cancer who have not received prior endocrine therapy for metastatic disease. The planned submission date is on or before August 11, 2017 and the priority review is requested.

Abemaciclib is a small molecule inhibitor of CDK4 and CDK6. CDK 4 and 6 are enzymes catalyzed by D-type cyclins that phosphorylate retinoblastoma protein (Rb) to allow progression through the cell cycle. In breast cancer, Cyclin D1/CDK4 complexes contribute to tumor growth through phosphorylation of Rb. Cyclin D3/CDK6 is associated with the maturation of hematopoietic stem cells within the bone marrow. In early development of abemaciclib, this agent has demonstrated single agent antitumor activity and decreased dose limiting neutropenia when compared to other CDK 4/6 inhibitors in the class. It is hypothesized that this is due to abemaciclib being more selective for Cyclin D1/CDK4 as compared to Cyclin D3/CDK6. In vitro studies in HR+ breast cancer cell lines demonstrated that single agent abemaciclib with continued target inhibition prevented rebound of Rb phosphorylation and cell cycle reentry that lead to senescence and apoptosis. In vivo studies demonstrated that abemaciclib dosed continuously at clinically relevant concentrations in xenograft models resulted in tumor inhibition. In HR+ breast cancer cell lines, abemaciclib combined with an anti-estrogen such as fulvestrant or tamoxifen is synergistic. The combination of abemaciclib with fulvestrant effectively blocks breast cancer cell line progression through cell cycle arrest, promotion of senescence, apoptosis, and alteration in metabolism.

Results of MONARCH 1, phase 2, multicenter, nonrandomized, open-label study to evaluate the antitumor activity of abemaciclib for patients with HR+, HER2- mBC who have progressed

despite prior endocrine therapy and had received 1-2 prior chemotherapy regimens in the metastatic setting demonstrated a durable investigator-assessed overall response rate (ORR) of 19.7%. MONARCH 2 is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study evaluating abemaciclib in combination with fulvestrant for women with HR+, HER2- locally advanced or metastatic breast cancer who have progressed following endocrine therapy and demonstrated a statistically significant improvement in investigator assessed progression-free survivial (PFS) of 16.4 months vs. 9.3 months for fulvestrant alone (hazard ratio 0.553, 95% CI 0.449, 0.681, $p<0.0000001$). The most frequent grade 3/4 TEAEs in the abemaciclib plus fulvestrant group included neutropenia (26.5%), diarrhea (13.4%, all grade 3); anemia (7.2%), and leukopenia (8.8%). On May 5, 2017, a New Drug Application was submitted for review to FDA for abemaciclib based on the results of each of these studies.

MONARCH 3 is a randomized, double-blind, placebo-controlled study for patients with HR+, HER2- advanced or metastatic breast cancer who have not received prior endocrine therapy for their metastatic disease. The primary endpoint was improvement in investigator-assessed PFS abemaciclib+NSAI median PFS not reached vs. placebo and NSAI PFS of 14.7 months (hazard ratio 0.543, $p=0.000021$) at the preplanned interim analysis. Based on this, the Sponsor plans to submit an NDA for review of these results on or before August 11, 2017 and requests priority review of this application.

Regulatory History

- September 15, 2009 Investigational New Drug (IND) 106100 for abemaciclib submitted to the Division of Oncology Products 1.
- October 16, 2009, the first human dose study, I3Y-MC-JPBA, was initiated.
- December 18, 2013 Type B EOP2 meeting to discuss the breast cancer development program including MONARCH 1, 2 and 3 studies.
- August 7, 2015 Breakthrough Therapy Designation (BTD) granted based on the breast cancer cohorts from the JPBA study.
- August 24, 2015 Type B EOP2 meeting for monarcHER study (HR+, HER-2+ mBC)
- October 5, 2015 BTD granted for abemaciclib in patients with refractory HR+ advanced or mBC.
- October 9, 2015 Fast Track designation requested.
- July 8, 2015 Pediatric Research Equity Act (PREA) Waiver of abemaciclib was granted
- May 5, 2017 New Drug Application 208716 submitted for abemaciclib as a single agent in refractory HR+ metastatic breast cancer based on the MONARCH 1 data and in combination with fulvestrant for patients with HR+ locally advanced or metastatic breast cancer who have progressed on initial endocrine therapy.

In the proposed NDA submission, the Sponsor proposes to submit the application and to cross reference the data from MONARCH 1 and MONARCH 2 in support of their application. The summary of clinical efficacy will focus on the Phase 3 registration studies, MONARCH 3 and MONARCH 2 with supporting data from the Phase 2 MONARCH 1 study. The Integrated Summary of Efficacy (ISE) will cross reference the Summary of Clinical Efficacy and no additional information will be provided from an integrated efficacy perspective.

The Summary of Clinical Safety data will focus on safety data from MONARCH 3, MONARCH 2 and MONARCH 1 studies with supportive safety data analyses from completed studies of abemaciclib as a single agent and in combination with endocrine therapies. The Integrated Safety Summary will cross reference the Summary of Clinical Safety and no additional information will be provided from an ISS perspective.

The 4-month safety update will be based on an updated safety review of the ongoing patients in the MONARCH 3 study with a proposed cutoff date on or before August 11, 2017. The update will be provided 120 days after the date of submission, that is no later than December 11, 2017. The Sponsor proposes this safety update be based on a safety update report with datasets not provided but made available upon request. The sponsor will provide narratives and case report forms (CRFs) for all notable patients in the 4-month safety update (that is, any patient who died on study or within 30 days of last study dose, discontinued treatment due to an AE, or had a suspected unexpected serious adverse reaction). If an update to the proposed labeling is necessary based on these updated safety data, then revised labeling will also be included.

The Sponsor anticipates performing the final PFS analysis in Q4 2017. They expect to submit the following update:

1. A CSR addendum to the MONARCH 3 clinical study report summarizing the final PFS, ORR, OS, and safety with patient narratives for notable patients
2. Corresponding study level datasets (SDTM and AdaM)
3. Updated efficacy and safety for MONARCH 3 in the proposed labeling (USPI, PPI)

2.0 QUESTIONS AND RESPONSES

Question 1: Does FDA agree that the Table of Contents (TOC) of the proposed MONARCH 3 NDA for abemaciclib and the proposal for cross-referencing the combined MONARCH 1 and MONARCH 2 NDA (NDA 208716) provides the appropriate content and organizational structure to support FDA's review of the MONARCH 3 NDA for regular approval?

FDA Response to Question 1: Yes.

Question 2: Does FDA agree that the Module 2 CTD summaries for 2.5, 2.7.3 and 2.7.4 prepared for the EU marketing application which includes a summary of the MONARCH 3 study as well as MONARCH 2 and MONARCH 1 studies would be acceptable to include in the MONARCH 3 NDA?

FDA Response to Question 2: Yes.

Question 3: Does FDA agree with the proposal for updated safety information to be provided in the 4 month safety update?

FDA Response to Question 3: Yes. You can also consider providing a 3-month safety update.

Question 4: Lilly anticipates submitting the MONARCH 3 NDA on or before 11 August 2017 and performing the final analysis of PFS in Q4 2017. Lilly would like FDA to comment on the latest time that the final PFS data from the MONARCH 3 study can be incorporated into the NDA during the review period without triggering a major amendment and be included in the final approved label.

FDA Response to Question 4: The latest time that the "updated" PFS data from the MONARCH 3 study can be incorporated into the NDA during the review period without triggering a major amendment is by the 90/120-day safety update. Whether this updated PFS data can be included in the final approved label will be a review issue.

Similar to MONARCH 2 NDA, please include an updated analysis of OS at the safety update. Please allocate a nominal alpha to the OS analysis.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE 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.

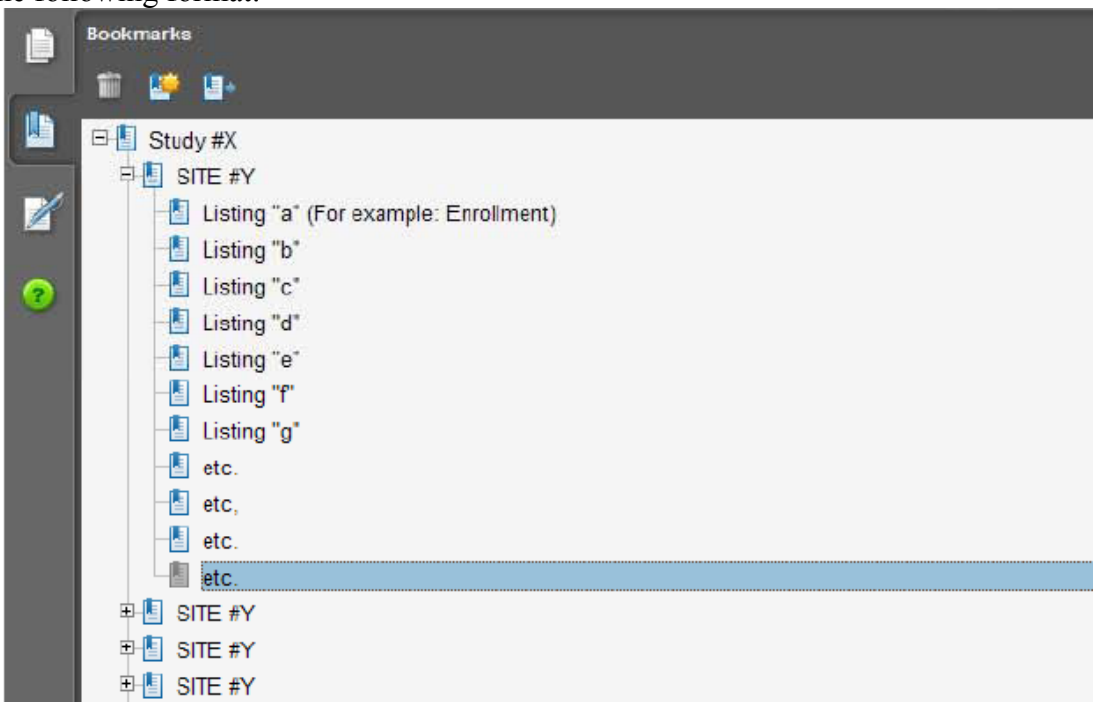
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

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

/s/

JANICE H KIM
07/07/2017

LALEH AMIRI KORDESTANI
07/07/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106100

MEETING MINUTES

Eli Lilly and Company
Attention: Guy C. Ruble, PharmD, RAC
Director, Global Regulatory Affairs-US
Lilly Corporate Center, Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Ruble:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for abemaciclib (LY2835219).

We also refer to the telecon between representatives of your firm and the FDA on August 24, 2015. The purpose of the meeting was to discuss the future clinical development of abemaciclib in HR+/HER2+ metastatic breast cancer (mBC) (monarcHER; Study JPBZ), have follow-up discussion from the EOP2 meeting held on December 18, 2013, related to the phase 3 mBC studies MONARCH 2 and MONARCH 3, (b) (4)

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

If you have any questions, please contact me, Regulatory Health Project Manager at (301) 796-9608 or Tracy.Cutler@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tracy Cutler, MPH, CCRP, CIP
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

Amy McKee, MD
Clinical Team Leader
Division of Oncology Products 1
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:	End of Phase 2 follow-up
Meeting Date and Time:	August 24, 2015; 3:00 pm – 4:00 pm
Meeting Location:	Teleconference
Application Number:	IND 106100
Product Name:	Abemaciclib (LY2835219)
Indication:	Breast Cancer
Sponsor/Applicant Name:	Eli Lilly and Company
Meeting Chair:	Amy McKee, MD
Meeting Recorder:	Tracy Cutler, MPH, CCRP, CIP

FDA ATTENDEES
Geoffrey Kim, MD, Director, DOP1
Amy McKee, MD, Clinical Team Leader, DOP1
Suparna Wedam, MD, Medical Officer, DOP1
Gwynn Ison, MD, Medical Officer, DOP1
Julia Beaver, MD, Medical Officer, DOP1
Chana Weinstock, MD, Medical Officer, DOP1
Harpreet Singh, MD, Medical Officer, DOP1
Erik Bloomquist, PhD, Biostatistics Reviewer, DBV
Haw-Jyh Chiu, PhD Pharmacology/Toxicology Reviewer, DHOT
Eias Zahalka, PhD, MBA, Pharmacology/Toxicology Reviewer DHOT
Frances Fahnbullah, PharmD, RPh, Safety Regulatory Project Manager, OSE
Tracy Cutler, MPH, Regulatory Health Project Manager, DOP1

SPONSOR ATTENDEES
Colleen Mockbee, RPh, Global Product Team Leader, Oncology
Ian Smith, MD, Senior Medical Director, Oncology
Martin Frenzel, PhD, Research Scientist, Statistics
Paul Cornwell, PhD, Senior Research Scientist, Toxicology
William Breslin, PhD, Senior Research Advisor, Toxicology
Guy Ruble, PharmD, Director, Global Regulatory Affairs – US

1.0 BACKGROUND

Abemaciclib is an oral, selective, and potent small molecule cyclin-dependent kinases (CDKs) 4 and 6 (CDK4 and CDK6) inhibitor with antitumor activity within multiple preclinical pharmacology models. Preliminary data from the ongoing Study I3Y-MC-JPBA (Study JPBA)

indicates that abemaciclib demonstrates, for women with hormone receptor positive (HR+) metastatic breast cancer (mBC), an objective response rate (ORR) of 33% and a clinical benefit rate (CBR) of 61%.

The specific objectives for the meeting are to:

- Discuss new clinical development in HR+, HER2+ mBC, Study JPBZ (monarcHER), and its acceptability, as designed, for accelerated approval.
- Review the status of ongoing breast cancer studies and estimated dates for top-line data results.
    - MONARCH 1 – Single-agent abemaciclib
    - MONARCH 2 – Discuss with the Agency the progression-free survival (PFS) interim analysis and the statistical boundary being utilized
    - MONARCH 3 – Discuss with the Agency the PFS interim and pooled overall survival (OS) analysis for MONARCH 2 and MONARCH 3
    - neoMONARCH
- Depending on results Lilly is considering conducting additional early stage breast cancer studies. (b) (4)

FDA sent Preliminary Comments to Eli Lilly and Company on August 20, 2015.

2.0 DISCUSSION

2.1 Accelerated Approval – HR+, HER2+mBC

Question 1: Does FDA agree that if the results from Study JPBZ (monarcHER) are positive, that is a clinically and statistically significant improvement in PFS favoring an abemaciclib arm over the control arm, Study JPBZ could support an accelerated approval for the proposed indication of (b) (4) *(Section 7.1.4.1)*

FDA Response: This will be a review issue based on the benefit-risk profile for abemaciclib. Accelerated approval requires the demonstration of "meaningful therapeutic benefit to patients over existing treatments" and that marketing approval may be granted if the drug product has an effect on a surrogate endpoint that is reasonable likely to predict clinical benefit. It is unlikely that the proposed improvement of median PFS by (b) (4) months will be considered to have meaningful therapeutic benefit. Additionally, controlling type I error at the one-sided 10% alpha level is unlikely to provide appropriate type I error control for a registration trial. Thus, we consider this an exploratory study.

Sponsor Response: Lilly acknowledges FDA's comment and would like to clarify that the study will be positive based on a one-sided alpha of .10, however for regulatory purposes the tests will be evaluated at a one-sided alpha level of .025 (page 26 of the briefing document).

Meeting Discussion: **No discussion took place during the meeting.**

Question 2: Does FDA have any comments on the use of trastuzumab plus physician's choice single-agent standard of care systemic therapy (i.e., single agent chemotherapy or endocrine therapy) is an appropriate control arm? *(Section 7.1.4.1)*

FDA Response: Single agent standard of care should be limited to chemotherapy or endocrine therapy. In addition, we recommend you provide a limited list of 3 or 4 single agents that a physician may choose from.

Sponsor Response: Lilly acknowledges FDA comment and will take this into consideration as the protocol is finalized.

Meeting Discussion: **No discussion took place during the meeting.**

Question 3: Does FDA agree that the inclusion/exclusion criteria are acceptable and identify a well-defined patient population that could support labeling for the proposed HR+, HER2+ mBC indication? *(Section 7.1.5.1)*

FDA Response: The eligibility criteria appear acceptable.

Sponsor Response: No further comment.

Meeting Discussion: **No discussion took place during the meeting.**

Question 4: Lilly proposes not to include central confirmation of HER2 status for study eligibility since all study arms contain trastuzumab and abemaciclib does not specifically target the HER2 receptor. Does FDA agree that central confirmation of HER2 status is not required in the monarcHER study which may support an accelerated approval for the proposed HER2+ indication? *(Section 7.1.5)*

FDA Response: Central confirmation of HER2 status is not needed.

Sponsor Response: No further comment.

Meeting Discussion: **No discussion took place during the meeting.**

2.2 Metastatic Breast Cancer

Question 5: Lilly is proposing to amend the interim analysis plans for MONARCH 2 and MONARCH 3. Does FDA agree with the proposed change to the statistical boundary for the interim PFS analysis of each study? *(Section 7.3)*

FDA Response: We do not recommend interim analysis for PFS. However, if you choose to perform an interim analysis at 70% of planned PFS events, you should adjust your efficacy boundary so that the minimum hazard ratio to declare statistical significance at

the interim analysis would be 0.56. Prior to initiating any change to the SAP, please submit the amendment to the Agency for review.

Upon receipt of the preliminary comments, the Sponsor inquired as to whether the hazard ratio was listed correctly. The following clarification was provided via email on August 21, 2015 by the Agency:

In our meeting preliminary comments, the HR=0.56 was the correct level. The advice we provided is consistent with that given to other sponsors developing drugs in the same class for the same indication.

Sponsor Response: Lilly thanks FDA for the clarification, acknowledges FDA's recommendations and will take it under advisement.

Meeting Discussion: **No discussion took place during the meeting.**

Question 6: Although the data monitoring committees (DMCs) for MONARCH 2 and MONARCH 3 have been instructed not to stop the studies for overwhelming efficacy (successfully crossing the interim PFS statistical boundary), in the event the DMC does recommend stopping for efficacy and crossing control patients over to the investigational arm, Lilly would consult with the FDA should Lilly agree with the DMC recommendation. Can FDA comment on the scenario above as it may impact the final PFS analysis? *(Section 7.3)*

FDA Response: Since the early stopping of a trial may influence the review process, we recommend you consult with us before stopping a trial early.

Sponsor Response: Lilly will plan to meet with FDA should the DMC recommend early stopping based on overwhelming efficacy in the MONARCH 2 or MONARCH 3 studies before Lilly decides to stop either of the studies.

Meeting Discussion: **No discussion took place during the meeting.**

Question 7: Lilly is proposing allocating some of the alpha from MONARCH 2 and MONARCH 3 towards a pooled OS analysis for these studies. Does FDA agree that if the result of this analysis is statistically significant, and not driven solely by one of the studies, (b) (4)

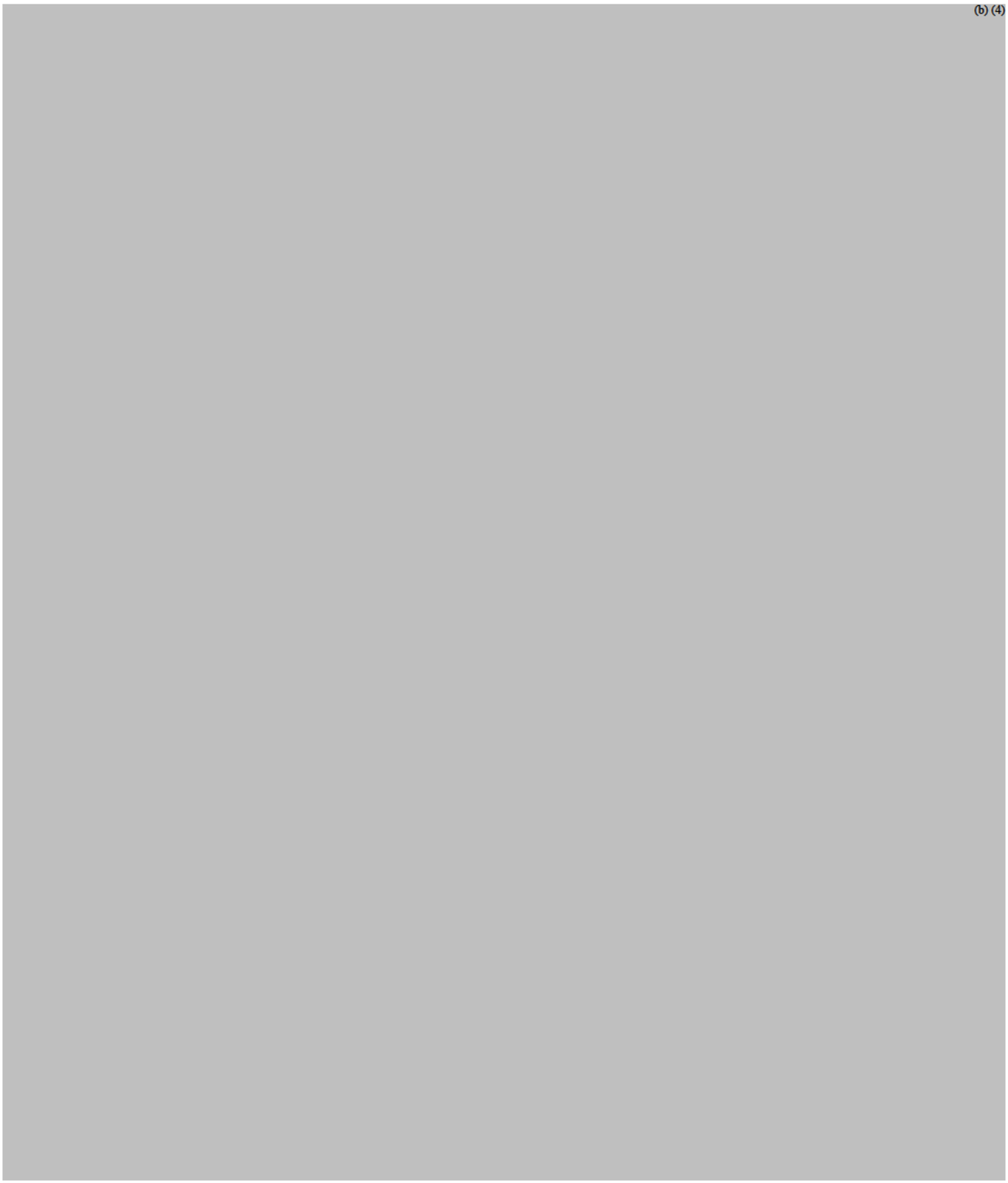
FDA Response: No. (b) (4)

Sponsor Response: Lilly acknowledges FDA's comments. Lilly agrees that the literature supports that endocrine sensitive and endocrine resistant populations have different prognoses. However, the purpose of the pooled OS analysis is to demonstrate that abemaciclib provides an OS benefit in a broad population of patients eligible for

endocrine therapy. To account for the heterogeneity of the analysis population, the analysis will be stratified by study and each study's individual stratification factors.

Meeting Discussion: **No discussion took place during the meeting.**

(b) (4)



(b) (4)

3.0 OTHER IMPORTANT MEETING LANGUAGE

3.1 Data Standards for Studies

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]". FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing

application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

3.2 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 the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

3.3 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.

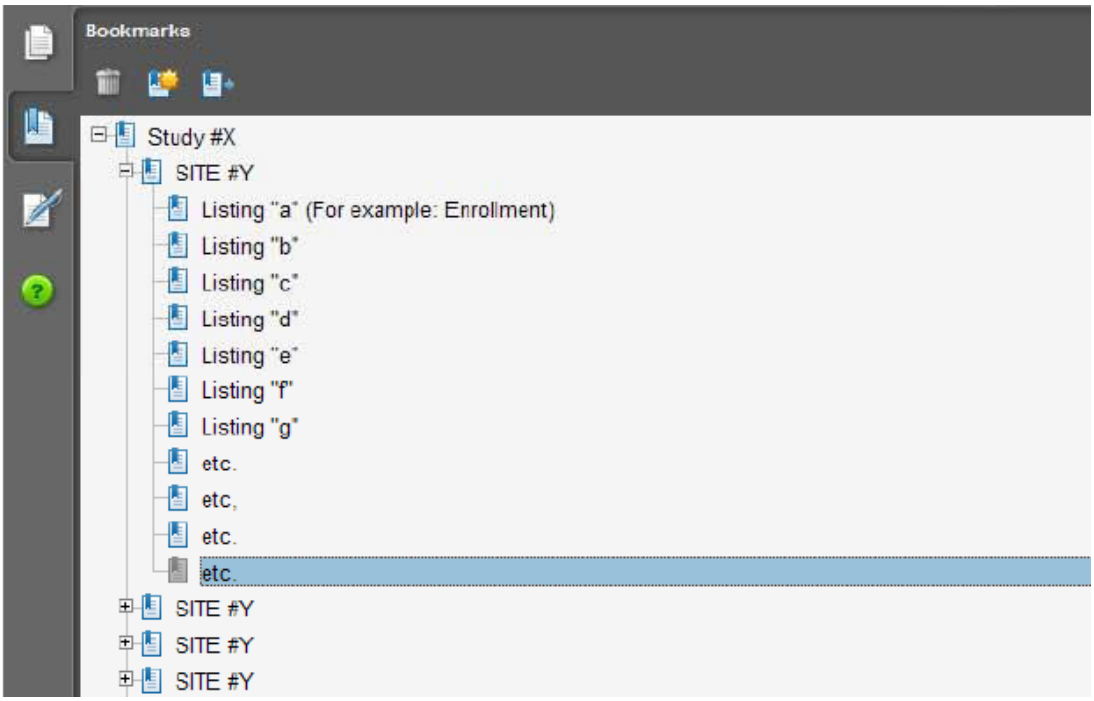
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, 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 identified that required further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor response (received via email August 22, 2015)

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

/s/

TRACY L CUTLER
09/08/2015

AMY E MCKEE
09/08/2015