CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208716Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208716 SUPPL # HFD #

Trade Name Verzenio

Generic Name abemaciclib

Applicant Name Eli Lilly

Approval Date, If Known September 29, 2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the

NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets

"clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support

the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Janice Kim, PharmD, MS
Title: Regulatory Project Manager
Date: September 28, 2017

Name of Division Director signing form: Julia Beaver, MD
Title: Acting Director, DOP1

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
09/28/2017

JULIA A BEAVER
09/28/2017

Debarment Certification Statement

NDA Application No. 208716

Drug Name: Abemaciclib

Eli Lilly and Company hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Sincerely,

ELI LILLY AND COMPANY

SAFE-BioPharma

Digitally signed by Guy C Ruble
DN: c=US, o=Eli Lilly, ou=69386d37-ef35-431d-a74d-ae7a96122b41, cn=Guy C Ruble
Reason: I agree to the terms defined by the placement of my signature on this document
Date: 2017.05.01 11:23:17 -04'00'
Adobe Acrobat version: 11.0.19

Guy C. Ruble, Pharm.D., RAC
Director
Global Regulatory Affairs-US

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208716 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Verzenio Established/Proper Name: abemaciclib Dosage Form: tablets		Applicant: Eli Lilly Agent for Applicant (if applicable):
RPM: Janice Kim, PharmD, MS		Division:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is January 5, 2018	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received N/A
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): cyclin dependent kinase 4 and 6 inhibitor
(confirm chemical classification at time of approval)

☒ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☒ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval -9/28/2017
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	6/8/2017 5/23/2017
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 7/21/2017 DMEPA: ☐ None 7/25/2017 DMPP/PLT (DRISK): ☐ None 8/28/2017 OPDP: ☐ None 9/1/2017 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None 8/17/17 Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing Review: July 12, 2017 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC September 6, 2017 If PeRC review not necessary, explain: _____	Full Waiver
❖ Breakthrough Therapy Designation	☐ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	10/5/2015
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	9/23/2015
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	N/A
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	Yes
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	None
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg None
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 4/9/2017, 3/1/2016
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 8/24/2015, 3/2015, 12/19/13
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 8/3/2017
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 9/11/2017
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	CMC EOP2 5/20/2015
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 9/28/2017 (Multidisciplinary Review)
Division Director Summary Review *(indicate date for each review)*	☐ None 9/28/2017 (Multidisciplinary Review)
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 9/28/2017 (Multidisciplinary Review)
PMR/PMC Development Templates *(indicate total number)*	☐ None 1 PMR, 2 PMC

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review See Multidisciplinary review dated 9/28/2017
• Clinical review(s) *(indicate date for each review)*	9/28/2017 (Multidisciplinary Review)
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	9/28/2017 (Multidisciplinary Review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 9/26/2017
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 9/28/2017 (Multidisciplinary Review)
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 9/28/2017 (Multidisciplinary Review)
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 9/28/2017 (Multidisciplinary Review)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☐ None Refer to Integrated Quality Assessment Review 9/7/2017, 9/15/2017, 9/20/2017
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None Refer to Integrated Quality Assessment Review 9/7/2017, 9/15/2017, 9/20/2017
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 9/22/2017, 9/20/2017, 9/15/2017, 9/7/2017, 8/17/2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	9/15/2017
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☒ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	Done
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	Done

---

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
09/28/2017

ALICE KACUBA
09/28/2017

Kim, Janice

From: Kim, Janice
Sent: Monday, September 25, 2017 10:29 AM
To: 'Guy C Ruble'
Subject: NDA 208716 PI Response

Dear Dr. Ruble,

The purpose of this email is to send you the following response regarding your USPI for NDA 208716:

We discussed the steady state clinical exposure with our clinical pharmacology review team to calculate the animal-to-human exposure margins. The steady state exposure from trial JPBA are accurate, and the NCA results were verified over the course of the review cycle by the FDA clinical pharmacology review team. Therefore, the original steady state exposure values from the JPBA NCA analysis were used for calculations to determine the animal-to-human exposure margins, and these are the best available steady state data available. In repeat-dose toxicology studies, exposure at 10 mg/kg in male rats on Day 28 of the 28-day study was 12415 ng·h/mL. Exposure at 0.3 mg/kg in male dogs on Day 91 of the 13-week study was 148 ng·h/mL. Therefore, we disagree with your changes to Section 13.1. The values should remain 2x and 0.02x the exposure at the maximum clinical dose of 200 mg BID.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
09/27/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, September 21, 2017 12:44 PM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request

Dear Dr. Ruble,

The purpose of this email is to convey to you the following information request for NDA 208716 abemaciclib:

“Please provide a list of the 18 subjects (16 LY2835219, 2=PLACEBO) that had ‘Recurrent or locally advanced disease’ in Table JPBL.14.4 under the subheading Study Entry: Disease Stage. You can simply provide the usubjid for the 18 subjects.”

Please provide a response by Friday, September 22 at 1 PM EST.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
09/21/2017

Kim, Janice

From: Kim, Janice
Sent: Tuesday, September 19, 2017 11:11 AM
To: 'Guy C Ruble'
Subject: NDA 208716 PI and PPI
Attachments: Abemaciclib Proposed PI.docx; abemaciclib proposed PPI.docx

Dear Dr. Ruble,

The purpose of this email is to send you FDA comments to you PI and PPI for NDA 208716 abemaciclib.

Please respond with your proposed changes/comments by September 21, 2017 4pm EST.

Please let me know if you have question.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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
09/20/2017

Kim, Janice

From: Kim, Janice
Sent: Tuesday, September 19, 2017 10:09 AM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request

Dear Dr. Ruble,

The purpose of this email is to convey to you the following advice/information request from DMEPA:

Your proposed PI submitted on August 31, 2017 indicated you do **not** plan (b) (4)

Please submit a response of acknowledgement by tomorrow, September 20, 2017 10AM EST.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
09/20/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, September 14, 2017 9:31 AM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request

Dear Dr. Ruble,

The purpose of this email is to convey to you the following information request from our clinical pharmacology team:

Reference is made to "Regulatory Response (PK Label)" in Submission 0051, submitted on September 13, 2017. On Page 4, Lilly stated that a total of 112 doses were given 12 hours apart. Because the first dose was given at time 0, the last dose should be given at time 1332 (111x12). Please confirm the time of last dose and verify the calculation of accumulation ratio, by 4PM, September 14, 2017.

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
09/14/2017

Kim, Janice

From: Kim, Janice
Sent: Wednesday, September 13, 2017 2:52 PM
To: 'Guy C Ruble'
Subject: NDA 208716 abemaciclib Information Request

Dear Dr. Ruble,

The purpose of this email is to convey to you the following information request:

> For financial disclosures, submit a summary of the total number of principal investigators and subinvestigators for each study (there were xxx Investigators and xxx subinvestigators for the I3Y-MC-JPBL study and likewise for I3Y-MC-JPBN). For I3Y-MC-JPBL, the attached data does not indicate whether you obtained financial information according to 21CFR54 and if not a reason for this as the attached data for I3Y-MC-JPBN did. Please submit these data for JPBL as was done for JPBN.

Please submit a response by Friday, September 15 at 12 PM EST.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
09/13/2017

Kim, Janice

From: Kim, Janice
Sent: Wednesday, September 13, 2017 2:24 PM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request

Dear Dr. Ruble,

The purpose of this email is to convey to you the following information request:

“What tumor response data are included in the bimo datalistings used for data verification at the clinical sites?”

Please submit a response by 4pm EST September 13, 2017.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
09/13/2017

Kim, Janice

From: Kim, Janice
Sent: Tuesday, September 12, 2017 9:29 AM
To: 'Guy C Ruble'
Subject: NDA 208716 PPI - FDA Comments
Attachments: NDA 208716 abemaciclib PPI.docx

Dear Dr. Ruble,

Please find attached your PPI with FDA comments. Please reply back in tracked changes; accept/reject changes and add comments where needed by Friday September 15, 2017 COB.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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
09/12/2017

Kim, Janice

From: Kim, Janice
Sent: Monday, September 11, 2017 10:09 AM
To: 'Guy C Ruble'
Subject: NDA 208716 abemaciclib PI FDA comments
Attachments: NDA 208716 abemaciclib PI FDA Comments (2).docx

Dear Dr. Ruble,

The purpose of this email is to convey to you your PI. Please find attached the remainder of the PI with FDA comments for abemaciclib NDA 208716.

Please submit a response to our comments by Friday September 15, 2017 by 2PM EST.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

---

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
09/11/2017

Kim, Janice

From: Kim, Janice
Sent: Friday, September 08, 2017 5:24 PM
To: 'Guy C Ruble'
Subject: NDA 208716 PI
Attachments: NDA 208716 PI - FDA Comments (2).docx

Dear Dr. Ruble,

The purpose of this email is to send you part of your PI for NDA 208716 abemaciclib with FDA responses to your comments. I have deleted the following sections as they are not ready yet for your review, I will send those and the PPI when they are ready.

- Deleted 7.1
- Deleted 12.2, 12.3
- Deleted 17 Drug Interactions

Once, the rest of the PI and PPI are ready to send to you I will give you a due date at that time. Please let me know if you have any questions.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
09/08/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, September 07, 2017 4:56 PM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request

Dear Ruble:

Please see information request from Clinical Pharmacology Team:

We refer to the data file submitted on August 7, 2017 entitled “active-species-calculation-with-efavirenz-qc-d.xlsx” and the information request conveyed to Eli Lilly on September 7, 2017.

The AUC ratio of 0.38 (refer to Q40 of the Excel file) is incorrect because the AUC values were not adjusted for the different molecular weight of each analyte (refer to E29-E36 of the Excel file). Furthermore, the calculation was based on predicted AUC values, not observed AUC values. Please recalculate the observed potency-adjusted unbound AUC ratio and submit a revised Excel file by COB, September 8, 2017.

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
09/08/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, September 07, 2017 1:35 PM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request

Dear Dr. Ruble,

The purpose of this email is to convey to you the following information request (please submit a response by September 11, 2017 12pm EST as an official submission to your NDA):

1. Please submit a table of ongoing safety studies in the abemaciclib clinical development program (for example, studies to evaluate antidiarrheal prophylaxis or in special patient populations).

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
09/07/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, September 07, 2017 9:12 AM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request

Dear Dr. Ruble,

The purpose of this email is to convey to you the following information request for NDA 208716:

Your proposed labeling states that [redacted] (b) (4) This information was not included in the Response to Information Request submitted on July 26, 2017 (Sequence No. 0027).

Please submit the detailed calculations and/or data files used to derive the value of [redacted] (b) (4) % by September 8, COB.

Thank you

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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.

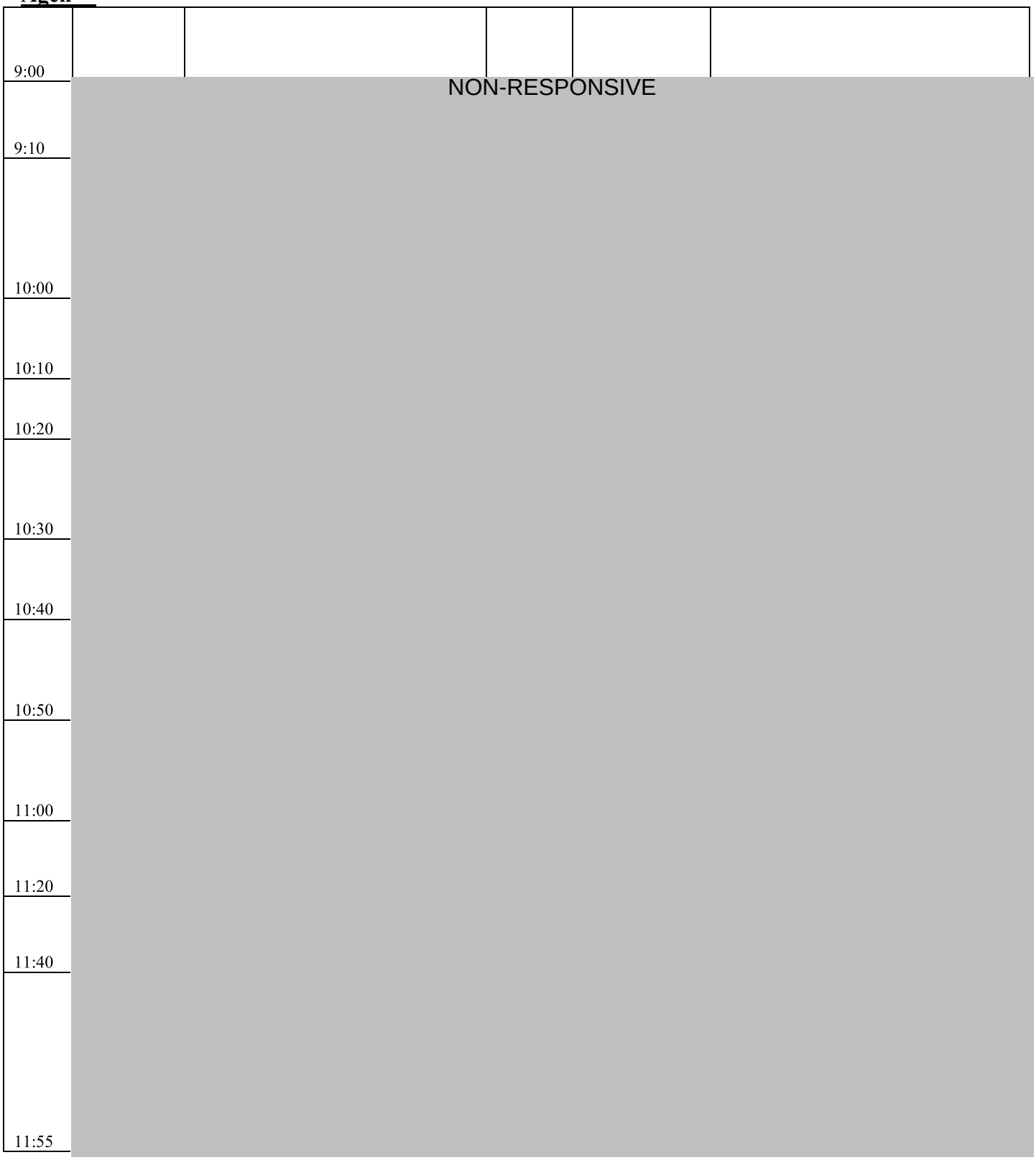
/s/

JANICE H KIM
09/07/2017

PeRC Meeting Minutes
September 6, 2017

PeRC Members Attending:
Lynne Yao
Skip Nelson
Meshaun Payne
Jacquline Yancy
Hari Cheryl Sachs
Susan McCune
Gil Burkhart
Donna Snyder
Lily Mulugeta
Dionna Green
Rosemary Addy
James Travis
Mark Rothmann
Raquel Tapia
Gerrie Baer
Victor Baum
Daiva Shetty
Kevin Krudys
Julia Pinto
Barbara Buch
Maura O'Leary

Agen


9:00
NON-RESPONSIVE
9:10
10:00
10:10
10:20
10:30
10:40
10:50
11:00
11:20
11:40
11:55

NON-RESPONSIVE

receptor 2 negative (HER2−) metastatic breast cancer in women whose disease has progressed following endocrine therapy and for (b) (4) the treatment of HR+, HER2− metastatic breast cancer (b) (4) whose disease has

(b) (4)

(b) (4)

NON-RESPONSIVE

Dr. Reaman presented on a proposal to form a oncology subcommittee to review oncology products that would require PeRC review. See slides provided by Dr. Reaman.
The subcommittee has a proposed start in October 2017.
PeRC would offer any member of the PeRC to attend the Oncology subcommittee meetings and vice versa.

NON-RESPONSIVE

7 Page(s) have been Withheld in Full as NON-RESPONSIVE immediately following this page

NON-RESPONSIVE

Abemaciclib Full Waiver with Agreed iPSP

- Proposed Indication: combination with fulvestrant for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−) metastatic breast cancer in women whose disease has progressed following endocrine therapy and for (b) (4) the treatment of HR+, HER2− metastatic breast cancer in (b) (4) whose disease has progressed following endocrine therapy and (b) (4) (b) (4) prior chemotherapy (b) (4) in the metastatic setting.

NON-RESPONSIVE

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

/s/

JACQULINE A YANCY
09/29/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, August 31, 2017 3:53 PM
To: 'Guy C Ruble'
Subject: RE: NDA 208716: 200 mg tablet biowaiver

Dr. Ruble,

Please see the response from our biopharmaceutics team:

We have completed our assessment of the Biowaiver request for the 200 mg strength and can confirm that it will be granted.

Thank you and please confirm receipt. Please let me know if you have additional issues that we can address regarding your PLAIR.

Janice

From: Guy C Ruble
Sent: Wednesday, August 23, 2017 10:56 AM
To: 'Kim, Janice' <Janice.Kim@fda.hhs.gov>
Subject: RE: NDA 208716: 200 mg tablet biowaiver

Janice,
This information is delaying us on making a few decisions in addition to the PLAIR request. (b) (4)

If you could provide an answer to this question about the acceptability of the 200 mg tablet and the biowaiver request, we would greatly appreciate it.

Best,
Guy

Guy C Ruble, PharmD, RAC
Global Regulatory Affairs - US, Oncology
Eli Lilly and Company
gcrx@lilly.com
317.276.8892
fax 317.276.1652
(b) (6)

From: Kim, Janice [mailto:Janice.Kim@fda.hhs.gov]
Sent: Tuesday, August 22, 2017 7:38 AM
To: Guy C Ruble <ruble_guy_c@lilly.com>
Subject: [EXTERNAL] RE: NDA 208716: Notice of Responses sent to 483 Manufacturing Site

If the biopharmaceutics team's review is the rate limiting step for submitting your PLAIR, please let me know.

Thank you,

Janice

From: Guy C Ruble [mailto:ruble_guy_c@lilly.com]
Sent: Monday, August 21, 2017 7:58 PM
To: Kim, Janice
Subject: RE: NDA 208716: Notice of Responses sent to 483 Manufacturing Site

Janice
Thanks for your email. Our team is meeting tomorrow to discuss if we want to go ahead with the PLAIR. Moving ahead with the PLAIR, may require is to do an amendment after it is granted if the biopharmaceutics review team does not approve the 200 mg tablet. It would be nice to have that decision made now but we understand that the FDA team is still reviewing the data.

Guy

From: Kim, Janice [mailto:Janice.Kim@fda.hhs.gov]
Sent: Monday, August 21, 2017 7:07 PM
To: Guy C Ruble <ruble_guy_c@lilly.com>
Subject: [EXTERNAL] RE: NDA 208716: Notice of Responses sent to 483 Manufacturing Site

Dr. Ruble,

Will the Sept 11th response date affect your PLAIR request timeline?

Please let me know. I am on leave but I am checking email intermittently throughout the day.

Thank you,

Janice

From: Guy C Ruble [mailto:ruble_guy_c@lilly.com]
Sent: Monday, August 21, 2017 1:19 PM
To: Venugopal, Rajesh
Cc: Kim, Janice
Subject: RE: NDA 208716: Notice of Responses sent to 483 Manufacturing Site

Thank you Rajesh!
We appreciate the quick follow-up.

Guy

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Monday, August 21, 2017 1:17 PM
To: Guy C Ruble <ruble_guy_c@lilly.com>
Cc: Kim, Janice <Janice.Kim@fda.hhs.gov>
Subject: [EXTERNAL] RE: NDA 208716: Notice of Responses sent to 483 Manufacturing Site

Hello Guy,

I'm told that the review team has a target date of Sept 11 to provide a response to you and that they hope to have an update for you by the end of next week.
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-4730
Fax: 301-796-9845
rajesh.venugopal@fda.hhs.gov

From: Guy C Ruble [mailto:ruble_guy_c@lilly.com]
Sent: Monday, August 21, 2017 12:51 PM
To: Venugopal, Rajesh
Subject: FW: NDA 208716: Notice of Responses sent to 483 Manufacturing Site

Rajesh
I just received Janice's OOO message. I was following up on a question to the biopharmaceutics team. See the email string below for details.

Regards
Guy

From: Guy C Ruble
Sent: Monday, August 21, 2017 12:15 PM
To: 'Kim, Janice' <Janice.Kim@fda.hhs.gov>
Subject: RE: NDA 208716: Notice of Responses sent to 483 Manufacturing Site

Janice
Sorry to send another email. Have you had any response from the biopharmaceutics team?

Thanks you
Guy

From: Kim, Janice [mailto:Janice.Kim@fda.hhs.gov]
Sent: Friday, August 18, 2017 10:30 AM
To: Guy C Ruble <ruble_guy_c@lilly.com>
Subject: [EXTERNAL] RE: NDA 208716: Notice of Responses sent to 483 Manufacturing Site

Dear Dr. Ruble,

I will let you know the response once I hear back from the biopharmaceutics team.

Thank you,

Janice

From: Guy C Ruble [mailto:ruble_guy_c@lilly.com]
Sent: Thursday, August 17, 2017 8:26 PM
To: Kim, Janice
Subject: RE: NDA 208716: Notice of Responses sent to 483 Manufacturing Site

Janice
Thanks for this information. In follow-up, it would be important for Lilly to understand where FDA is at regarding the acceptability of the biowaiver for the 200 mg tablet. We can not include this tablet in the PLAIR if FDA has objections to the request for the biowaiver.

We look forward to your response.

Guy

From: Kim, Janice [mailto:Janice.Kim@fda.hhs.gov]
Sent: Thursday, August 17, 2017 4:33 PM
To: Guy C Ruble <ruble_guy_c@lilly.com>
Subject: [EXTERNAL] RE: NDA 208716: Notice of Responses sent to 483 Manufacturing Site

Dear Dr. Ruble,

As a follow up to my response, you should submit the PLAIR now.

Thank you,

Janice

From: Guy C Ruble [mailto:ruble_guy_c@lilly.com]
Sent: Tuesday, August 15, 2017 1:40 PM
To: Kim, Janice
Subject: NDA 208716: Notice of Responses sent to 483 Manufacturing Site

Janice
My CMC colleagues have alerted me that Lilly has submitted the 483 inspection responses to FDA from the PR01 manufacturing site inspection in Puerto Rico. A hard copy was sent last Thursday 10 August 2017 to the San Juan FDA office as requested and an email copy was sent on Friday 11 August 2017 to the lead FDA inspector in DC.

I just wanted to make sure that this was communicated to the DOP1 review team as I was just made aware.

Please let me know if these responses have sufficiently addressed the FDA issues so that we might proceed with our discussion on the PLAIR request from the mid-cycle meeting.

Kind regards
Guy

Guy C Ruble, PharmD, RAC
Global Regulatory Affairs - US, Oncology
Eli Lilly and Company
gcrx@lilly.com
317.276.8892
fax 317.276.1652
(b) (6)

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
09/01/2017

Kim, Janice

From: Kim, Janice
Sent: Wednesday, August 30, 2017 1:37 PM
To: 'Guy C Ruble'
Subject: NDA 208716 abemaciclib information request

Dear Dr. Ruble,

The purpose of this email is to send you the following information request from our clinical reviewer:

Information Request #1:

1. Based on the 90 day safety update received 8/2/17, one adverse event in the I3Y-MC-JPCD Expanded Access Program is reported. Please indicate how many patients were a part of the expanded access program at the time of that report and what was the data cutoff date for AE reporting for this program cohort.

Information Request #2:

For the dose intensity in mg/day in the MONARCH 2 ADEX dataset, please clarify why the following subjects have values >500 mg/day:
I3Y-MC-JPBL-202-01652
I3Y-MC-JPBL-323-01899
I3Y-MC-JPBL-108-01214
I3Y-MC-JPBL-606-01992
I3Y-MC-JPBL-606-01972

In MONARCH 1, for Dose Intensity mg/day in the MONARCH 1 ADEX dataset, please clarify why the following subjects have values >500 mg/day:
I3Y-MC-JPBN-400-01103
I3Y-MC-JPBN-400-01149
I3Y-MC-JPBN-701-01126
I3Y-MC-JPBN-310-01215
I3Y-MC-JPBN-601-01033

Please respond to these requests by Friday, September 1, at 12 PM EST.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
09/01/2017

For CDER NDA/BLA reviews only: We are requesting that Division RPMs upload the PeRC PREA Template as a Memo To File into DARRTS in advance of your scheduled PeRC meeting.

Note: The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. The final PeRC meeting minutes are linked to the NDA/BLA application in DARRTS.

Complete the section(s) of this template that are relevant to your current review. Sections that are not applicable can be deleted.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Definitions:

Deferral *– A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.*

Full Waiver *– On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information MUST be included in the pediatric use section of labeling.*

Partial Waiver *– FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.*

Pediatric Assessment *– The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and*

administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

***Pediatric Plan** – A pediatric plan is the applicant's statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.*

***Pediatric Population/Patient**- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.*

***PREA Pediatric Record/Pediatric Page** – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.*

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: ☒ **Full Waiver** ☐ **Partial Waiver** ☐ **Pediatric Assessment** ☐ **Deferral/Pediatric Plan**

BLA/NDA#: NDA 208716

PRODUCT PROPRIETARY NAME: VERZENIO
ESTABLISHED/GENERIC NAME: abemaciclib

APPLICANT/SPONSOR: Eli Lilly

PREVIOUSLY APPROVED INDICATION/S:
(1) _____
(2) _____
(3) _____
(4) _____

PROPOSED INDICATION/S:
(1) hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−) advanced or metastatic breast cancer

in combination with fulvestrant for women with disease progression following endocrine therapy

(2) hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−) advanced or metastatic breast cancer

[redacted] (b) (4) with disease progression following endocrine therapy and [redacted] (b) (4) prior chemotherapy [redacted] (b) (4) in the metastatic setting

(3) _____
(4) _____

BLA/NDA STAMP DATE: May 5, 2017

PDUFA GOAL DATE: January 5, 2018; Target Action Date; September 29, 2017

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER:

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☒ ***active ingredient(s) (includes new combination);*** ☐ ***indication(s);*** ☐ ***dosage form;*** ☐ ***dosing regimen; or*** ☐ ***route of administration?***

Did the sponsor submit an Agreed iPSP? Yes ☒ ***No*** ☐

Are there any changes to the Agreed iPSP that are different than the sponsor's current pediatric plan?
Yes ☐ ***No*** ☒

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)
Yes ☐ ***No*** ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ ***No*** ☒
If Yes, PMR #_____ NDA #_____
Does the division agree that this is a complete response to the PMR?
Yes ☐ ***No*** ☐
If Yes, to either question Please complete the Pediatric Assessment Template.
If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

☒ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change.***

If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.

☐ ***Pediatric Record***

1 Pediatric age group(s) to be waived.

2 Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

☒ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.

☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **<u>and</u>** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted***. (This reason is for Partial Waivers Only)***

3 Provide justification for Waiver: Limited applicability to pediatric patients because the pathophysiology of breast cancer occurs for the most part in the adult population

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language: None at this time

APPEARS THIS WAY ON ORIGINAL

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
08/25/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, August 24, 2017 7:45 AM
To: 'Guy C Ruble'
Subject: RE: NDA 208716 Information Request

Dear Dr. Ruble,

Please see DMEPA's response to your inquiry:

We agree to just mock up one packaging file for now.
All packaging files and color scheme change can be submitted to NDA. As long as the color scheme change is to colors that still adequately differentiates the different strengths, then it should not prolong our review.

Thank you,

Janice

From: Guy C Ruble [mailto:ruble_guy_c@lilly.com]
Sent: Tuesday, August 22, 2017 6:33 PM
To: Kim, Janice
Subject: RE: NDA 208716 Information Request

Janice
Hi, we will be providing our response to FDA tomorrow. In the response, we are only mocking up one of the packaging files to show FDA what the requested changes look like. If FDA agrees, we will update the remaining files and submit to the NDA.

Since Lilly is making the FDA proposed changes to the packaging, Lilly is now considering changing the primary color scheme for the 200 mg tablet and the 150 mg tablet packages. Would it be possible to make that change when we submit all the files to the NDA with the FDA requested changes? Or would it possibly cause a delay in the review of the materials. We don't want to make any changes that might prolong the FDA review of packaging.

Thanks for your input.

Guy

From: Kim, Janice [mailto:Janice.Kim@fda.hhs.gov]
Sent: Thursday, August 17, 2017 10:28 AM
To: Guy C Ruble <ruble_guy_c@lilly.com>
Subject: [EXTERNAL] NDA 208716 Information Request

Dear Dr. Ruble,

In reference to NDA 208716 abemaciclib, we recommend the following:

A. Container Labels – Pull Out Blister Cards
1. Revise the pull out blister cards so that the information, "PUSH tablet through the card to the other side of the package" and the product name, strength, and dose information on the backside are readily visible. As currently

proposed and based on the physical sample blister pack submitted to the Agency, when the pull out blister card is fully pulled out, the text that is located on the leftmost side is not readily visible.

B. Carton Labeling – Blister Card Sleeves

(b) (4)

Please submit a response by August 23, 2017 COB as an official submission to your NDA.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
08/24/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, August 17, 2017 10:28 AM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request

Dear Dr. Ruble,

In reference to NDA 208716 abemaciclib, we recommend the following:

A. Container Labels – Pull Out Blister Cards

1. Revise the pull out blister cards so that the information, "PUSH tablet through the card to the other side of the package" and the product name, strength, and dose information on the backside are readily visible. As currently proposed and based on the physical sample blister pack submitted to the Agency, when the pull out blister card is fully pulled out, the text that is located on the leftmost side is not readily visible.

B. Carton Labeling – Blister Card Sleeves

(b) (4)

[redacted]

Please submit a response by August 23, 2017 COB as an official submission to your NDA.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
08/17/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, August 17, 2017 6:50 AM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request

Dear Dr. Ruble,

In reference to NDA 208716 abemaciclib, we have the following clinical information request:

1) Using the combined safety database from the abemaciclib development program, characterize the incidence of deep venous thrombosis, pulmonary embolism, and other venous thromboembolic events. Characterize these separately from arterial events and provide the incidence of arterial events as well. Report the number of deaths associated with venous events separately from arterial events across the abemaciclib safety database.

2) Using the combined safety database from the abemaciclib development program, characterize the incidence of pneumonitis, including pulmonary fibrosis and organizing pneumonia (bronchiolitis obliterans). Additionally, report the number of deaths thought due to pneumonitis and break down events thought to be associated with disease progression vs. no disease progression.

Please submit a response by Thursday, August 24, 2017 by noon.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
08/17/2017

Kim, Janice

From: Kim, Janice
Sent: Monday, August 14, 2017 12:53 PM
To: 'Guy C Ruble'
Subject: NDA 208716 abemaciclib Information Request

Dear Dr. Ruble,

In reference to your NDA 208716 (abemaciclib), we have the following clinical information request:

1. For MONARCH 1, please clarify the source of the data that you used to generate Table JPBN.10.2 Summary of Major and Important Major Protocol Deviations on page 65 of the MONARCH 1 CSR. Using ADDV, our analysis demonstrates that 16 patients had protocol deviations due to improper treatment discontinuation as compared to your table which indicates that there were 7 patients in this category.
2. For MONARCH 2, please clarify the source of the data that you used to generate Table JPBL.10.2 Summary of Major Protocol Deviations in the ITT population on page 85 of the MONARCH 2 CSR. Using ADDV, our analysis demonstrates a total of 442 patients in the ITT population with major protocol deviations and 474 protocol deviations when EN patients are included

Please submit a response by Thursday, August 17 at noon. Let me know if any questions.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
08/14/2017

Kim, Janice

From: Kim, Janice
Sent: Tuesday, August 08, 2017 9:16 AM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request

Dear Dr. Ruble,

In reference to your NDA 208716 the clinical pharmacology review team has the following information request, please submit a response by August 9, 2017 COB by email to facilitate review and by official submission to your NDA:

The effects of loperamide on the unbound exposure of abemaciclib and its active metabolites were not provided in study report JPCA. Please submit supportive data to corroborate the appropriate labeling language describing the effects of co-administration of loperamide on the unbound exposure of abemaciclib and its active metabolites. Specifically, provide the necessary information to complete this sentence: "Co-administration of a single 8 mg dose of loperamide with a single 400 mg dose of VERZENIO [increased (b) (4) the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2 (b) (4) and M20) by XX% in healthy subjects."

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
08/08/2017

Marshall, Christina

From: Marshall, Christina
Sent: Thursday, August 03, 2017 1:31 PM
To: 'gcrx@lilly.com'
Cc: Kim, Janice; Dinin, Jeannette
Subject: NDA 208716 Abemaciclib Post marketing Requirement and Commitments

Good Morning Dr. Ruble,

Let me formally introduce myself, I am the Safety Project Manager for Division of Oncology Product -1, and I am your point of contact for all postmarketing submissions and/or correspondences. I ask that you submit your submissions and/or correspondences the same way that you have done previously; however, email me (cc: project manager assigned to your product) or call me directly for anything concerning postmarketing to ensure adequate and immediate responses to your inquiry.

We have the following postmarketing requirement and commitments for your NDA for your review and that requires agreement by your team:

PMC Description:

3254-X Conduct a pharmacokinetic trial to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of abemaciclib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."
Submit final report and data sets.

PMR/PMC Schedule Milestones:
Final Protocol Submission: MM/DD/YYYY
Trial Completion: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY

3254-X Submit the overall survival (OS) data and final report from clinical trial MONARCH 2: Entitled "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer"

PMR/PMC Schedule Milestones:
Trial Completion: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY

PMR Description:

3254-X Submit a final report and data sets from an ongoing or new clinical trial to evaluate the incidence of dose reductions and dose interruptions due to severe diarrhea when abemaciclib is administered with a meal, compared to abemaciclib taken in the modified fasted condition, and when it is administered without regard to food in patients.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY

Please confirm and/or provide milestone dates for each time point data will be submitted. Please respond via email by COB Thursday, August 11, 2017 (if not sooner) with a proposal of the date for each milestone.

Thank You,

Christina Marshall, M.S.
Safety Regulatory Health Project Manager
DOP1/OHOP/CDER
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 2181
Silver Spring, MD 20993
Phone: 301-796-3099
Fax: 301-796-9881

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

/s/

CHRISTINA D MARSHALL
08/07/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208716

MID-CYCLE COMMUNICATION

Eli Lilly and Company
Attention: Guy Ruble, PharmD
Director, Global Regulatory Affairs, Oncology, North America
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Ruble:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Verzenio (abemaciclib); 50 mg, 100 mg, 150 mg, and 200 mg tablets.

We also refer to the teleconference between representatives of your firm and the FDA on August 3, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

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:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: August 3, 2017; 2:00 PM to 3:00 PM

Application Number: NDA 208716
Product Name: Verzenio (abemaciclib) tablets
Indication: combination with fulvestrant for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer in women whose disease has progressed following endocrine therapy and for use (b) (4) in the treatment of HR+, HER2- metastatic breast cancer (b) (4) whose disease has progressed following endocrine therapy and (b) (4) prior chemotherapy (b) (4) in the metastatic setting.
Applicant Name: Eli Lilly

Meeting Chair: Laleh Amiri-Kordestani, MD
Meeting Recorder: Jeannette Dinin

FDA ATTENDEES
Julia Beaver, MD, Acting Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Laleh Amiri-Kordestani, MD, Clinical Team Leader, DOP1
Lynn Howie, MD, Clinical Reviewer, DOP1
Katherine Fedenko, MS, CRNP, Deputy Director (Safety), DOP1
William Pierce, PharmD, Associate Director for Labeling / Clinical Reviewer, DOP1
Jeanne Fourie Zirkelbach, PhD, Clinical Pharmacology Team Leader
Vadryn Pierre, PhD, Clinical Pharmacology Reviewer
Okpo Eradiri, PhD, Biopharmaceutics Reviewer, OPQ /ONDP/DB/BBI
Shenghui Tang, PhD, Biostatistics Team Leader, OTS/OB/DBV
Erik Bloomquist, PhD, Biostatistics Reviewer, OTS/OCP/DCPV
Carolyn McCloskey, PhD, Epidemiology Reviewer
Todd Palmby, PhD, Pharmacology Toxicology Team Leader, DHOT
Xiao Chen, PhD, Chemistry Lead, OPQ
Sithamalli Chandramouli, PhD, Chemistry Reviewer, OPQ
Krishnakali Ghosh, PhD, Facility Reviewer, OPQ/OPF/DIA/IABIII
Jeannette Dinin, MS, Regulatory Project Manager, DOP1

APPLICANT ATTENDEES
Allen Melemed, MD, Senior Director, Global Regulatory Affairs N. America
Guy Ruble, PharmD, RAC, Director, Global Regulatory Affairs N. America

Jole Rodriguez, MS, Senior Research Scientist, Global Regulatory Affairs -CMC
Colleen Mockbee, RPh, Global Product Team Leader, Oncology
Ian Smith, MD, Senior Medical Director
Nawel Bourayou, MD, Clinical Research Advisor
Yanping Wang, PhD, Senior Director, Statistics
Martin Frenzel, PhD, Senior Research Scientist, Statistics
Shivani Nanda, MS, Associate Director, Statistics
Yong Lin, PhD, Senior Research Scientist, Statistics
Tammy Forrester, MS, Research Scientist, Statistics
Joanne Cox, MD, Senior Medical Advisor, Global Patient Safety
Paul Cornwell, PhD, DABT, Principal Research Scientist, Toxicology
Jill Chappell, PharmD, Principal Research Scientist, Clinical Pharmacology
Michael Turik, MD, Senior Director, Clinical Pharmacology
Kellie Turner, PharmD, PhD, Senior Research Scientist, PK/PD
Lan Ni, PhD, Senior Director, PK/PD
Steve Hall, PhD, Senior Research Fellow, Drug Disposition
Susan Holsmer-Brand, MS, Manager, Global Regulatory Affairs N. America
Akthum Aburub, PhD, Research Advisor, Pharmaceutical Product Design
Leanne Hickman, VP Global Quality
Patrice Bradley, Senior Advisor, Pharmaceutical Project Management

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

a) Post Marketing Commitments and Requirement
   - CMC PMC may be needed depending on the outcome of the review of the Applicant's response to the 483 observations.

Meeting Discussion: FDA is waiting on Sponsor's responses to the 483.

   - PMR– CLINICAL PHARMACOLOGY
     - Amend an ongoing trial to include an evaluation of the incidence of dose reductions and dose interruptions due to severe diarrhea when abemaciclib is administered with a meal compared to abemaciclib taken in the

modified fasted condition and when it is administered without regard to food in patients. Final PMR language will be provided at a later date.

Meeting Discussion: FDA clarified that this is a PMR and not a PMC, because previous clinical experience indicates that severe diarrhea is a serious risk associated with the use of abemaciclib. Lilly informed FDA that there is an ongoing trial evaluating administration of abemaciclib with food vs. without food, and that the design includes patient food diaries. FDA clarified that the aim of the PMR is to determine if administration of abemaciclib with food vs. administration in the fasted state or without regard to food can improve tolerability and decrease the incidence of severe diarrhea that occurs in early treatment cycles. Lilly indicated that a proposal will be submitted for review by FDA.

- Additional PMC from CLINICAL PHARMACOLOGY:
  - 3254-X Conduct a pharmacokinetic trial to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of abemaciclib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations." Submit final report and data sets.

Meeting Discussion: Lilly proposed to submit additional physiologically based pharmacokinetic (PBPK) modeling to evaluate the effects of a moderate CYP3A4 inducer on abemaciclib pharmacokinetics (PK) and apply the same adjustments made to this model (fraction unbound in plasma [fu] and potency of each metabolite relative to parent were applied to the area under the curve [AUC] ratios) that were submitted in the regulatory response dated July 26, 2017 (Sequence No. 0027).

- PMC REQUEST – CLINICAL
  - We will be requesting that you commit to submit the overall survival data and final report from clinical trial MONARCH 2: Entitled "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer." Final PMC language will be provided at a later date.

b) Discussion regarding Clinical Pharmacology findings
   - Exposure response analysis with simulations support higher response rate (target lesion) with higher exposure at 200 mg BID vs. 150 mg BID.
   - Further dose optimization may be considered in some subset of patients in the early line indication with the proposed abemaciclib dose administered in combination with fulvestrant.

- Such dose optimization could include a study of antidiarrheal prophylaxis during the early treatment cycles, followed by incremental dose escalation in patients who can tolerate a higher dose (e.g., 200 mg BID).

Meeting Discussion: FDA presented an overview of review findings indicating the potential for further dose optimization in the early line indication (150 mg BID with fulvestrant) using antidiarrheal prophylaxis to minimize severe diarrhea during early treatment cycles, followed by incremental dose escalation in patients who can tolerate a higher dose (e.g., 200 mg BID). Lilly indicated that there is an ongoing trial to assess the potential of further dose optimization. In the ongoing trial, loperamide prophylaxis (once daily dosing) is being evaluated in combination with abemaciclib 200 mg BID. Lilly indicated that the results from the trial will be available in early 2018, and that Lilly commits to discussing the results from this study with FDA.

3.0 INFORMATION REQUESTS

- Clinical Information Request sent July 31, 2017. Response due on August 3, 2017.

- CMC Information Request sent July 25, 2017. Response due on August 8, 2017. The commercial manufacturing process descriptions in the P.3 section of the NDA have insufficient information for FDA to perform an informed review of your proposed commercial manufacturing process. Please update the NDA with the following information.

(b) (4)

(b) (4)

- CMC Information Request sent July 25, 2017. Response due on August 8, 2017.

(b) (4)

- CMC Information Request sent July 25, 2017. Response due on August 8, 2017.

(b) (4)

Question to the Applicant: Are you planning on submitting additional drug product stability data? If the answer is yes, please indicate when you plan to submit the data.

Discussion: Applicant indicated that they are not planning on submitting additional drug product stability data.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC Meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for **September 11, 2017**. We intend to send the briefing package to you approximately 3 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review. You may choose altogether to cancel the Late Cycle Meeting, if you feel it is not needed, given our continued and regular communications. The PDUFA Action Date is January 5, 2018.

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
08/17/2017

LALEH AMIRI KORDESTANI
08/17/2017

From:	Tilley, Amy
To:	ruble_guy_c@lilly.com
Cc:	Kim, Janice; Wahby, Sakar
Bcc:	Howie, Lynn
Subject:	TIME SENSITIVE re NDA 208716 Verzenio - Clinical IR
Date:	Tuesday, August 01, 2017 5:50:00 PM
Attachments:	image013.png image014.png
Importance:	High

Guy, on behalf of my colleague, Janice Kim, the purpose of this email is to send you the following Clinical Information Request regarding NDA 208716 for Verzenio. We request your emailed response **by 2 pm on Friday, August 4, 2017**, then follow up with an official response to the NDA. Please "reply to all" when responding. Kindly confirm receipt of this email.

1. Provide data to support your statement on page 184 of the CSR for MONARCH 2, I3Y-MC-JPBL, "Increases in serum creatinine…were reversible upon treatment discontinuation."
2. Provide data to support your statement on page 192 of the CSR for MONARCH 2, I3Y-MC-JPBL, "The incidence of increased ALT and AST…Generally these increases were manageable…and resolved upon discontinuation of study treatment."

Regards,

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Follow @FDAOncology on Twitter

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

/s/

AMY R TILLEY
08/01/2017

From:	Tilley, Amy
To:	ruble_guy_c@lilly.com
Cc:	Kim, Janice; Dinin, Jeannette
Subject:	NDA 208716 Verzenio - Mid-Cycle Communication Agenda
Date:	Tuesday, August 01, 2017 3:31:39 PM
Attachments:	NDA 208716 abemaciclib Mid Cycle Communications Agenda.doc image013.png image002.png

Guy, on behalf of my colleague Janice Kim, the purpose of this email is to send you the attached Mid-Cycle Communication Agenda regarding our teleconference on August 3 2017, from 2:00 pm – 3:00 pm.

Please note that in Janice's absence, our colleague Jeannette Dinin will be facilitating the August 3rd teleconference.

Regards,

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Follow @FDAOncology on Twitter

NDA 208716 PDUFA V Program Mid-Cycle Communication Agenda

Meeting Date:	August 3, 2017; 2:00 PM – 3:00 PM
Meeting Location:	Teleconference
Application Number:	NDA 208716
Product:	Verzenio (abemaciclib) tablets
Applicant Name:	Eli Lilly
Proposed Indication:	combination with fulvestrant for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−) metastatic breast cancer in women whose disease has progressed following endocrine therapy and for use (b) (4) in the treatment of HR+, HER2− metastatic breast cancer (b) (4) whose disease has progressed following endocrine therapy and (b) (4) prior chemotherapy (b) (4) in the metastatic setting.

FDA Attendees: ***Tentative***

Richard Pazdur, MD, Acting Director, Oncology Center of Excellence, Office of the Commissioner
Julia Beaver, MD, Acting Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Laleh Amiri Kordestani, MD, Clinical Team Leader, DOP1
Lynn Howie, MD, Clinical Reviewer, DOP1
William Pierce, PharmD, Associate Director for Labeling / Clinical Reviewer, DOP1
Jeanne Fourie Zirkelbach, PhD, Clinical Pharmacology Team Leader
Vadryn Pierre, PhD, Clinical Pharmacology Reviewer
Angelica Dorantes, PhD, Biopharmaceutics Team Leader, OPQ/ONDP/DB/BBI
Okpo Eradiri, PhD, Biopharmaceutics Reviewer, OPQ /ONDP/DB/BBI
Banu Zolnik, PhD Bioequivalence Reviewer, OPQ /ONDP/DB/BBI
Shenghui Tang, PhD, Biostatistics Team Leader, OTS/OB/DBV
Erik Bloomquist, PhD, Biostatistics Reviewer, OTS/OCP/DCPV
Carolyn McCloskey, PhD, Epidemiology Reviewer
Grace Jones, PhD, Medication Error Reviewer
Todd Palmby, PhD, Pharmacology Toxicology Team Leader, DHOT
Tiffany Ricks, PhD, Pharmacology Toxicology Reviewer, DHOT
Frances Fahnbulleh, RPh, PharmD, Safety Regulatory Project Manager, OSE/PMS
Chi-Ming Tu, PhD, DMEPA Team Leader, OSE/OMEPRM/DMEPA
Grace Jones, PhD, DMEPA Reviewer, OSE/OMEPRM/DMEPA
Peter Waldron, MD, OSE Team Leader, OPE/DPVII
Steven Bird, PhD, OSE Reviewer, OPE/DPVII
Ingrid Chapman, PhD, Risk Management Reviewer
Pritpal Singh, PhD, Pharmacovigilance Reviewer
Anamitro Banerjee, PhD, Branch Chief, OPQ
Xiao Chen, PhD, Chemistry Lead, OPQ
Olen Stephens, PhD, Chemistry Reviewer, OPQ
Sithamalli Chandramouli, PhD, Chemistry Reviewer, OPQ
Katherine Fedenko, MS, CRNP, Deputy Director Safety, DOP1

Krishnakali Ghosh, PhD, Facility Reviewer, OPQ/OPF/DIA/IABIII
Christina Marshall, MS, Safety Regulatory Health Project Manager
Kristine Leahy, PhD, OPQ Regulatory Project Manager, OPQ/OPRO/DRBPMI/RBPM
Jeannette Dinin, MS, Regulatory Project Manager, DOP1

Applicant Attendees:
Allen Melemed, MD, Senior Director, Global Regulatory Affairs North America
Guy Ruble, PharmD, RAC, Director, Global Regulatory Affairs North America
Jole Rodriguez, MS, Senior Research Scientist, Global Regulatory Affairs CMC
Colleen Mockbee, RPh, Global Product Team Leader, Oncology
Ian Smith, MD, Senior Medical Director
Nawel Bourayou, MD, Clinical Research Advisor
Yanping Wang, PhD, Senior Director, Statistics
Martin Frenzel, PhD , Senior Research Scientist, Statistics
Shivani Nanda, MS, Associate Director, Statistics
Yong Lin, PhD, Senior Research Scientist, Statistics
Tammy Forrester, MS, Research Scientist, Statistics
Joanne Cox, MD, Senior Medical Advisor, Global Patient Safety

Tentative:
Paul Cornwell, PhD, DABT, Principal Research Scientist, Toxicology
Jill Chappell, PharmD, Principal Research Scientist, Clinical Pharmacology
Michael Turik, MD, Senior Director, Clinical Pharmacology
Kellie Turner, PharmD, PhD, Senior Research Scientist, PK/PD
Lan Ni, PhD, Senior Director, PK/PD
Steve Hall, PhD, Senior Research Fellow, Drug Disposition
Susan Holsmer-Brand, MS, Manager, Global Regulatory Affairs North America

PDUFA V Program Mid-Cycle Communication Agenda Template

1. **Introduction**

We are providing these comments to you before we complete our review of the entire application to give you **preliminary** notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2. **Significant Issues**

a) Post marketing Commitments and Requirement

- CMC PMC may be needed depending on the outcome of the review of the Applicant's response to the 483 observations.

- PMR REQUEST– CLINICAL PHARMACOLOGY
  - Amend an ongoing trial to include an evaluation of the incidence of dose reductions and dose interruptions due to diarrhea when abemacicib is administered with a meal compared to abemaciclib taken in the modified fasted condition and when it is administered without regard to food in patients. Final PMR language will be provided at a later date.

- PMC REQUEST – CLINICAL
  - We will be requesting that you commit to submit the overall survival data and final report from clinical trial MONARCH 2: Entitled "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer". Final PMC language will be provided at a later date.

b) Discussion regarding Clinical Pharmacology findings

- Exposure response analysis with simulations support higher response rate (target lesion) with higher exposure at 200 mg BID vs 150 mg BID.
- Further dose optimization may be considered in some subset of patients in the early line indication with the proposed abemaciclib dose administered in combination with fulvestrant.
  - Such dose optimization could include a study of antidiarrheal prophylaxis during the early treatment cycles, followed by incremental dose escalation in patients who can tolerate a higher dose (e.g., 200 mg BID).

2. Information Requests

- Clinical Information Request sent July 31, 2017. Response due on August 3, 2017.

- CMC IR sent July 25, 2017. Response due on August 8, 2017
  The commercial manufacturing process descriptions in the P.3 section of the NDA have insufficient information for FDA to perform an informed review of your proposed commercial manufacturing process. Please update the NDA with the following information.

- 

- (b) (4)

A Question To The applicant: are you planning on submitting additional drug product stability data? If the answer is yes, please indicate when you plan to submit the data.

4. Major Safety Concerns/Risk Management

There are no major safety concerns identified at this time and there is currently no need for a REMS.

5. Advisory Committee Meetings

There are no plans at this time for an AC Meeting.

6. Proposed Date and Format for Late-Cycle Meeting/Other Projected Milestones

The Late Cycle Meeting is currently planned for September 11, 2017.

We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of the review. You may choose altogether to cancel the Late Cycle Meeting, if you feel it is not needed, given our continued and regular communications. The PDUFA Action Date is January 5, 2018.

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

/s/

AMY R TILLEY
08/01/2017

From: Tilley, Amy
To: ruble_guy_c@lilly.com
Subject: TIME SENSITIVE re NDA 208716 Verzenio - Clinical IR
Date: Monday, July 31, 2017 4:40:06 PM
Attachments: image013.png
image014.png

Guy, on behalf of my colleague Janice Kim, the purpose of this email is to send you the following Clinical Information Requests. We request your emailed response **no later than 3 pm on Wednesday, August 2, 2017**, then follow up with an official response to the NDA. Please confirm receipt of this email.

1. Regarding section 6.1 of the label, for "VERZENIO in Combination with Fulvestrant," it is reported that permanent discontinuation of VERZENIO due to an adverse [redacted] (b) (4) is [redacted] (b) (4)% in patients who receive VERZENIO and fulvestrant and [redacted] (b) (4)% in placebo and fulvestrant. Based on our analysis, we found the discontinuation rate to be [redacted] (b) (4)% and [redacted] (b) (4)%, respectively. Please clarify which flags were used in your analysis.
2. Continuing in section 6.1, you state that [redacted] (b) (4) of the "VERZENIO in Combination with Fulvestrant" study. [redacted] (b) (4) Please clarify how you arrived at your results.
3. In section 6.1, it was noted that [redacted] (b) (4) However, we note that [redacted] (b) (4)

Regards,

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Follow @FDAOncology on Twitter

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

/s/

AMY R TILLEY
07/31/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208716

INFORMATION REQUEST

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

Dear Dr. Ruble:

Please refer to your New Drug Application (NDA) submitted May 5, 2017, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abemaciclib tablet.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Manufacturing Drug Process:

1. The commercial manufacturing process descriptions in the P.3 section of the NDA have insufficient information for FDA to perform an informed review of your proposed commercial manufacturing process. Please update the NDA with the following information.

a. (b) (4)

b.

c.

d.

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

If you have any questions, please contact me, Kristine Leahy, RPh., Regulatory Business Process Manager, at (240) 402-5834. Please respond to Manufacturing Drug Process comments by **August 8, 2017.**

Sincerely,

Kristine F. Leahy -S

Digitally signed by Kristine F. Leahy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001815977, cn=Kristine F. Leahy -S
Date: 2017.07.25 14:56:58 -04'00'

Kristine Leahy, RPh.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kim, Janice

From: Kim, Janice
Sent: Monday, July 24, 2017 7:40 AM
To: 'Guy C Ruble'
Subject: NDA 208716 abemaciclib information request

Dear Dr. Ruble,

Please see the following information request from our clinical team:

1. For Request 1, the request for narratives of patients who were hospitalized in association with the AE of diarrhea, in the regulatory response provided on 7/21/17, it appears that only MONARCH 1 results were included. Clarify this and if you have not, provide MONARCH 2 results as well, including lab results and stool studies if performed.

Please submit a response by tomorrow, July 25 2017 COB. Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
07/24/2017

Kim, Janice

From: Kim, Janice
Sent: Friday, July 21, 2017 9:44 AM
To: 'Guy C Ruble'
Subject: NDA 208716 abemaciclib Information Request

Dear Dr. Ruble,

In reference to NDA 208716, I have the following information request:

In Section 17, the introductory statement currently reads: "Advise patients to read the FDA-approved Patient Information. (b) (4) *The term "patients" should be singular, not plural* (b) (4)

Please submit a response by July 25, 2017 COB.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
07/21/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, July 20, 2017 11:47 AM
To: 'Guy C Ruble'
Subject: NDA 208716 abemaciclib IR

Dear Dr. Ruble,

Please see the following IR from our clinical team for NDA 208716:

1. Based on our analysis using adexsum.xpt dataset, [redacted] (b) (4) You have reported in the section 6.1 of label and on page 136 of the CSR [redacted] (b) (4) Please clarify the discrepancy.

Please respond by Monday, July 24th COB.

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
07/21/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208716

INFORMATION REQUEST

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

Dear Dr. Ruble:

Please refer to your New Drug Application (NDA) submitted May 5, 2017, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abemaciclib tablet.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Product:

(b) (4)

If you have any questions, please contact me, Kristine Leahy, RPh., Regulatory Business Process Manager, at (240) 402-5834. Please respond by July 26, 2017.

Sincerely,
Kristine F. Leahy -S

Digitally signed by Kristine F. Leahy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001815977, cn=Kristine F. Leahy -S
Date: 2017.07.20 19:02:49 -04'00'

Kristine Leahy, RPh.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208716

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Eli Lilly and Company
Attention: Guy Ruble, PharmD
Director, Global Regulatory Affairs, Oncology, North America
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Ruble:

Please refer to your New Drug Application (NDA) dated May 5, 2017, received May 5, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Verzenio (abemaciclib); 50 mg, 100 mg, 150 mg, 200 mg tablets.

We also refer to your amendments(s) dated June 30, 2017.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* 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 in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

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

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Acting Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

JULIA A BEAVER
07/19/2017

Kim, Janice

From: Kim, Janice
Sent: Wednesday, July 19, 2017 7:28 AM
To: 'Guy C Ruble'
Subject: NDA 208716 abemaciclib information request

Dear Dr. Ruble,

The purpose of this email is to convey to you the following information request from our clinical team:

1. For patients who were hospitalized in association with an AE of diarrhea, please provide narratives of patients who have lab results including stool studies if performed (e.g. stool cultures, stool osmolality)
2. For MONARCH 1 data, please provide updated topline efficacy results (response rate and duration of response only) using the most recent cut off date.
3. Clarify which cut off date will be used for MONARCH 1's safety update.
4. Clarify the menopausal status of patients in MONARCH 1.

Please provide a response by July 24, 2017 COB.

Thank you

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
07/19/2017

Kim, Janice

From: Kim, Janice
Sent: Monday, July 10, 2017 5:53 PM
To: 'Guy C Ruble'
Subject: RE: NDA 208716 Information Request

Yes July 14th, my apologies.

Thank you,

Janice

From: Guy C Ruble [mailto:ruble_guy_c@lilly.com]
Sent: Monday, July 10, 2017 5:48 PM
To: Kim, Janice
Subject: RE: NDA 208716 Information Request

Janice, I just wanted to clarify the due date, is it Fri July 14th? Thanks
Guy

From: Kim, Janice [mailto:Janice.Kim@fda.hhs.gov]
Sent: Monday, July 10, 2017 5:26 PM
To: Guy C Ruble <ruble_guy_c@lilly.com>
Subject: [EXTERNAL] NDA 208716 Information Request

Dear Dr. Ruble,

Please see the information request from our clinical pharmacology review team members regarding abemaciclib NDA 208716.

Reference is made to Sponsor's IR response dated June 30, 2017 ("response.pdf" in Submission 0013). Please simulate the time-course of tumor size change at 200 mg BID and 150 mg BID dosing regimen in patient populations in MONARCH 1 trial. The PK/PD simulations for tumor size change should incorporate the exposure change due to the dose modifications as observed in clinical trials. Submit the results, codes and datasets by July 15th COB.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
07/14/2017

Kim, Janice

From: Kim, Janice
Sent: Tuesday, July 11, 2017 1:54 PM
To: 'Guy C Ruble'
Subject: NDA 208716 Abemaciclib Information Request

Dear Dr. Ruble,

The following is an information request from our clinical team, please submit a response by July 14, 2017 12PM EST.

1. Submit data from JPBH study as you cite this as informing the dose reduction from 200 mg BID to 150 mg BID.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
07/11/2017

Kim, Janice

From: Kim, Janice
Sent: Monday, July 10, 2017 7:47 AM
To: 'Guy C Ruble'
Subject: NDA 208716 abemaciclib Information Request

Dear Dr. Ruble,

The purpose of this email is to convey to you the following information request from the clinical team for NDA 208716 abemaciclib, please submit a response by July 13, 2017 12PM EST:

1. For the MONARCH 2 study, clarify how the safety tables presented in the label were created. Based on the ADAE dataset, there are 437 patients in the abemaciclib and fulvestrant arm and 205 patients in the placebo arm included in the safety population.
2. In MONARCH 2, there were endocrine therapy naïve patients who were excluded from the ITT efficacy population, but should be considered part of the safety population if they received drug. Please provide safety tables including these patients in the analysis.

Thank you

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
07/10/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, June 29, 2017 8:12 AM
To: 'Guy C Ruble'
Subject: NDA 208716 abemaciclib Information Request - ClinPharm

Dear Dr. Ruble,

The purpose of this email is to convey to you the following information request:

Reference is made to Table 5 of the draft labeling text in module 1.14.1.3 of NDA 208716 submitted on May 5th, 2017:

(b) (4)

Please submit a response by July 5, 2017 COB.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
06/29/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208716

PRIORITY REVIEW DESIGNATION

Eli Lilly and Company
Attention: Guy Ruble, PharmD
Director, Global Regulatory Affairs, Oncology, North America
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Ruble:

Please refer to your New Drug Application (NDA) dated May 5, 2017, received May 5, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Verzenio (abemaciclib); 50 mg, 100 mg, 150 mg, 200 mg tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is January 5, 2018.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 22, 2017

While conducting our filing review, we identified potential review issues and will communicate them to you on or before July 18, 2017.

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

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Acting Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

JULIA A BEAVER
06/28/2017

Kim, Janice

From: Kim, Janice
Sent: Tuesday, June 27, 2017 3:57 PM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request

Dear Dr. Ruble,

The purpose of this email is to convey to you're the following information requests (please note 2 IRs are included in this email) both due July 10, 2017 COB.

1. Reference is made to the report "Pop PK 02 Report" in Module 5.3.3.5 (Submission 0000) and the report "Clinical Pharm Summary" in Module 2.7.2 (Submission 0000). Data from Study JPCA (C3 capsule) suggested dose proportional PK from 200 mg to 600 mg. Please provide rationale for the saturable absorption process in the final mechanistic model. If evidence suggested that the absorption process differed from one formulation to another, it should be modeled differently for different formulations. Alternatively, popPK modeling can be conducted based on data from the C3 formulation only to support labeling and subsequent ER analysis. Please update report with refined popPK and ER analysis accordingly, if needed.

2. Your PBPK report states that "The difference between the 50mg and 200mg models is primarily in the fraction of abemaciclib escaping first pass gut metabolism (F_G)." Please provide the mechanistic rationale for differences in Fg based on the dose of 50 mg versus 200 mg.

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
06/28/2017

From:	Fahnbulleh, Frances
To:	Guy C Ruble
Cc:	Kim, Janice
Subject:	NDA 208716 Verzenio
Date:	Wednesday, June 21, 2017 10:12:13 PM

Dear Guy,

Reference is made to NDA 208716 submitted and received on May 5, 2017 for Verzenio (abemaciclib). Further reference is made to the Labeling submitted there in. We have the following information request:

To facilitative our review of NDA 208716, please submit one representative, intend-to-market physical samples for each of your proposed packaging configuration, which includes the Verzenio (b) (4) *Submit the physical samples by June 30, 2017.*

The physical samples should be mailed to:

Frances Fahnbulleh

Safety Regulatory Health Project Manager

10903 New Hampshire Avenue

White Oak, Building 22

Rm 4404

Silver Spring, MD 20993-002

Best Regards,

Frances

Frances Fahnbulleh, RPh, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
CDER/FDA/WO22 , Rm#4404
Ph: 301-796-0942/Fax: 301-796-9835
Email: Frances.Fahnbulleh@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/

FRANCES G FAHNBULLEH
06/22/2017

Wahby, Sakar

From: Wahby, Sakar
Sent: Tuesday, June 20, 2017 9:51 AM
To: 'ruble_guy_c@lilly.com'
Cc: Kim, Janice
Subject: Re: NDA 208716

Importance: High

Dr. Ruble,

I'm covering for my colleague Janice Kim today, in regards to your question below, #2 is the correct rationale (FDA is asking for an analysis of MONARCH 1 and MONARCH 2 based on the data .. (2) for the first 6 mo of treatment of randomized and treated patients). Feel free to contact me if you have any questions.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP1
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
(P): 240-402-5364
(F): 301-796-9845

From: Guy C Ruble [mailto:ruble_guy_c@lilly.com]
Sent: Tuesday, June 20, 2017 8:32 AM
To: Minie, Leyish
Cc: Kim, Janice
Subject: RE: NDA 208716

Hi Minie
I am acknowledging receipt. And my team has a clarification question. Lilly would like to confirm our understanding.

Could FDA explain what is the rationale for the analysis?

Is FDA asking for an analysis of MONARCH 1 and MONARCH 2 based on the data ..

(1) From start of study conduct to 6 months (there is typically a lower enrollment of patients at the beginning of a study so this approach would results in a smaller dataset for comparison)

OR

(2) for the first 6 mo of treatment of randomized and treated patients

Thanks for clarifying.
Guy

From: Minie, Leyish [mailto:Leyish.Minie@fda.hhs.gov]
Sent: Monday, June 19, 2017 9:45 PM
To: Guy C Ruble <ruble_guy_c@lilly.com>
Cc: Kim, Janice <Janice.Kim@fda.hhs.gov>
Subject: [EXTERNAL] NDA 208716

Dear Dr. Ruble,

The purpose of this email is to convey an Information Request from the clinical reviewer team. Please respond by Friday, June 23, 12pm EST. I'm covering for Janice.

For the first six months of study conduct for each MONARCH 1 and MONARCH 2, please provide the following:

1. The incidence of all grades of diarrhea
2. The incidence of grade 3/4 diarrhea
3. The rate of dose reductions/modifications
4. The average dose of loperamide used to manage diarrhea by study

Best Regards,

Leyish Minie, MSN, RN
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
leyish minie@fda hhs.gov
Tel: 301-796-5522
Fax: 301-796-9845

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

/s/

SAKAR M WAHBY
06/20/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, June 15, 2017 1:50 PM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request - Clinical

Dear Dr. Ruble,

Please provide responses to the following information requests regarding the data contained within the I3Y-MC-JPBN Clinical Study Report (NDA 208716) and submit a response by Monday, June 19th.

1. On page 130 of the I3Y-MC-JPBN CSR, it was claimed that "The median duration of diarrhea in Study 2 for Grades 2 and 3 were 7.5 days and 4.5 days, respectively". Please clarify the location of the datasets and the coding scripts that derived these results.
2. On page 108 of the I3Y-MC-JPBN CSR, it is noted that the median duration of therapy is 138.5 days. Please clarify the location of the datasets and the coding scripts that derived this result.
3. For "Table JPBN.12.17: Summary of Treatment-Emergent Maximum Postbaseline CTCAE Laboratory Abnormalities Based on Central Laboratory Analysis" located on page 144 of the I3Y-MC-JPBN CSR, please clarify the location of the datasets and the coding scripts that derived these results.
4. For Baseline Disease Characteristics described on page 106 of the I3Y-MC-JPBN CSR, please clarify the location of the datasets and the coding scripts that derived the results for:
    a. Metastatic Disease Site, n (%)
    b. Number of Metastatic Sites, n (%)
    c. Prior Chemotherapy, Metastatic Setting, n (%)

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
06/15/2017

Kim, Janice

From: Kim, Janice
Sent: Wednesday, June 14, 2017 4:38 PM
To: 'Guy C Ruble'
Subject: NDA 208716 abemaciclib IR

Dear Dr. Ruble,

Please find an information request from our clinical pharmacology reviewers, please note two different due dates:

Reference is made to the report "Pop PK 02 Report" in Module 5.3.3.5 (Submission 0000), the report "Clinical Pharm Summary" in Module 2.7.2 (Submission 0000), the biopharm summary report in Module 2.7.1 (Submission 0000), and the FDA Information Request on May 30, 2017.

Based on Table 2.7.2.19 in Clinical Pharm Summary, the variability in non-compartment PK parameters appears to be much larger in cancer patients than in healthy subjects. However, the observed PK difference might be attributed to formulation differences since Studies JPBA and JPBC used C1 capsules while the other studies used C2/C3 capsules. In Figure 2.7.1.12. of the biopharm summary report, PK variability in subjects taking C3 capsule appears smaller than in subjects taking C1 capsules.

1. Please evaluate the potential formulation effect on PK variability using the post-hoc estimates from your popPK analysis. Please submit your response and model output files for run1102c and run51 (e.g. sdtab1102C, sdtab51, and patab51), **by June 16, 2017.**
2. If a formulation effect on between subject variability is evident, please integrate this information in your updated popPK analysis with MONARCH 2 data. Update your simulation results to justify the dose selection and proposed dose reduction in patients taking T1 tablet (which is bioequivalent to C3 capsule with similar between subject variability). **Please submit the analysis by June 30, 2017.**

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
06/15/2017

Kim, Janice

From: Kim, Janice
Sent: Wednesday, June 14, 2017 4:37 PM
To: 'Guy C Ruble'
Subject: NDA 208716 IR

Dear Dr. Ruble,

Please refer to your NDA 208716 submitted on May 5th, 2017. Provide a written response to the following information request by COB June 16th, 2017:

1) Submit a table summarizing the results of Incurred Samples Reanalysis conducted for the trials included in this application. Specifically denote the percentage of the samples that fail and provide specific reasons for each failure in the table.

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
06/15/2017

Kim, Janice

From: Kim, Janice
Sent: Monday, June 12, 2017 12:36 PM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request

Dear Dr. Ruble,

Please refer to your NDA208716 submitted on May 5th, 2017. Provide a written response to the following information request by COB June 16th, 2017, along with relevant plots, datasets and programs:

1) Submit a table summarizing the efficacy outcomes of all patients with 2 or more dose reductions from both registration trials (Monarch 1 and 2). In addition, include efficacy results and survival graphs stratifying by dose levels with longest duration for both registrations trials. The response to this request would be used to further assess the adequacy of the proposed dose modification of abemaciclib from 200 mg down to 50 mg twice daily.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
06/12/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, June 08, 2017 8:41 AM
To: 'Guy C Ruble'
Subject: Abemaciclib NDA 208716

Dear Dr. Ruble,

Reference is made to Lilly's 5-Jun-2017 responses to FDA's 30-May-2017 information request. FDA responses to Lilly's proposals are provided below.

FDA response to Lilly responses to Request 1:
FDA agrees with Lilly's proposed analysis plan and submission timeline.

FDA response to Lilly responses to Request 2:

1. FDA agrees with Lilly's proposed exposure-response analysis plan (i.e. dynamic PK/PD modeling) and submission timeline for MONARCH 2.
2. Exposure measures in jpbn_pp.xpt are not adequate for exposure-response analysis for MONARCH 1. Most safety and sometimes efficacy events occur before the end of treatment. Some safety events triggered dose reduction. Therefore, the average exposure during the course of treatment tends to underestimate drug exposure up to the time of event. Using individual predicted steady state exposures for the average dose each patient received from the beginning of treatment **to the time of event** or the end of treatment, whichever happened earlier, may reduce bias introduced by late exposures after the event. Please include individual predicted exposure measures, time to events, average daily dose, and events (i.e. safety or efficacy endpoints) in the same analysis dataset.

FDA response to Lilly responses to Request 3:
FDA agrees with Lilly's proposed submission timeline. Please include exposure measures, time to events, and events in the same analysis dataset.

FDA response to Lilly responses to Request 4:
FDA agrees with Lilly's proposed submission timeline.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
06/08/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106100
NDA 208716

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Eli Lilly and Company
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

ATTENTION: Guy C. Ruble, PharmD, RAC
Director, Global Regulatory Affairs-US

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 and to your New Drug Application (NDA) dated and received May 5, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abemaciclib Tablets, 50mg, 100mg, 150mg and 200mg.

We also refer to your March 29, 2017, IND correspondence, received March 29, 2017, and to your May 5, 2017, NDA correspondence, received May 5, 2017, requesting review of your proposed proprietary name, Verzenio.

We have completed our review of the proposed proprietary name, Verzenio, and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your May 5, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Janice Kim, Regulatory Project Manager in the Office of New Drugs, at (301) 796-9628.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
06/08/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO: **CDER-DMPP-PatientLabelingTeam**	FROM: (Name/Title, Office/Division/Phone number of requestor) Janice Kim/Regulatory Project Manager/DOP1/301-796-9628

REQUEST DATE: May 31, 2017	NDA/BLA NO.: NDA 208716	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW) New NDA

NAME OF DRUG: Abemaciclib	PRIORITY CONSIDERATION: YES	CLASSIFICATION OF DRUG: Oncology	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) August 31, 2017

SPONSOR: Eli Lilly	PDUFA Date: January 5, 2018; **TARGET Action Date = September 29, 2017**

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☒ ORIGINAL NDA/BLA/ANDA
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☒ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission:
Application 208716 - Sequence 0000 - 0000 () /

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

Filing/Planning Meeting: 6/7/2017

Mid-Cycle Meeting: 7/25/2017

Labeling Meetings: 7/18/2017, 725/2017, 8/3/2017, 8/7/2017, 8/15/2017, 8/17/2017

Wrap-Up Meeting: 9/8/2017

SIGNATURE OF REQUESTER
Janice Kim, PharmD, MS

SIGNATURE OF RECEIVER

Version: 06/06/2016

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
05/31/2017

Kim, Janice

From: Kim, Janice
Sent: Tuesday, May 30, 2017 2:08 PM
To: 'Guy C Ruble'
Subject: NDA 208716 - Abemaciclib Information Request

Dear Dr. Ruble,

The purpose of this email is to convey to you the following information request:

Reference is made to the Report "Pop PK 02 Report" in Module 5.3.3.5.

1. Incorporate diarrhea AE into the population PK analysis dataset, and evaluate the covariate effect of diarrhea as a time-dependent event on abemaciclib PK. For example, patient I3Y-MC-JPBN-100-01061 in Study JPBN had one diarrhea AE record between 2014-11-13 and 2014-11-15, in dataset AE.xpt. For Patient I3Y-MC-JPBN-100-01061, dosing records and PK records between 2014-11-13 and 2014-11-15 should be labeled with a positive diarrhea flag, while dosing records and PK records outside this period should be labeled with a negative diarrhea flag. Please provide the datasets/codes and update the popPK report accordingly.
2. Update exposure-response analysis using individual predicted steady state maximum and trough concentrations for the average dose each patient received from the beginning of treatment to the time of event or the end of treatment, whichever happened earlier. Please provide the datasets/codes and update the popPK report accordingly.
3. Submit the dataset/code for the exposure-response using the individual predicted minimum concentration after a single dose of 200 mg. If the information has been provided already, please identify location of the submission.
4. Update the timing of submission of updated population PK and exposure-response analyses and reports with data from MONARCH 2.

Please respond to the following requests by June 14, 2017 by 3:00 PM EST by official submission to your NDA.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
05/30/2017

Kim, Janice

From: Kim, Janice
Sent: Tuesday, May 23, 2017 2:27 PM
To: 'Guy C Ruble'
Subject: NDA 208716 Information Request

Dear Dr. Ruble,

The purpose of this email is to convey to you the following information request for NDA 208716 (abemaciclib) from our clinical pharmacology review team, please respond by May 25, 2017 by 2pm by email to facilitate review and by official submission to your NDA:

1. Please provide executable SimCYP model files associated with the following modeling reports: LY2835219 MM CYP3A4 INH 200mg, LY2835219 MM INH PBPK 50mg, and LY2835219 MM IND CYP3A Report Amendment as listed in module 5 section 3.2.2. Specifically include the following information as previously mentioned in the Note to Reviewer document:
    a. Abemaciclib and 3 metabolites drug model, workspace, and population files
    b. Parameter estimation files for abemaciclib and all relevant metabolites used in the model for prediction purposes and labeling claims
    c. Verification workspace, model, and population files for midazolam and quinidine with perpetrators
    d. PDF copies of relevant literature references, non-clinical, and clinical reports which were used as data sources for modeling

Note: CDs are no longer being accepted. Instead, you should submit these materials through the Gateway. For the various file types included in your PBPK analysis, please provide the various files as described below:

- For ASCII or XML file types, please provide a copy of these files as the native file extension and a second copy renamed as Name_extention.txt (or.xml).
- Software specific e files such as parameter estimation data files and simulation outputs should be submitted in acceptable archival file format .(xml or .xls).

2. Submit any additional calculations and assumptions used to facilitate the modeling exercise in a pdf document or excel file.
3. Submit any other reviewer aids that can facilitate the reviewer's ability to efficiently verify the PBPK modeling results on which the proposed labeling claims are made.

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
05/23/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, May 18, 2017 7:37 AM
To: 'Guy C Ruble'
Subject: NDA 208716 abemaciclib information request

Dear Dr. Ruble,

The purpose of this email is to convey to you the following information request:

With regards to Study I3Y-MC-JPCA, please upload digital ECGs with annotations (b) (4) (b) (4)

Thank you,

Janice

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
05/18/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM: Janice Kim, RPM
OND/OHOP/DOP1 phone: 301-796-9628

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5/17/17		208716	NDA	May 5, 2017

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
abemaciclib	Priority	Oncology	September 21 2017 **(See disclaimer below)

NAME OF FIRM: Eli Lilly

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Request feedback on carton and container labels.**
Application Orientation Meeting: June 16, 2017
Filing meeting: June 7, 2017
Mid-Cycle Meeting: July 25, 2017
Labeling Meetings: July 18 – August 17
Wrap-Up Meeting: September 8, 2017
PDUFA DATE: 1/5/2018 TARGET DATE: 9/29/17

Note due to the expedited nature of this application review deadlines may change.
EDR link to submission: \\CDSESUB1\evsprod\NDA208716\208716.enx

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply)
Janice Kim	☐ MAIL ■ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

APPEARS THIS WAY ON ORIGINAL

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
05/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208716

NDA ACKNOWLEDGMENT

Eli Lilly and Company
Attention: Guy Ruble, PharmD
Director, Global Regulatory Affairs – Oncology, North America
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Ruble:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Verzenio (abemaciclib); 50 mg, 100 mg, 150 mg, 200 mg tablets

Date of Application: May 5, 2017

Date of Receipt: May 5, 2017

Our Reference Number: NDA 208716

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 4, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 14.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

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).

If you have any questions, call me at (301) 796-9628.

Sincerely,

{See appended electronic signature page}

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

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

/s/

JANICE H KIM
05/12/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: QT-IRT

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Janice Kim, DOP1, 301-796-9628

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5/11/17		208716	NDA	5/5/17

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
abemaciclib	Yes	Oncology	07/18/17

NAME OF FIRM: Eli Lilly

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Priority NDA review

SIGNATURE OF REQUESTOR
Janice Kim

METHOD OF DELIVERY (Check all that apply)
☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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
05/11/2017

Kim, Janice

From: Kim, Janice
Sent: Thursday, May 11, 2017 9:10 AM
To: 'Guy C Ruble'
Cc: Kacuba, Alice
Subject: NDA 208716 IR

Dear Dr. Ruble,

For your NDA 208716, we have the following information request:

> We have attempted to load the data from the clinsite.xpt file that was submitted on 10May2017 into CDER's Clinical Investigator Site Selection Tool, but it has failed QC process. The submitted dataset appears to be missing summary site level data for Site 151 and Site 345. Explain why data for these two sites was excluded from the clinsite.xpt file that was submitted for the Monarch 2 study.

Please submit a response by noon tomorrow by email to facilitate review and by official submission to your NDA.

Thank you,

Janice Kim

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
05/11/2017

Kim, Janice

From: Kim, Janice
Sent: Tuesday, May 09, 2017 4:36 PM
To: 'Guy C Ruble'
Cc: Kacuba, Alice
Subject: NDA 208716 IR

Dear Dr. Ruble,

The purpose of this email is to convey to you the following information request:

Based on meeting minutes from April, it was indicated that MONARCH-2 datasets for OSI would be submitted in the first wave (deadline 5/5) if possible, but that if not you would submit as soon as possible. When are you planning to submit MONARCH-2 data sets for OSI to facilitate site inspection selection?

Please submit a response by noon tomorrow by email to facilitate review and by official submission to your NDA .

Janice Kim, PharmD, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@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
05/11/2017

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 March 31, 2017, containing a Pre-NDA meeting request. The purpose of the requested meeting was to receive input from the Agency regarding your proposed plan for your combined NDA submission.

Further reference is made to our Meeting Granted letter dated April 6, 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 March 31, 2017 correspondence.

If you have any questions, call me 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

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:	(b) (4) breast cancer, (b) (4)
Sponsor/Applicant Name:	Eli Lilly and Company
Regulatory Pathway:	505(b)(1)

1.0 BACKGROUND

Abemaciclib is a selective oral small molecule inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). Abemaciclib was granted a Breakthrough Therapy Designation on October 5, 2015 for patients with refractory Hormone Receptor-positive (HR +) advanced or metastatic breast cancer (mBC) based on results from the breast cancer cohorts in the first in human Study JPBA.

The Sponsor met with the Agency in December 2015 and March 2016 to reach agreement on the content, format and submission timing for the proposed MONARCH 1 New Drug Application (NDA). MONARCH 1 is a Phase 2 study that was designed to evaluate the single-agent activity and to characterize the AE profile of abemaciclib in women with refractory HR+, HER2- mBC.

In the most recent informal teleconferences on March 28, 2017, the Sponsor informed the Agency about the positive results of MONARCH 2. The Agency recommended a combined MONARCH 1 and MONARCH 2 NDA submission to achieve the most efficient and expeditious review of both studies. MONARCH 2 is a randomized, double-blind, placebo-controlled, Phase 3 study of fulvestrant with or without abemaciclib, a CDK4/6 inhibitor, for women with hormone receptor positive, HER2 negative locally advanced or metastatic breast cancer. FDA specifically requested MONARCH 2 topline datasets and a DRAFT U.S. Prescribing information which included the MONARCH 2 study. FDA also conveyed that the remaining information for MONARCH 2 could be submitted at a later date (60-90 days after the initial submission).

Based on this discussion, the Sponsor has decided to combine MONARCH 1 and MONARCH 2 for submission. The proposed timing and contents for the combined MONARCH 1/MONARCH 2 NDA are as follows:

3.1.1. On or before May 5, 2017 (Initial Wave)

Location	Content	Notes
Module 1	Content complete for both MONARCH 1 and MONARCH 2 with noted exceptions below	
Module 1: 1.6.2 Briefing documents for relevant meetings	Topline summary of MONARCH 2 (pre-NDA Briefing Document)	
Module 1 1.14.1.3 Draft Labeling Text	DRAFT USPI (Not annotated) Packaging files (b) (4) (b) (4) No PPI	DRAFT USPI will include MONARCH 2 information in the following locations: Section 1 Indication Section 2 Dosage and Administration Section 6 Adverse Reactions and Lab Abnormalities (only those ADRs that are clearly established) Section 14 Clinical Studies
Module 1 1.3.4 Financial Disclosure (FD)	FD for MONARCH 1	FD for MONARCH 2 are being collected and if complete, Lilly intends to include in the initial wave. If they are not complete, Lilly will submit them as soon as possible after the initial wave.
Module 2	Summaries included will only contain previously agreed MONARCH 1 NDA content 2.3 Quality Overall Summary	

Module 3	Complete CMC sections including both Drug Substance and Drug Product	The 12 month time point for the stability program for tablets 50-,100-, 150- and 200 mg within 30 days of the initial submission. An updated P.8.3., Stability data component will be submitted. As agreed during the January 26-27, 2017 Pre-Operational visit Lilly will provide processing and analytical information obtained from abemaciclib tablet process validation batches manufactured at the commercial manufacturing site (Carolina, Puerto Rico) within 60 days of the initial submission.
Module 4	Complete Nonclinical for MONARCH 1 and MONARCH 2	
Module 5	Pivotal CSRs: MONARCH 1 (JPBN) Safety CSRs: JPBA, JPBB, JPBC Clinical Pharmacology CSRs: JPBD, JPBE, JPBF, JPBG, JPBS, JPBU, JPBV, JPCA, JPCC	See Appendix 1 for study titles. MONARCH 2 (JPBL) CSR will be included if available. ECGs from clinical studies (JPBS, JPBC, JPBN, JPCA) have been uploaded to the warehouse and will be made available to FDA at the time of initial submission

Module 5 5.3.5 Reports of Efficacy and Safety Studies	MONARCH 1 complete datasets MONARCH 2 topline datasets	For MONARCH 2: 1. All SDTM in xpt format 2. Annotated CRF 3. 12 topline ADaM datasets in xpt format. These 12 cover everything in the pre-NDA BD and should cover the draft label: ADSL, ADPTDC, ADAE, ADLB, ADCM, ADEXSUM, ADRS, ADEVENT, ADTTE, ADEVENTIR, ADTTEIR, ADDS (disposition). 4. Define doc and specifications for these 12 topline ADaM datasets.
Module 5 5.3.5.4 Other Study Reports	Office of Scientific Investigations (OSI) Requests for MONARCH 1 and MONARCH 2	Lilly plans to include MONARCH 2 OSI requests in the initial wave but if they are not yet available, Lilly will submit as soon as possible to facilitate inspection planning

3.1.2. On or before July 5, 2017 (Final Wave)

Location	Content	Notes
Module 1	Final proposed USPI, annotated USPI PPI Packaging files (b) (4) (b) (4)	
Module 2	Updates will be made to 2.4 2.5 2.6 2.7	Updated to include nonclinical pharmacology reports of abemaciclib plus fulvestrant, clinical studies JPCK and MONARCH 2

Module 5 5.3.3 Reports of human pharmacokinetic (PK) studies	JPCK iohexol study MONARCH 2 Pop PK report	
Module 5 5.3.5 Reports of Efficacy and Safety Studies	MONARCH 2 CSR MONARCH 2 complete datasets	ADaM datasets covering: PROs, performance status, ECGs (local), hospitalizations, medical history, prior procedures, and vital signs. And supportive documentation

2.0 QUESTIONS AND RESPONSES

Question 1: Does FDA agree with the proposed initial submission (initial wave) content for the combined MONARCH 1 and MONARCH 2 NDA?

FDA Response to Question 1: Yes.

Question 2: Does FDA agree with the proposed final wave (~60 day after initial wave) content and timing for the combined MONARCH 1 and MONARCH 2 NDA?

FDA Response to Question 2: Yes. In addition, updated survival data should be included with the 90-day Safety update.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 6, 2017 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

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

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

3.1.1. On or before May 5, 2017 (Initial Wave)

Location	Content	Notes
Module 1	Content complete for both MONARCH 1 and MONARCH 2 with noted exceptions below	
Module 1: 1.6.2 Briefing documents for relevant meetings	Topline summary of MONARCH 2 (pre-NDA Briefing Document)	
Module 1 1.14.1.3 Draft Labeling Text	DRAFT USPI (Not annotated) Packaging files (b) (4) (b) (4) No PPI	DRAFT USPI will include MONARCH 2 information in the following locations: Section 1 Indication Section 2 Dosage and Administration Section 6 Adverse Reactions and Lab Abnormalities (only those ADRs that are clearly established) Section 14 Clinical Studies
Module 1 1.3.4 Financial Disclosure (FD)	FD for MONARCH 1	FD for MONARCH 2 are being collected and if complete, Lilly intends to include in the initial wave. If they are not complete, Lilly will submit them as soon as possible after the initial wave.
Module 2	Summaries included will only contain previously agreed MONARCH 1 NDA content 2.3 Quality Overall Summary	

Module 3	Complete CMC sections including both Drug Substance and Drug Product	The 12 month time point for the stability program for tablets 50-,100-, 150- and 200 mg within 30 days of the initial submission. An updated P.8.3., Stability data component will be submitted. As agreed during the January 26-27, 2017 Pre-Operational visit Lilly will provide processing and analytical information obtained from abemaciclib tablet process validation batches manufactured at the commercial manufacturing site (Carolina, Puerto Rico) within 60 days of the initial submission.
Module 4	Complete Nonclinical for MONARCH 1 and MONARCH 2	
Module 5	Pivotal CSRs: MONARCH 1 (JPBN) Safety CSRs: JPBA, JPBB, JPBC Clinical Pharmacology CSRs: JPBD, JPBE, JPBF, JPBG, JPBS, JPBU, JPBV, JPCA, JPCC	See Appendix 1 for study titles. MONARCH 2 (JPBL) CSR will be included if available. ECGs from clinical studies (JPBS, JPBC, JPBN, JPCA) have been uploaded to the warehouse and will be made available to FDA at the time of initial submission

Module 5 5.3.5 Reports of Efficacy and Safety Studies	MONARCH 1 complete datasets MONARCH 2 topline datasets	For MONARCH 2: 1. All SDTM in xpt format 2. Annotated CRF 3. 12 topline ADaM datasets in xpt format. These 12 cover everything in the pre-NDA BD and should cover the draft label: ADSL, ADPTDC, ADAE, ADLB, ADCM, ADEXSUM, ADRS, ADEVENT, ADTTE, ADEVENTIR, ADTTEIR, ADDS (disposition). 4. Define doc and specifications for these 12 topline ADaM datasets.
Module 5 5.3.5.4 Other Study Reports	Office of Scientific Investigations (OSI) Requests for MONARCH 1 and MONARCH 2	Lilly plans to include MONARCH 2 OSI requests in the initial wave but if they are not yet available, Lilly will submit as soon as possible to facilitate inspection planning

3.1.2. On or before July 5, 2017 (Final Wave)

Location	Content	Notes
Module 1	Final proposed USPI, annotated USPI PPI Packaging files (b) (4) (b) (4)	
Module 2	Updates will be made to 2.4 2.5 2.6 2.7	Updated to include nonclinical pharmacology reports of abemaciclib plus fulvestrant, clinical studies JPCK and MONARCH 2

Module 5 5.3.3 Reports of human pharmacokinetic (PK) studies	JPCK iohexol study MONARCH 2 Pop PK report	
Module 5 5.3.5 Reports of Efficacy and Safety Studies	MONARCH 2 CSR MONARCH 2 complete datasets	ADaM datasets covering: PROs, performance status, ECGs (local), hospitalizations, medical history, prior procedures, and vital signs. And supportive documentation

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.

  Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

  NDA NUMBER: LATE COMPONENT - BIOMETRICS
  NDA NUMBER: LATE COMPONENT - CLINICAL
  NDA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY
  NDA NUMBER: LATE COMPONENT - NONCLINICAL
  NDA NUMBER: LATE COMPONENT - QUALITY

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. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** 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.

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

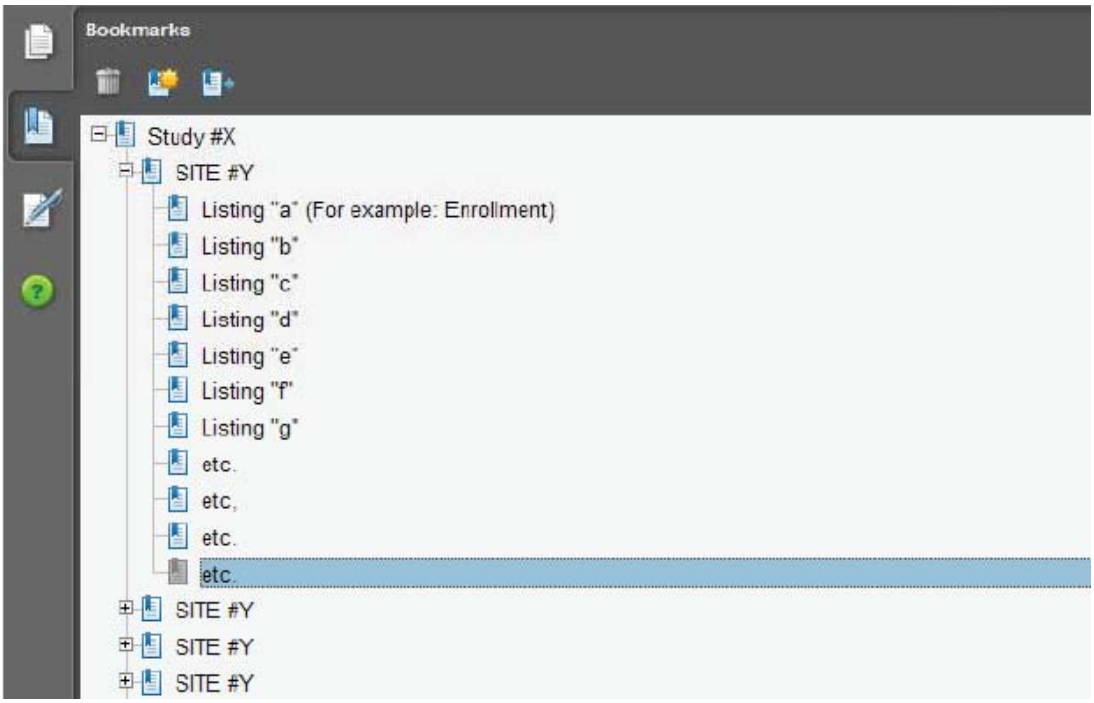
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571,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

APPEARS THIS WAY ON ORIGINAL

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
04/09/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106100

MEETING MINUTES

Eli Lilly and Company
Attention: Guy 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 meeting between representatives of your firm and the FDA on March 1, 2016. The purpose of the meeting was to discuss the clinical results of the MONARCH 1 study and other relevant data as well as reach agreement on submission plans for the proposed NDA.

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

If you have any questions, contact Tracy Cutler, 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}

Julia Beaver, MD
Acting 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:	Pre-NDA
Meeting Date and Time:	March 1, 2016; 2:00 pm – 3:00 pm
Meeting Location:	White Oak Campus, Building 22, Room 1419
Application Number:	IND 106100
Product Name:	Abemaciclib (LY2835219)
Indication:	Breast cancer
Sponsor/Applicant Name:	Eli Lilly and Company
Meeting Chair:	Julia Beaver, MD
Meeting Recorder:	Tracy Cutler, MPH, CCRP, CIP

FDA ATTENDEES

Amy McKee, MD, Acting Deputy Director, OHOP
Geoffrey Kim, MD, Director, DOP1
Amna Ibrahim MD, Deputy Director, DOP1
Laleh Amiri-Kordestani, MD, Acting Clinical Team Leader, DOP1
Julia Beaver, MD, Acting Clinical Team Leader, DOP1
Suparna Wedam, MD, Clinical Reviewer, DOP1
Michael Brave, MD, Clinical Reviewer, DOP1
Chana Weinstock, MD, Clinical Reviewer, DOP1
Amanda Walker, MD, Clinical Reviewer, DOP1
Xiao Hong Chen, PhD, Product Quality Team Leader, OPQ
Haw-Jyh Chiu, PhD Pharmacology/Toxicology Reviewer, DHOT
Jeanne Fourie Zirkelbach, PhD, Clinical Pharmacology Reviewer, DCP5
Shenghui Tang, PhD, Biostatistics Team Leader, DBV
Erik Bloomquist, PhD, Biostatistics Reviewer, DBV
Joyce Cheng, PhD, Biostatistics Reviewer, DBV
Christy Cottrell, Chief Project Management Staff, DOP1
Tracy Cutler, MPH, Regulatory Health Project Manager, DOP1

EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein, Independent Assessor

SPONSOR ATTENDEES

Richard Gaynor, MD, VP, Oncology Clinical & Product Development, Medical Affairs
Colleen Mockbee, RPh, Global Product Team Leader, Oncology
Ian Smith, MD, Senior Medical Director, Oncology
Andrew Koustenis, RPh, Clinical Research Advisor

Martin Frenzel, PhD, Senior Research Scientist, Statistics
Jon Denne, PhD, Senior Director, Statistics
Allen Melemed, MD, Distinguished Medical Fellow & Senior Director, Global Regulatory Affairs (GRA) – North America/Oncology
Guy Ruble, PharmD , Director, GRA – North America/Oncology
Richard Beckman, PhD, Senior Research Advisor, Biology
Joanne Cox, MD, Senior Medical Advisor, Global Patient Safety*
Dennis J. Slamon, MD, PhD, Chief, Division of Hematology-Oncology, and Executive Vice-Chair for Research, Department of Medicine; (b) (4) (b) (4)

**Attended via telephone.*

1.0 BACKGROUND

Abemaciclib is an oral, selective, and potent small-molecule CDK4 and CDK6 inhibitor. Data from the phase 1 study, I3Y-MC-JPBA (Study JPBA), demonstrated an objective response rate (ORR) of 33% and a median duration of response (DOR) of 13.4 months in women with hormone receptor (HR) positive advanced or metastatic breast cancer (JPBA Part D). The patients enrolled in this Part D were heavily pretreated: 36 of 47 patients received at least 4 systemic regimens prior to enrollment and the median number of prior regimens was 7. An ORR of 36% in patients with measurable disease was noted in a cohort of women with advanced or metastatic breast cancer that had progressed on prior fulvestrant therapy (JPBA Part G, combination with fulvestrant). The Food and Drug Administration (FDA) granted abemaciclib Breakthrough Therapy Designation on October 5, 2015, and Fast Track Designation on November 12, 2015, based on these results.

The purpose of this pre-NDA meeting is to discuss the suitability of the proposed contents and submission timeline for a New Drug Application (NDA) with abemaciclib. Based on the interim results from MONARCH 1, Lilly plans to submit a NDA for accelerated approval with the following indication: "*Abemaciclib is indicated for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−) metastatic breast cancer* (b) (4) *whose disease has progressed* (b) (4) *after endocrine therapy and who previously received* (b) (4) *chemotherapy* (b) (4)*, one of which was in the metastatic setting. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of the clinical benefit in a confirmatory trial.*"

MONARCH 1 (Study I3Y MC JPBN) is a phase 2, multicenter, nonrandomized, open-label study with single agent abemaciclib in patients with HR-positive, HER2-negative MBC who have progressed on or after prior endocrine therapies. To be eligible, patients must have received prior treatment with at least 2 chemotherapy regimens; at least 1 of these regimens must have been administered in the metastatic setting, and at least 1 regimen must have contained a taxane. Patients could not have received more than 2 prior chemotherapy regimens in the metastatic setting. The primary endpoint was investigator assessed ORR.

A total of 132 patients were enrolled from June 10, 2014, to April 30, 2015. Enrolled patients had a median of 3 prior therapies for locally advanced or MBC and 90% had visceral disease. Results from a planned interim analysis performed 8 months after the last patient entered treatment demonstrated a confirmed investigator-assessed ORR of 17.4% (95% confidence interval [CI]: 11.4%, 25.0%). The median duration of response was estimated to be 9.3 months.

The most common adverse events (AE) in MONARCH 1 were diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, and anemia. Patients experiencing one or more ≥Grade 3 CTCAE was 56.8%, those occurring in ≥10% included neutropenia, and diarrhea. Diarrhea was the most common AE, experienced by 90% of the patients (Grade 1: 42.4%, Grade 2: 28%, Grade 3: 19.7%). The sequelae of diarrhea caused hospitalization in 3 patients and study drug discontinuation in 1 patient. Sixty two patients (47%) required dose reductions, with most of these due to diarrhea (27 patients). The discontinuation rate due to AEs was 6.8%. There were 3 deaths due to AEs (sepsis, lung infection and pneumonitis).

Lilly plans to use FDA's responses at this pre-NDA meeting to finalize plans for the proposed NDA.

FDA sent Preliminary Comments to Eli Lilly and Company on February 24, 2016.

2.0 DISCUSSION

Question 1: Does FDA agree that the interim results of the MONARCH 1 study provided in the briefing document (that is, confirmed objective response rate supported by duration of response) can form the basis for initiating a rolling submission of an NDA for accelerated approval of the proposed indication?

FDA Response: No. We do not recommend the submission of an application based on the results of MONARCH 1.

Based on results from MONARCH 1, abemaciclib does not appear to provide a meaningful therapeutic benefit over existing treatments based on efficacy, safety, or novel mechanism of action, which would justify accelerated approval. We have decided not to rescind the Breakthrough Therapy Designation for abemaciclib at this time. We will continue to provide guidance with the abemaciclib clinical development program and await the results from the ongoing randomized studies.

Sponsor Response: Lilly would like to discuss FDA's response and the criteria for Accelerated Approval as they apply to the MONARCH 1 study result, population studied, and available therapies with regard to novel mechanism and potential advantages in efficacy and safety.

Meeting Discussion: **The Sponsor stated that they will return with final results from the MONARCH 1 study to discuss plans with the Agency regarding the abemaciclib development program and regulatory pathway.**

Question 2: Can FDA provide guidance on the need to submit patient scans proactively in the NDA or can the scans be available upon request?

FDA Response: See response to Question #1. Generally scans can be available upon request and do not require submission with the NDA.

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

Question 3: Based on preliminary review of the efficacy and safety data from the MONARCH 1 study, does FDA agree that a REMS is not required for inclusion in the NDA?

FDA Response: See response to Question #1. This would be a review issue.

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

Question 4: Can FDA comment on the initial dose and dose reduction guidelines for abemaciclib outlined in the Target Product Profile (TPP) Section 2?

FDA Response: See response to Question #1. This would be a review issue.

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

Question 5: Does FDA agree with the proposed content and timing for the updated safety information to be provided in the 4-month safety update?

FDA Response: The proposed plan appears acceptable; however, see response to Question #1.

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

Question 6: Does FDA agree that the proposed clinical pharmacology package to be included in the NDA is sufficient to support labeling?

FDA Response: In general the proposed clinical pharmacology development package appears acceptable, however the final determination will be made once additional results from your ongoing randomized studies are available. See response to Question # 1.

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

Question 7: Can FDA comment on the labeling approach being proposed in Sections 6.1, (b) (4), (b) (4), and 12.3 of the Target Product Profile describing abemaciclib effects on serum creatinine and whether this is adequate for informing prescribers?

FDA Response: Labeling is not discussed prior to NDA review. The impact of the abemaciclib associated increase in serum creatinine on the safety of abemaciclib will be a review issue.

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

Question 8: Can FDA comment on the labeling approach being proposed in Section 7.2 and 12.3 of the Target Product Profile describing the drug-drug interaction data with CYP3A inducers, given the clinical and supporting PBPK modeling results?

FDA Response: Your approach of using PBPK to predict the effect of other CYP3A modulators on the PK of abemaciclib is reasonable. The adequacy of your model in supporting dose recommendations of abemaciclib under different drug-drug interaction scenarios, including the labeling claims, will be a review issue.

At the NDA stage, submit PBPK study report and model related files for review. Model files are those generating final PBPK simulations (e.g., drug model files, population files, workspace files and output files). These files should be executable by the FDA reviewers. Based on initial review of your PBPK submission, FDA may request additional information.

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

Question 9: Does FDA agree that the nonclinical package to be included in the NDA is sufficient to support approval and labeling of abemaciclib for the proposed indication?

FDA Response: We agree that the nonclinical studies outlined in the meeting briefing package appear sufficient to support submission of an NDA for abemaciclib for the proposed indication. The adequacy of the resulting nonclinical data to support approval of abemaciclib for the proposed indication will be determined following review of all data included in the NDA submission.

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

Question 10: Can FDA provide preliminary comment on the abemaciclib blister package presentations, (b) (4)

FDA Response: We agree that blister packaging is a better packaging design (b) (4) for patient compliance provided the stability of the drug product is not compromised. (b) (4)

[redacted] (b) (4)

Sponsor Response: Lilly thanks FDA for their comments, and clarifies that Module 3, Quality, will include drug product stability data to support the adequacy of the primary blister container closure.

Lilly would appreciate the opportunity to have a brief, separate follow-up teleconference within the next three weeks (March 1 through March 18) with the reviewers to seek clarification on their recommendations [redacted] (b) (4) The Lilly team would consist of members of the Regulatory CMC and Packaging Development organizations.

Meeting Discussion: **Discussion deferred to a separate CMC follow-up meeting.**

3.0 OTHER IMPORTANT MEETING LANGUAGE

3.1 Discussion of the Content of a Complete Application

As stated in our January 20, 2016, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

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

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

3.2 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 (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. 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 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.

3.3 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 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.

3.4 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.				

3.5 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.

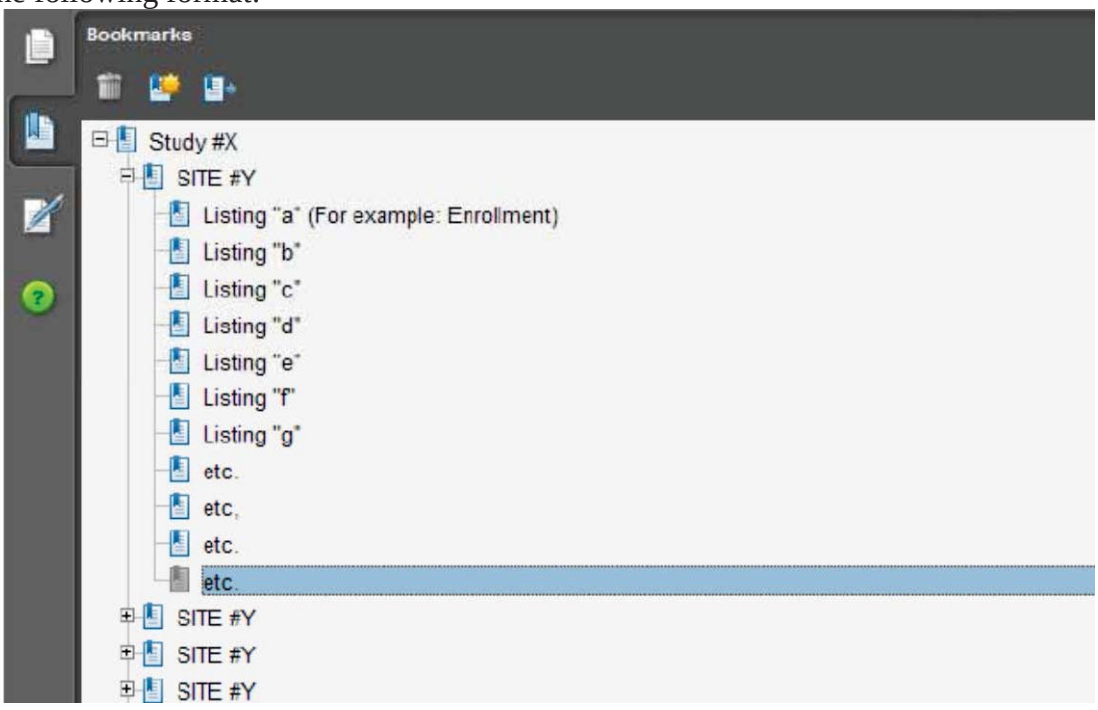
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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:

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

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.

APPEARS THIS WAY ON ORIGINAL

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

Eli Lilly and Company response to preliminary comments – received via email on February 29, 2016

2.1 DISCUSSION

Question 1: Does FDA agree that the interim results of the MONARCH 1 study provided in the briefing document (that is, confirmed objective response rate supported by duration of response) can form the basis for initiating a rolling submission of an NDA for accelerated approval of the proposed indication?

FDA Response: No. We do not recommend the submission of an application based on the results of MONARCH 1.

Based on results from MONARCH 1, abemaciclib does not appear to provide a meaningful therapeutic benefit over existing treatments based on efficacy, safety, or novel mechanism of action, which would justify accelerated approval. We have decided not to rescind the Breakthrough Therapy Designation for abemaciclib at this time. We will continue to provide guidance with the abemaciclib clinical development program and await the results from the ongoing randomized studies.

Lilly response:
Lilly would like to discuss FDA's response and the criteria for Accelerated Approval as they apply to the MONARCH 1 study result, population studied and available therapies with regard to novel mechanism and potential advantages in efficacy and safety.

Question 2: Can FDA provide guidance on the need to submit patient scans proactively in the NDA or can the scans be available upon request?

FDA Response: See response to Question #1. Generally scans can be available upon request and do not require submission with the NDA.

Lilly response: No further comment

Question 3: Based on preliminary review of the efficacy and safety data from the MONARCH 1 study, does FDA agree that a REMS is not required for inclusion in the NDA?

FDA Response: See response to Question #1. This would be a review issue.

Lilly response: No further comment

Question 4: Can FDA comment on the initial dose and dose reduction guidelines for abemaciclib outlined in the Target Product Profile (TPP) Section 2?

FDA Response: See response to Question #1. This would be a review issue.

Lilly response: No further comment

Question 5: Does FDA agree with the proposed content and timing for the updated safety information to be provided in the 4-month safety update?

FDA Response: The proposed plan appears acceptable; however, see response to Question #1.

Lilly response: No further comment

Question 6: Does FDA agree that the proposed clinical pharmacology package to be included in the NDA is sufficient to support labeling?

FDA Response: In general the proposed clinical pharmacology development package appears acceptable, however the final determination will be made once additional results from your ongoing randomized studies are available. See response to Question # 1.

Lilly response: No further comment

Question 7: Can FDA comment on the labeling approach being proposed in Sections 6.1, (b) (4), (b) (4), and 12.3 of the Target Product Profile describing abemaciclib effects on serum creatinine and whether this is adequate for informing prescribers?

FDA Response: Labeling is not discussed prior to NDA review. The impact of the abemaciclib associated increase in serum creatinine on the safety of abemaciclib will be a review issue.

Lilly response: No further comment

Question 8: Can FDA comment on the labeling approach being proposed in Section 7.2 and 12.3 of the Target Product Profile describing the drug-drug interaction data with CYP3A inducers, given the clinical and supporting PBPK modeling results?

FDA Response: Your approach of using PBPK to predict the effect of other CYP3A modulators on the PK of abemaciclib is reasonable. The adequacy of your model in supporting dose recommendations of abemaciclib under different drug-drug interaction scenarios, including the labeling claims, will be a review issue.

At the NDA stage, submit PBPK study report and model related files for review. Model files are those generating final PBPK simulations (e.g., drug model files, population files, workspace files and output files). These files should be executable by the FDA reviewers. Based on initial review of your PBPK submission, FDA may request additional information.

Lilly response: No further comment

Question 9: Does FDA agree that the nonclinical package to be included in the NDA is sufficient to support approval and labeling of abemaciclib for the proposed indication?

FDA Response: We agree that the nonclinical studies outlined in the meeting briefing package appear sufficient to support submission of an NDA for abemaciclib for the proposed indication. The adequacy of the resulting nonclinical data to support approval of abemaciclib for the proposed indication will be determined following review of all data included in the NDA submission.

Lilly response: No further comment

Question 10: Can FDA provide preliminary comment on the abemaciclib blister package presentations, specifically regarding the "Initial Dose" pack, which is intended to support dosage adjustments if patients have tolerability issues when starting treatment with abemaciclib?

FDA Response: We agree that blister packaging is a better packaging design (b) (4) for patient compliance provided the stability of the drug product is not compromised. (b) (4)

Lilly response: Lilly thanks FDA for their comments, and clarifies that Module 3, Quality, will include drug product stability data to support the adequacy of the primary blister container closure.

Lilly would appreciate the opportunity to have a brief, separate follow-up teleconference within the next three weeks (March 1 through March 18) with the reviewers to seek clarification on their recommendations (b) (4) The Lilly team would consist of members of the Regulatory CMC and Packaging Development organizations.

APPEARS THIS WAY ON ORIGINAL

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
03/15/2016

JULIA A BEAVER
03/15/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106100

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

Eli Lilly and Company
Attention: Guy Ruble, PharmD, RAC
Director, Global Regulatory Affairs-US
Lilley 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 your August 7, 2015, request for Breakthrough Therapy designation. We have reviewed your request and have determined that abemaciclib (LY2835219) for patients with refractory hormone receptor positive (HR+) advanced or metastatic breast cancer meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of abemaciclib (LY2835219) for patients with refractory hormone receptor positive (HR+) advanced or metastatic breast cancer to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.*[1]

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics,* Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting[2]. Please refer to the *Guidance for Industry: Formal*

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf
[2] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/Ma

Meetings between FDA or Sponsors and Applicants[3] for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the breakthrough therapy designation for abemaciclib (LY2835219) for patients with refractory hormone receptor positive (HR+) advanced or metastatic breast cancer is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

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

Sincerely,

{See appended electronic signature page}

Geoffrey S. Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

---

nualofPoliciesProcedures/default.htm.

[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

---

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

/s/

GEOFFREY S KIM
10/05/2015

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 106100
Request Receipt Date	8/7/2015
Product	Abemaciclib
Indication	Hormone receptor positive metastatic breast cancer
Drug Class/Mechanism of Action	CDK 4/6 Inhibitor
Sponsor	Eli Lilly
ODE/Division	DOP1
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	10/6/2015

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   "Patients with hormone receptor positive advanced or metastatic breast cancer that are no longer benefiting from endocrine therapy or that have progressed on multiple lines of chemotherapy"

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Breast cancer is the most commonly diagnosed malignancy in women, and the second leading cause of cancer deaths in women in the United States (US), with 231,840 new cases of breast cancer and 40,000 deaths estimated in 2015. The hormone receptor+ (HR+)/HER2- subtype is the most prevalent subtype of breast cancer and accounts for approximately 70% of all breast cancers. The HR+/HER2+ subtype is estimated to be approximately 10%).

Women with Stage IV breast cancer have a 5-year survival rate of 26%. Stage IV or metastatic breast cancer (MBC) is incurable and considered a serious and life-threating disease. Despite the availability of endocrine therapies for treatment of HR+ advanced breast cancer, patients ultimately develop resistance, progressive disease (PD), and go on to receive multiple additional therapies including several different

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

cytotoxic chemotherapies. Likewise, women with HR+/HER2+ MBC once treated with standard HER2+ directed therapies eventually progress and have limited effective treatment options. After progressing on 1 to 2 cytotoxic chemotherapy regimens in the metastatic setting, life expectancy is only 12 to 15 months).

Patients presenting with HR+/HER2- MBC are typically treated initially with endocrine therapies if the cancer is not progressing rapidly and/or if urgent palliation of symptoms is not required If a patient initially has responded to endocrine therapy but eventually progresses, a second or even third endocrine therapy may be tried in order to avoid initiation of cytotoxic chemotherapy. FDA-approved endocrine therapies available HR+ MBC include tamoxifen, anastrozole, letrozole, toremifene, exemestane, and fulvestrant. In addition, everolimus has been approved in combination with exemestane and palbociclib has been approved in combination with letrozole.

For HR+ breast cancer, most patients will eventually receive cytotoxic chemotherapy at some point through the course of their treatment either as initial treatment or following endocrine therapy(ies). FDA-approved cytotoxic chemotherapies for MBC include gemcitabine, docetaxel, paclitaxel, nab-paclitaxel, capecitabine, ixabepilone, eribulin and ixabepilone.

For patients presenting with HR+/HER2+ MBC, HER2-directed therapies are the current standard of care in combination with chemotherapy. Once relapse or progression occurs, a second HER2 targeted agent is administered. HR+/HER2+ patients may or may not receive concomitant endocrine therapy. FDA-approved HER2 directed therapies include trastuzumab, lapatinib, pertuzumab and ado-trastuzumab emtansine.

Abemaciclib is a potent and selective small molecule inhibitor of CDK4 and CDK6. CDK4 and CDK6 are that are catalyzed by D-type cyclins to phosphorylate their substrate, retinoblastoma protein (Rb), resulting in progression of the cell cycle. In breast cancer, the Cyclin D1/CDK4 complexes contribute to tumor cell growth by directly phosphorylating Rb, thereby reducing the growth-suppressive effects exerted by this protein. Cyclin D3/CDK6 is particularly relevant in regulating the maturation of hematopoietic stem cells within the bone marrow by promoting the exit of such stem cells from quiescence.

Palbociclib is a CDK4/6 inhibitor approved by the FDA in 2015 for first line therapy in patients with advanced or metastatic hormone receptor positive breast cancer in combination with letrozole. Abemaciclib differs from palbociclib in that it appears to have single agent activity in a heavily pretreated population. One small study has shown limited activity for single agent palbociclib (ORR 6%) In contrast, abemaciclib monotherapy data in abemaciclib has demonstrated an overall repsonse rate (ORR) of 33% (12/36) and a median duration of response (DOR) of 13.4 months in heavily pretreated (median of 7 prior therapies) patients with HR+ MBC. Results are further detailed below in Question 10.

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The Sponsor is using overall response rates (along with duration of response) results from Study JPBA to support this BTDR. ORR was a secondary endpoint from this Phase I study. ORR has been used by the FDA previously to give regular approval for drugs used in the treatment of metastatic breast cancer. The Sponsor has several clinical studies in development to confirm the results from Study JPBA. These include:

MONARCH 1 (Study I3Y-MC-JPBN)

- *A non-randomized study of abemaciclib 200 mg twice daily as a single-agent treatment for women with HR+, HER2- MBC after prior endocrine therapy and failure of 1 to 2 prior systemic chemotherapies for metastatic disease*
- *Active; Primary endpoint=ORR*

neoMONARCH (Study I3Y-MC-JPBY)

- *A randomized, controlled study of abemaciclib 150 mg twice daily alone or in combination with anastrozole to evaluate the biological effect in early-stage HR+/HER2- breast cancer*
- *Planned for August 2015; Primary endpoint=Change from baseline to 2 wks in Ki67 expression*

Study I3Y-MC-JPBO

- *A non-randomized study of abemaciclib 200 mg twice daily alone or in combination with endocrine or HER2 therapy in women with HR+ MBC (HER2- or HER2+) who have developed brain metastases.*
- *Active; Primary endpoint=objective intracranial response rate (OIRR)*

monarcHER (Study I3Y-MC-JPBZ)

- *A randomized, controlled study of abemaciclib 150 mg twice daily in combination with herceptin (± fulvestrant) for treatment of women with HR+/HER2+ MBC after prior therapy with trastuzumab emtansine (TDM1).*
- *Planned for January 2016; Primary endpoint=PFS*

MONARCH 2 (Study I3Y-MC-JPBL)

- *A randomized, controlled study of abemaciclib 150 mg twice daily in combination with fulvestrant in postmenopausal women with HR+/HER2- advanced or MBC after prior endocrine therapy*
- *Active; Primary endpoint=PFS*

MONARCH 3 (Study I3Y-MC-JPBM)

- *A randomized, controlled study of abemaciclib 150 mg twice daily in combination with nonsteroidal aromatase inhibitors (anastrozole or letrozole) as initial treatment for postmenopausal women with HR+/HER2- advanced or MBC*
- *Active; Primary endpoint=PFS*

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

Clinical trial endpoints that have been used to support traditional approval of drugs used in patients with metastatic breast cancer include: *ORR, TTP, PFS, and OS*

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None other than tumors that are HR+.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

Table 5.1. FDA-Approved Endocrine Therapies for HR+ Metastatic Breast Cancer

Drug	Year Approved	ORR (%) [1]	DOR (months)	PFS or TTP (months)	Line of Therapy
Tamoxifen[2]	1977	17 vs. 21.1 (anastrozole); 32.6 vs. 32.9 (anastrozole)	NR	NR	1
Anastrozole	1995	21.1 vs. 17 (tamoxifen); 32.9 vs. 32.6 (tamoxifen)	NR	11.1 vs. 5.6; 8.2 vs. 8.3	1
Letrozole	1997	32 vs. 21 (tamoxifen)	18	9.4 vs. 6.0	1
Toremifene	1997	21.3 vs. 19.1 (tamoxifen 20 mg), 20.4 vs. 20.8 (tamoxifen 40 mg), 31.3 vs. 37.3 (tamoxifen 40 mg)	NR	5.6 vs. 5.8; 4.9 vs. 5.0; 7.3 vs. 10.2	1
Letrozole + palbociclib[3]	2015	55.4 vs. 39.4 (letrozole)	NR	20.2 vs. 10.2	1
Exemestane	1999	15.0 vs. 12.4 (megesterol)	17.8 vs. 16.6	4.7 vs. 3.9	2
Fulvestrant	2002	17 vs. 17 (anastrozole); 20.3 vs. 14.9 (anastrozole)	NR	5.5 vs. 3.4; 5.5 vs. 5.2	2
	2010	13.8 (500 mg) vs. 14.6 (250 mg)	NR	6.5 vs. 5.4;	2
Exemestane + everolimus	2012	12.6 vs. 1.7 (exemestane)	NR	11.0 vs. 4.1 (ind); 7.8 vs. 3.2; (inv)	2

Abbreviations: CI = confidence interval; DOR = duration of response; FDA = Food and Drug Administration; HR+ = hormone receptor positive; ind = independent radiologic review; inv = investigator assessed; NR = no response; ORR = objective response rate; PFS = progression-free survival; TTP = time to progression.

1 Data from United States prescribing information unless otherwise noted.
2 Data from Arimidex labeling.
3 Accelerated approval.

Palbociclib received accelerated approval in February 2015 based on an improvement in PFS. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. The confirmatory Phase 3 trial, PALOMA-2, is fully enrolled and results are pending. The primary endpoint for that trial is also PFS.

Table 5.2. FDA-Approved Agents for HER2+ Metastatic Breast Cancer

Drug	Year Approved	ORR (%) [1,2]	DOR (months)	PFS or TTP (months)[2]	Line of Therapy
Trastuzumab + paclitaxel	1998	38 vs. 15 (paclitaxel)	8.3 vs. 4.3	6.7 vs. 2.5	1
Lapatinib + letrozole (HER2+, HR+)	2010	27.9 vs. 14.8 (letrozole) (inv)	NR	8.3 vs. 3.0 (inv)	1
Pertuzumab + trastuzumab + docetaxel (CLEOPATRA)	2012	80.2 vs. 69.3 (trastuzumab+docetaxel)	20.2 vs. 12.5	18.5 vs. 12.4	1
Lapatinib + capecitabine	2007	23.7 vs. 13.9 (capecitabine) 31.8 vs. 17.4 (inv)	NR	6.3 vs. 4.3; 5.6 vs. 4.3 (inv)	2
Ado-trastuzumab emtansine	2013	43.6 vs. 30.8 (lapatinib+capecitabine)	12.6 vs. 6.5	9.6 vs. 6.4	2
Trastuzumab	1998	14 (2% CR)	NR		2+
Ado-trastuzumab emtansine (TH3RESA)	Krop et al. 2014	31 vs. 9 (physician's choice) (inv)	9.7 vs. NR	6.2 vs. 3.3 (inv)	3+

Abbreviations: CR = complete response; DOR = duration of response; FDA = Food and Drug Administration; HER2+ = human epidermal growth factor receptor 2 positive; HR+ = hormone receptor positive; inv = investigator assessed; NR = not reported; ORR = objective response rate; PFS = progression-free survival; TTP = time to progression.

1 Data from United States prescribing information unless otherwise noted.

2 Results based on independent review unless otherwise noted.

Table 5.3. FDA-Approved Cytotoxic Chemotherapy for Metastatic Breast Cancer

Drug	Year Approved	RR (%) [1]	DOR (months)	PFS or TTP (months)	Line of Therapy
Gemcitabine + paclitaxel	2004	40.8 vs. 22.1 (paclitaxel)	NR	5.2 vs. 2.9	1
Docetaxel	1996, 1998	28.1 vs. 9.5 (mitomycin/vinblastine); 45.3 vs. 29.7 (doxorubicin)	NR	4.3 vs. 2.5; 6.5 vs. 5.3	1+
Nab-paclitaxel	2005	21.5 vs. 11.1 (paclitaxel)	NR	5.4 vs. 3.9 (Gradishar et al. 2005)	1+
Paclitaxel	1994	26 (175 mg and 135 mg combined)	8.1	3.5	1+ (70% failed prior chemo in the metastatic setting)
Capecitabine + docetaxel	2001	32 vs. 22 (docetaxel)	NR	6.2 vs. 4.3	2
Capecitabine[2,3]	1998	18.5 (all); 25.6 (subgroup)	NR	3 (all)	2+
Ixabepilone + capecitabine (47% ER+)	2007	34.7 vs. 14.3 (capecitabine)	6.4 vs. 5.6 (cape)	5.7 vs. 4.1	2+ (89% received 1 or 2 regimens in metastatic setting)
Eribulin (67% ER+)	2010	11-12 vs. 5 (physician's choice)	4.2	3.7 vs. 2.2 (Cortes et al. 2011)	3
Ixabepilone (48% ER+)	2007	12.4 (ind), 18.3 (inv)	6	NR	3+

Abbreviations: cape = capecitabine; CI = confidence interval; doc = docetaxel; DOR = duration of response; ER+ = estrogen receptor positive; FDA = Food and Drug Administration; ind = independent radiologic review; inv = investigator assessed; nab = nanoparticle albumin-bound; NR = no response; pac = paclitaxel; PFS = progression-free survival; RR = response rate; TTP = time to progression.

1 Data from United States prescribing information unless otherwise noted.

2 Accelerated approval.

3 Kaufman et al. 2015: capecitabine ORR and PFS by investigator (19.9% and 4.2 months, respectively).

These data are from unselected breast cancer populations. Presently, there are no data demonstrating the efficacy of cytotoxic chemotherapy for patients specifically with HR+ MBC.

Table 5.4. Other Commonly Used Cytotoxic Chemotherapy Agents for Metastatic Breast Cancer

Drug	Reference	RR (%) [1]	DOR (months)	Line of Therapy
Vinorelbine	Zelek et al. 2001	25	5	2+
Gemcitabine	Rha et al. 2005	20	9	3/4

Abbreviations: DOR = duration of response; RR = response rate.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

Palbociclib is a CDK4/6 inhibitor that was approved in February 2015 for first line therapy in patients with advanced or metastatic hormone receptor positive breast cancer in combination with letrozole. Prior to FDA approval, palbociclib received a Breakthrough Therapy designation in April 2013. The Breakthrough Therapy designation was based on preliminary Phase 2 data. Interim data showed that postmenopausal women with HR+ MBC treated first line with the combination of palbociclib plus letrozole achieved a statistically significant improvement in median progression free survival (PFS) compared to women who received letrozole alone (26.1 months and 7.5 months, respectively).

Entinostat is a HDAC inhibitor that received a Breakthrough Therapy designation in September 2013 for patients with advanced estrogen receptor (ER)-positive breast cancer. The designation was based on results from a phase 2 study in which entinostat was administered in combination with exemestane to 130 postmenopausal women with locally recurrent or metastatic ER-positive breast cancer following progression on a nonsteroidal AI (NSAI). The primary endpoint of the trial was progression-free survival (PFS) by RECIST criteria. In a March 2012 analysis published in the Journal of Clinical Oncology, the median PFS was 4.3 months versus 2.3 months, for entinostat and placebo, respectively (HR = 0.73; P = 0.06). In patients resistant to NSAIs (n = 45), the median PFS was 3.72 months compared to 1.78 months, in favor of the combination (HR = 0.47).The median overall survival in the combination arm was 28.1 months compared to 19.8 months in the exemestane arm (HR = 0.59; P = 0.036). In a subset of patients (n = 49) with increased protein acetylation, the median PFS with the combination was 8.5 months compared with 2.8 months for patients without acetylation (HR = 0.32).

10. Information related to the preliminary clinical evidence:

There is a single Phase 1 study to support this BTDR (Study I3Y-MC-JPBA). Study I3Y-MC-JPBA (JPBA) is an ongoing multicenter, nonrandomized, open-label, dose-escalation Phase 1 trial of abemaciclib for patients with advanced or metastatic cancer. The primary objective of this study is to the safety and tolerability of abemaciclib when administered orally to patients with advanced cancer. The secondary objectives of this study are to determine the pharmacokinetics (PK) of abemaciclib; to evaluate pharmacodynamics and predictive biomarkers; to document the antitumor activity of abemaciclib; and to establish a recommended dose range for Phase 2 studies. A total of 225 patients with advanced cancer have been treated with abemaciclib in the dose escalation part and 6 tumor expansion part (Part B-G). Results from 47 patients enrolled in the Part D breast cancer expansion cohort are presented in this BTDR.

Patients were eligible for enrollment after they had ceased to receive benefit from standard therapies. All subtypes of breast cancer were eligible to enroll. At the discretion of the investigator, patients progressing on endocrine therapies at the time of study entry were allowed to continue treatment with endocrine therapy (it did not have to be the same endocrine therapy as they received previously). The patients enrolled in this study cohort were heavily pretreated: 36 of 47 patients received at least 4 systemic regimens prior to enrollment and the median number of prior regimens was 7. In addition, the majority of patients had visceral disease (77%), and 83% of patients had metastatic disease present in 2 or more sites. The majority of patients, 36 of 47 (77%), were reported to have HR+ disease, including 25 patients with HR+, HER2- disease and 11 patients with HR+, HER2+ disease. Ten patients received concomitant endocrine therapy, including 9 HR+ patients and 1 patient with unknown HR status.

The best overall response for the 47 patients in this cohort along with the 36 patients that had HR+ tumors are presented in the following table (Table 7.3). A total of 12 PRs were observed for an ORR of 26%. All responses occurred in patients with HR+ disease (results below in Table 7.4), leading to an ORR of 33% in this population. The median time to response was 3.9 months. Responses were durable: 75% of responses lasted at least 6 months and the Kaplan-Meier estimate of the median duration of response was 13.4 months, with 5 responders (42%) remaining on treatment at the time of analysis. In addition to patients with confirmed tumor response, there were 11 patients with prolonged SD ≥ 24 weeks (10/36 HR+ and 1/9 HR-).

Table 7.3. Best Overall Response

Response	All Patients (N = 47) n (%)	HR+ Patients (N = 36) n (%)
Complete response	-	-
Partial response	12 (26)	12 (33)
Stable disease		
Stable disease ≥24 weeks	11 (23)	10 (28)
Stable disease <24 weeks	10 (21)	7 (19)
Progressive disease	11 (23)	5 (14)
Not evaluable	3 (6)	2 (6)

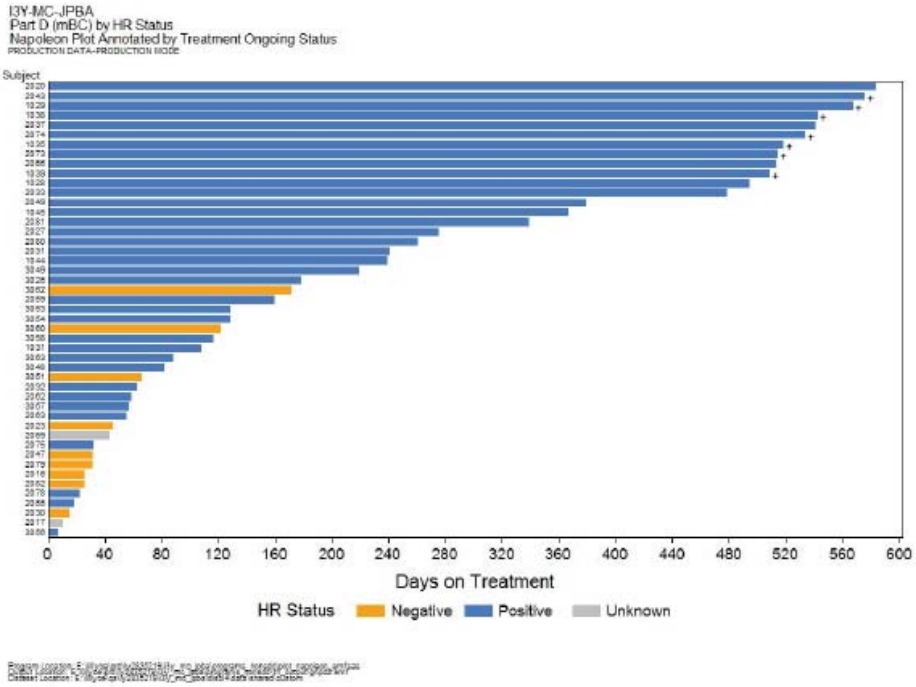
Abbreviations: HR+ = hormone receptor positive; N = number of patients in group; n = number of patients with given response.

Table 7.4. Best Overall Response for HR+ Patients

Response	HR+ Patients Monotherapy (N = 27) n (%)	HR+ Patients Endocrine Therapy (N = 9) n (%)	HR+, HER2- Patients (N = 25) n (%)	HR+, HER2+ Patients (N = 11) n (%)
Complete response	-	-	-	-
Partial response	7 (26)	5 (56)	8 (32)	4 (36)
Stable disease				
Stable disease ≥24 weeks	6 (22)	4 (44)	8 (32)	2 (18)
Stable disease <24 weeks	7 (26)	0 (0)	2 (8)	5 (46)
Progressive disease	5 (19)	0 (0)	5 (20)	0 (0)
Not evaluable	2 (7)	0 (0)	2 (8)	0 (0)

Abbreviations: HER2- = human epidermal growth factor receptor 2 negative; HER2+ = human epidermal growth factor receptor 2 positive; HR+ = hormone receptor positive; N = number of patients in group; n = number of patients with given response.

A change in tumor size over time for all 47 patients in Part D are shown below.



Abbreviations: HR = hormone receptor; mBC = metastatic breast cancer.
+ Ongoing therapy at time of analysis.

The most frequently reported (≥10%) treatment emergent adverse events (TEAEs) possibly related to study drug in the expansion cohorts for Study JPBA include: diarrhea, nausea, fatigue, vomiting, decreased WBC, decreased platelets, decreased neutrophil count, anemia, anorexia, creatinine increased and weight loss. Median duration of treatment was 4 cycles in the breast cancer cohort (Part D).

A total of 34 patient deaths were reported, including 1 patient in Part A (Cohort 9 – abemaciclib 275 mg Q12H), 16 patients in the NSCLC cohort (Part B), 6 patients in the GBM cohort (Part C), 3 patients in the breast cancer cohort (Part D), 6 patients in the melanoma cohort (Part E), and 2 patients in the HR+ breast cancer cohort (Part G). The majority of deaths (29) were due to study disease; no deaths were considered related to study drug.

Serious adverse events possibly related to study drug were experienced by 12 patients (5.8%) in Parts A through F and included confusion and diarrhea (2 patients each) and colitis; GI disorders – other, specify (pneumatosis intestinalis by MedDRA preferred term); hypokalemia; lung infection (pneumonia by MedDRA preferred term); neutrophil count decreased; rectal hemorrhage; platelet count decreased; pneumonitis; and WBC count decreased (1 patient each). In the JPBA clinical database, 4 patients were listed as having discontinued study drug due to AEs. There were no patients that discontinued due to an AE in Part D.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

HR+ MBC is an incurable disease that eventually often requires treatment with cytotoxic chemotherapy. Abemaciclib is a CDK 4/6 inhibitor exhibiting single agent activity in a heavily pretreated population (median of 7 previous treatments and all patients had received previous chemotherapy). Abemaciclib offers an alternative to chemotherapy for these patients with a different toxicity profile from standard cytotoxic agents. The confirmed ORR in Study JPBA (Cohort D) for HR+ patients was 33%. This is much higher than single agent activity that has been reported with the recently FDA approved CDK 4/6 inhibitor palbociclib. Presently, there are no data demonstrating the efficacy of cytotoxic chemotherapy for patients specifically with HR+ MBC in a heavily pretreated population. In addition, although the numbers are small, there appears to single agent activity with abemaciclib in both HER2- and Her2+ patients.

☐ DENY:

Provide brief summary of rationale for denial:

12. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Sponsor has already initiated and completed enrollment in a Phase 2 study (MONARCH 1: A non-randomized study of abemaciclib 200 mg twice daily as a single-agent treatment for women with HR+, HER2- MBC after prior endocrine therapy and failure of 1 to 2 prior systemic chemotherapies for metastatic disease) to confirm the initial results seen in Part D of Study JPBA. Interim results are expected in January of 2016.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

American Cancer Society Statistics 2015: http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2015/

Barrios CH, Sampaio C, Vinholes J,Caponero R. What is the role of chemotherapy in estrogen receptor-positive, advanced breast cancer? Ann Oncol. 2009;20(7):1157-1162.

Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(7):vii11-vii19.

DeMichele A, Clark AS, Heitjan D, Randolph s, Gallagher M, Lal P, Feldman MD, Zhang PJ, Schnader A, Zafman K, Domchek SM, Gogineni K, Keefe SM, Fox KR, O'Dwyer PJ. A phase II trial of an oral CDK 4/6 inhibitor, PD0332991, in advanced breast cancer. J Clin Oncol. 2013;31(suppl; abstr 519).

Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, Cronin KA. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. 2014;106(5):1-8.

Patnaik A, Rosen LS, Tolaney SM, Tolcher AW, Goldman JW, Gandhi L, Papadopoulos KP, Beeram M, Rasco DW, Myrand SP, Kulanthaivel P, Andrews JM, Frenzel M, Cronier D, Chan EM, Flaherty K, Wen PY, Shapiro G. LY2835219, a novel cell cycle inhibitor selective for CDK4/6, in combination with fulvestrant for patients with hormone receptor positive (HR+) metastatic breast cancer. J Clin Oncol. 2014;32(suppl):5s. Abstract 534.

Shapiro G, Rosen LS, Tolcher AW, Goldman JW, Gandhi L, Papadopoulos KP, Tolaney SM, Beeram M, Rasco DW, Kulanthaivel P, Li Q, Hu T, Cronier D, Chan EM, Flaherty K, Wen PY, Patnaik A. A first-in-human phase I study of the CDK4/6 inhibitor, LY2835219, for patients with advanced cancer. J Clin Oncol. 2013;31(suppl):S15. Abstract 2500.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?
YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

5-7-15/M. Raggio

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

/s/

SANDRA J BENTON
09/25/2015

GEOFFREY S KIM
09/25/2015

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 2 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, then it could support a labeling claim of improved OS for patients receiving abemaciclib in combination with nonsteroidal aromatase inhibitors (NSAIs) or fulvestrant? *(Section 7.4)*

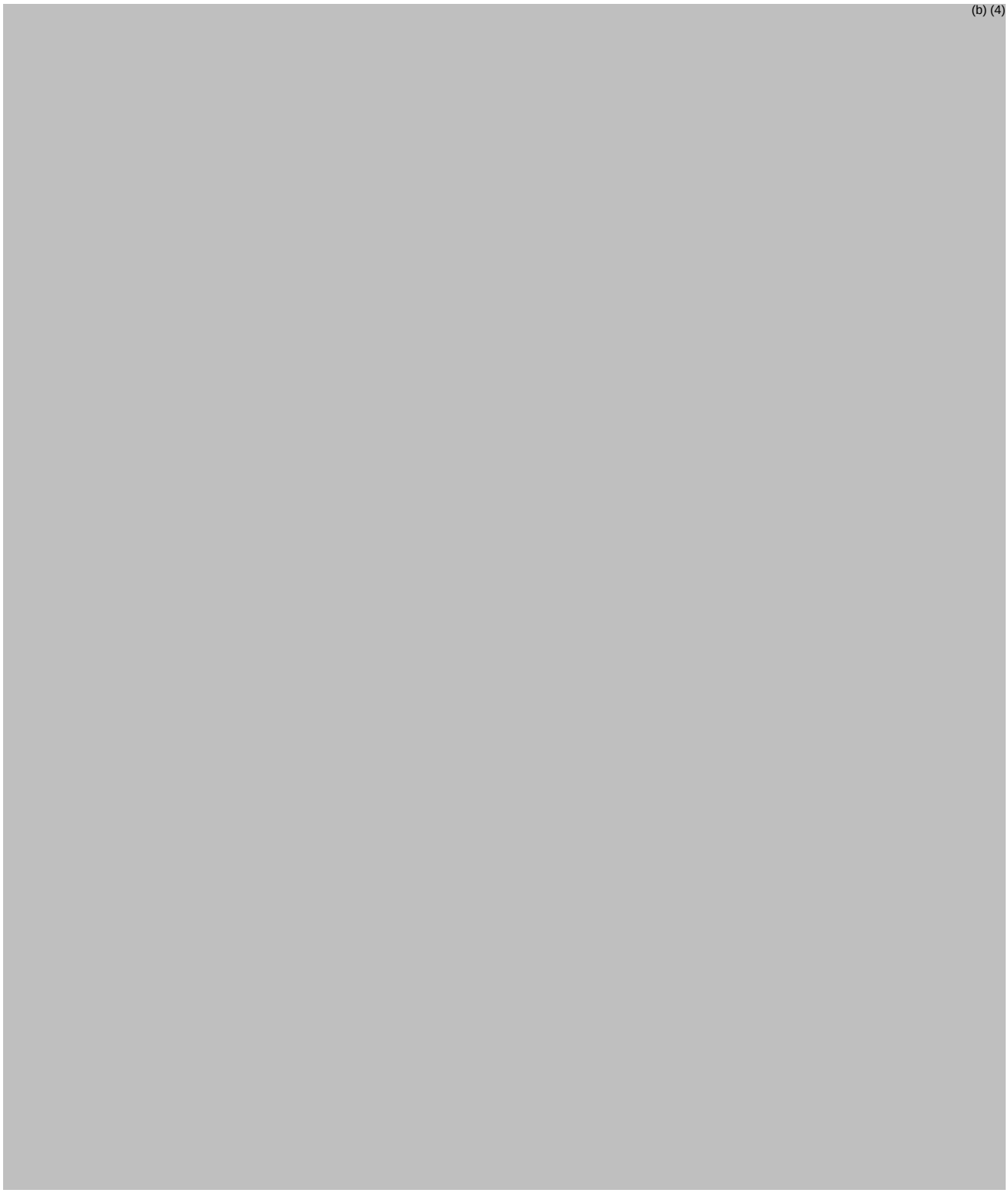
FDA Response: No. The two populations are not similar enough to combine for a pooled analysis. They differ by treatment (fulvestrant vs. NSAI) and line of therapy (1st line treatment vs. all comers). We consider your pooling plan to be an exploratory analysis.

> **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)



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.

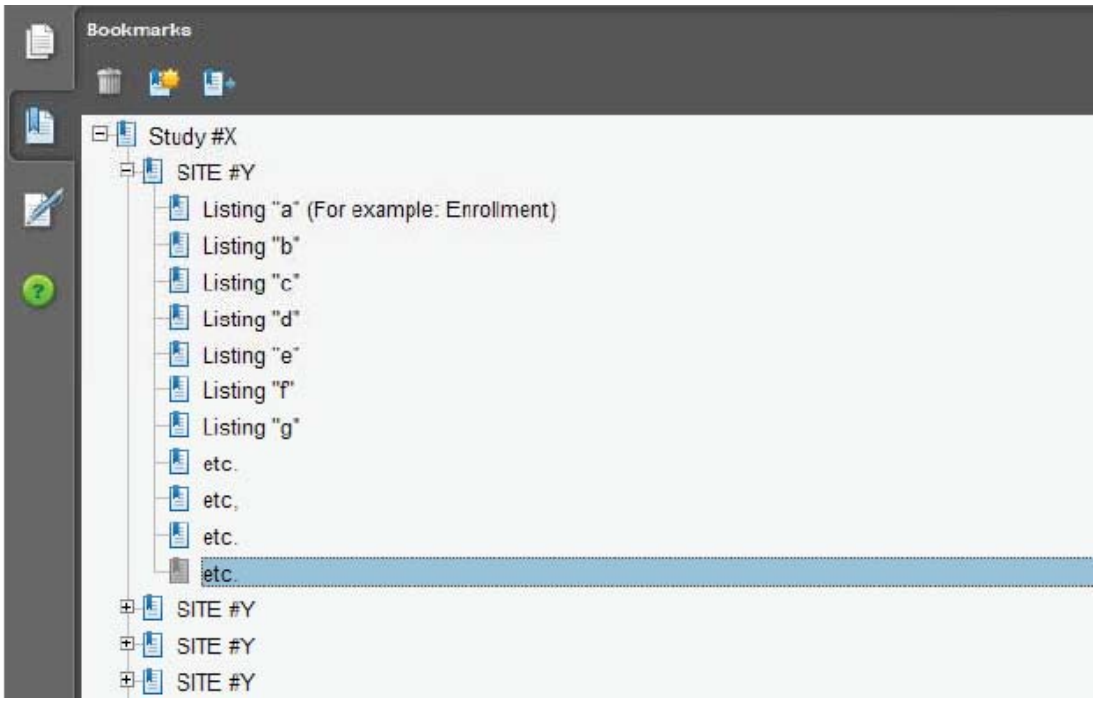
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571,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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND106100

MEETING MINUTES

Eli Lilly and Company
Attention: Anne Kathleen McCasland-Keller, Ph.D., Regulatory Affairs-CMC
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. McCasland-Keller:

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 teleconference between representatives of your firm and the FDA on Thursday, May 20, 2015. The purpose of the meeting was to discuss Chemistry, Manufacturing, and Controls development plans for abemaciclib (LY2835219).

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

If you have any questions, call Rabiya Laiq, PharmD., Regulatory Business Process Manager at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
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: CMC-End of Phase 2

Meeting Date and Time: May 20, 2015 from 2:00 PM- 3:00 PM

Meeting Location: Teleconference

Application Number: IND 106100
Product Name: abemaciclib (LY2835219)
Indication: Cancer
Sponsor/Applicant Name: Eli Lilly and Company

Meeting Chair: Olen Stephens, Ph.D.
Meeting Recorder: Rabiya Laiq, Pharm.D.

FDA ATTENDEES
Office of Pharmaceutical Quality
Office of New Drug Product
Olen Stephens, Ph.D., Acting Branch Chief
Okpo Eradiri, Ph.D., Acting Biopharmaceutics Chief

Office of Program and Regulatory Operations
Rabiya Laiq, Pharm.D., Regulatory Business Process Manager

SPONSOR ATTENDEES
Carrie Coutant, Ph.D., Principal Research Scientist, Analytical Development
Cynthia L. Hammill, Ph.D., Principal Research Scientist, Analytical Development
David Hollowell, Ph.D., Research Advisor, Analytical Development
Anne Kathleen McCasland-Keller, Ph.D., Director-Global Regulatory Affairs CMC
Brian W. Pack, Ph.D., Sr. Research Advisor, Analytical Development
William F. Kluttz, M.S., Research Advisor, Global RACMC
Jole O. Rodriguez, M.S., Sr. Research Scientist-Global RACMC and Meeting Contact

1.0 BACKGROUND

Purpose of meeting is to discuss Chemistry, Manufacturing, and Controls development plans for abemaciclib (LY2835219). FDA sent preliminary comments to Eli Lilly on Tuesday, May 12, 2015.

2. DISCUSSION

Question 1
Does FDA agree with the starting material designation and control strategy for the following as starting materials in the synthesis of LY2835219 (abemaciclib) drug substance?

(b) (4)

FDA Response: *We agree with your proposal to designate* (b) (4) *as starting materials for the synthesis of LY2835219 (abemaciclib) drug substance, as well as the corresponding control strategies. We remind you that final assessment of specifications and control strategies, including impurity qualification, will be re-evaluated or performed during NDA review.*

Meeting Discussion: Eli Lilly accepted FDA's response, no discussion occurred.

Question 2
Does FDA agree that the data presented supports the granting of a waiver of an RBA or BE study between proportionally similar abemaciclib 50- and 75-mg strength capsules?

FDA Response: *Yes, we agree with your biowaiver request proposal for the 75 mg strength of Abemaciclib Capsules. Provide the biowaiver request and the complete information/data supporting this request in your NDA submission. Note that the evaluation and granting of the biowaiver request is a review issue under the NDA.*

Meeting Discussion: Eli Lilly accepted FDA's response, no discussion occurred.

Question 3
Does FDA agree that the proposed drug product dissolution method conditions (e.g., medium, apparatus conditions) are appropriately discriminating to generate the required data for determination of acceptance criteria at the time of registration?

FDA Response: *The experiments conducted to demonstrate suitability of the proposed dissolution method for Abemaciclib Capsules seem to be adequate. The summary of the investigation of discriminating ability of the method and its validation, as presented in the Briefing Package, also seem adequate. However, acceptability of the dissolution method will be determined during review of the totality of the data in the NDA. Please note the following regarding setting of the proposed dissolution acceptance criterion in the NDA:*

- *The dissolution profile data (e.g., 10, 15, 20, 30, 45, 60, 90, 120 min; n = 12) from the pivotal clinical batches and primary (registration) batches (throughout the stability*

program) should be used for the setting of the dissolution acceptance criterion(a) of your product (i.e., specification-sampling time point and specification value).

- *The in vitro dissolution profile should encompass the timeframe over which at least (b) (4)% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.*
- *The selection of the specification time point should be where Q= (b) (4) % dissolution occurs. However, if you have a slowly dissolving product, specifications at two time points may be adequate for your product. The first time point should be selected during the initial dissolution phase (i.e., 15-30 minutes about (b) (4)% dissolution) and the second time point should be where Q = (b) (4)% dissolution occurs.*

Additionally, in the dissolution method development report, present detailed experimental data as follows:

- *Include individual vessel data as much as possible in the narrative portion of the report, particularly regarding investigation of selection of equipment, media, agitation speed, etc.*
- *Submit all individual vessel data as ".xpt" format.*
- *Batch release and stability dissolution data should be presented graphically; the plot(s) of individual vessel data for the clinical and stability batches should include data at release, zero time stability time point and over the duration of stability testing under long-term storage conditions.*

A detailed discussion of the justification of the proposed dissolution acceptance criterion should also be included in the appropriate section of the CTD.

Meeting Discussion:

Up to now the studies conducted by Lilly appear adequate. However, a detailed review of the dissolution method and its development has not been performed. FDA advised Lilly that the dissolution method development report will be reviewed in the NDA. Lilly has the option to request evaluation of the dissolution method development report prior to the NDA filing; however FDA will only review the dissolution method development report if sufficient resources are available. The method development report should appear in module 3.P.2. FDA clarified that the dissolution data should be submitted in SAS transport file format (.xpt).

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

/s/

RABIYA LAIQ
05/27/2015

OLEN M STEPHENS
05/28/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND106100

MEETING MINUTES

Eli Lilly and Company
Attention: Guy C. Ruble, PharmD, RAC
Lily Corporate Center MC Carty St.
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 LY2835219 (abemaciclib).

We also refer to the teleconference between representatives of your firm and the FDA on March 2, 2015. The purpose of the meeting was to discuss follow up clinical pharmacology and toxicology questions from your End-of-Phase 2 meeting that was held on December 18, 2013.

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

If you have any questions, call Jeannette O'Donnell, Regulatory Project Manager at (240) 402-4978 or email: Jeannette.Odonnell@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Qi Liu, PhD
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology V
Office of Clinical Pharmacology
Center for Drug Evaluation and Research

Enclosure:
Teleconference Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2 - follow up
Meeting Date and Time:	March 2, 2015; 3:00-4:00 pm
Meeting Location:	Teleconference
Application Number:	IND 106100
Product Name:	LY2835219 (abemaciclib)
Indication:	Breast Cancer
Sponsor/Applicant Name:	Eli Lilly and Company
Meeting Chair:	Qi Liu, PhD
Meeting Recorder:	Jeannette O'Donnell

FDA ATTENDEES
Amna Ibrahim, MD, Acting Director, Division of Oncology Products 1 (DOP1)
Geoffrey Kim, MD, Acting Deputy Directory, DOP1
Qi Liu, PhD, Team Leader, Office of Clinical Pharmacology, DCPV
Pengfei Song, PhD, Pharmacology Reviewer, Office of Clinical Pharmacology, DCPV
Liang Zhao, PhD, Pharmacometrics Team Leader, Office of Clinical Pharmacology, DPM
Jingyu Yu, PhD, Pharmacometrics Reviewer, Office of Clinical Pharmacology, DPM
Amy McKee, MD, Clinical Team Leader, DOP1
Sanjeeve Balasubramaniam, MD, Clinical Reviewer DOP1
Todd Palmby, PhD, Pharmacology/Toxicology Supervisor, DHOT
Haw-Jyh Chiu, PhD, Pharmacology/Toxicology Reviewer, DHOT
Jeannette O'Donnell, Regulatory Project Manager

SPONSOR ATTENDEES
Paul Cornwell, PhD, Sr. Research Scientist, Toxicology
Jill Chappell, PharmD, Principal Research Scientist, Clinical Pharmacology
Patricia Kellie Turner, PhD, Sr. Research Scientist, PK/PD
Palaniappan Kulanthaivel, PhD, Research Advisor, Drug Disposition
Katie Sugarman, MD, Sr. Director, Global Regulatory Affairs - US
Guy Ruble, PharmD, Director, Global Regulatory Affairs – US
Michelle Neff, JD, Manager, Global Regulatory Affairs – US
Donald Thornton, MD, Sr. Medical Director, Oncology

1.0 BACKGROUND

LY2835219 (abemaciclib) is an oral, selective, and potent small molecule (Mw: 506 (b) (4) g/mol) cyclin-dependent kinases 4 and 6 (CDK4/6) dual inhibitor being developed for breast cancer under IND106100 (b) (4).

This Type B meeting is a follow-up to the EOP2 meetings held on December 18, 2013 with DOP1 and DOP2 discussing abemaciclib development in mBC (b) (4), respectively. The purpose of this meeting is to discuss and reach agreement with FDA on the completed and planned nonclinical studies as well as the clinical pharmacology studies needed to support the approval and labeling of abemaciclib in the proposed mBC (b) (4) indications discussed at the EOP2 meetings.

To support an NDA submission for abemaciclib in patients with advanced cancer, the Sponsor proposed to submit nonclinical safety pharmacology studies, ADME studies, repeat-dose toxicity studies in rats and dogs of up to 3 months in duration, a complete battery of genetic toxicology studies, an embryo-fetal developmental toxicity study in rats, an in vitro local tolerance study, and an in vivo phototoxicity study in pigmented rats. Two active metabolites of abemaciclib, LSN2839567 (M2) and LSN3106726 (M20), have been found to be present at > 10% of the total drug exposure in humans. LSN2839567 (M2) was present at similar proportion in the plasma from rats and humans administered abemaciclib. LSN3106726 (M20) was at disproportionally higher levels in humans when compared to rats or dogs. The Sponsor proposed that no additional nonclinical assessment of these metabolites are warranted based on the intended patient population of advanced cancers and exposure levels noted in repeat-dose toxicity studies in rats and dogs.

The Sponsor proposed the clinical pharmacology development plan to support registration of abemaciclib, as summarized below:

- Characterizing the PK of abemaciclib and metabolites in healthy subjects and in patients with cancer

  Several clinical pharmacology studies have been completed, are in progress, or are planned to characterize the single- and multiple-dose PK of abemaciclib and its metabolites in healthy subjects and in patients with advanced cancer:

  - A Phase 1 study was conducted to evaluate abemaciclib disposition in healthy subjects (JPBD).
  - A Phase 1 study is ongoing to determine the absolute bioavailability in healthy subjects (JPBS).
  - Four Phase 1 dose-escalation studies are ongoing to evaluate the safety, tolerability, and PK in patients with advanced cancer (Studies JPBA, JPBC, JPBH, and JPBJ).

- Planning a population PK/PD analysis for Phase 2 Study JPBN to support initial registration for mBC. The analysis will describe abemaciclib PK across 8 clinical studies, identify covariates that may influence abemaciclib disposition, estimate abemaciclib PK parameters in Study JPBN, and characterize any relationship between abemaciclib PK and outcome (response). A similar approach will be used for the additional Phase 3 studies in patients

with mBC (Phase 3 Studies JPBL and JPBM) [redacted] (b) (4)
(b) (4).

In order to allow time for analysis and submit the results of the Study JPBN population PK analysis with the NDA, population PK analysis will begin prior to the database lock for the primary objective of the study. As Study JPBN is a single-arm, open-label study, the Sponsor believes that this early PK lock poses minimal risk to study data integrity.

- Identifying intrinsic and extrinsic factors that may affect abemaciclib PK and/or PD response

  Potentially clinically-relevant intrinsic and extrinsic factors will be evaluated as covariates during the planned population PK/PD analysis for Study JPBN.

  Hepatic impairment: The sponsor is currently conducting a Phase 1 single dose study (Study JPBV) to evaluate the PK of abemaciclib and its active metabolites in subjects with mild, moderate, or severe hepatic impairment compared to healthy control subjects.

  Renal Impairment: abemaciclib undergoes approximately 3% renal excretion. Preliminary analysis suggested that moderately impaired renal function at baseline did not lead to significant changes in abemaciclib exposure. The sponsor believes population PK analysis will be adequate to support dosing recommendations for patients with mild to moderate renal impairment.

- Evaluating potential for, and identify any drug-drug interactions between abemaciclib and other commonly co-administered drugs

  I*n vitro* studies have been completed, are in progress, or are planned to evaluate abemaciclib and its major metabolites as substrates, inhibitors, and inducers of CYP enzymes; and as substrates and/or inhibitors of transporter processes, including P-gp, BCRP, and renal and hepatic uptake transporters.

  Effect of co-administration of other drugs on abemaciclib

  In vitro, abemaciclib and its major metabolites are primarily metabolized by CYP3A. The following clinical DDI studies are currently in progress:

  - A Phase 1 clinical DDI study to evaluate the impact of CYP3A inhibition (using clarithromycin, a strong inhibitor) on the PK of abemaciclib and its metabolites in patients with cancer (Study JPBE).
  - A Phase 1 clinical DDI study to evaluate the impact of CYP3A induction (using rifampin, a strong inducer) on the PK of abemaciclib and its metabolites in healthy subjects (Study JPBF).

  Preliminary data from 10 patients in study JPBE suggested that clarithromycin increased the levels of abemaciclib but did not alter the AUC of metabolites significantly, with the ratios of geometric means for abemaciclib $AUC_{0-\infty}$ and C_{max} were 3.66 (90% CI, 3.01-4.45) and 1.45 (90% CI, 1.20-1.76), respectively. A mechanistic static model was used to predict AUC ratio for clarithromycin. When final results from Study JPBE become available, if needed, the model will be updated. Based on the final results and available dose strengths, the sponsor will propose inhibitor-specific dosing recommendations. These drug-specific dosing recommendations will be updated based on final PK data and exposure-response relationships.

Abemaciclib is a substrate of P-glycoprotein (P-gp) and BCRP. Inhibitors or inducers of these efflux transporters are less likely to have clinically significant effect on the disposition of abemaciclib, as less than 10% of unchanged abemaciclib is recovered in the feces. Combined effects of CYP3A and P-gp inhibition by clarithromycin on the PK of abemaciclib and its metabolites are currently being investigated in Study JPBE.

Abemaciclib is extensively metabolized in humans and approximately 32% of the administered dose is recovered as LSN2839567 (M2) via biliary excretion. *In vitro* assessments of M2 as a substrate of P-gp and BCRP are currently in progress or planned.

In vitro studies evaluating abemaciclib and its major metabolites M2 and LSN3106726 (M20) as substrates of hepatic uptake transporters OCT1, OATP1B1, and OAT1B3 are planned.

Food did not have a clinically-relevant impact on the PK of abemaciclib and its major active metabolites in Study JPBG. The sponsor believes that co-administration of abemaciclib with loperamide or other drugs that impact gastrointestinal transit time are unlikely to affect abemaciclib PK and its major active metabolites.
Abemaciclib is a weak base that demonstrates pH-dependent solubility; up to pH 6.0, abemaciclib solubility is ≥2 mg/mL, which is greater than the proposed clinical dose divided by 250 mL, which is 0.8 mg/mL. The sponsor believes that a clinical DDI evaluation with acid reducing agents is not necessary.

Effect of abemaciclib on co-administered drugs

In vitro, abemaciclib and its major circulating metabolites M2 and M20 did not induce CYP1A2, CYP2B6, and CYP3A. Abemaciclib and its metabolites do not inhibit major CYPs directly. However, abemaciclib and its major metabolites down regulate mRNA of several CYPs (including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6 and CYP3A) *in vitro*. The mechanism of this down regulation and its clinical relevance are presently not understood. In addition, abemaciclib is an inhibitor of P-gp.

The sponsor will use the following approach to evaluate potential drug-drug interactions:

- The sponsor will evaluate the impact of abemaciclib on CYP3A activity using cortisol as an endogenous marker clinically in Phase 2 Study JPBN. If the cortisol assessment for CYP3A activity is positive in Study JPBN, the sponsor would plan to conduct a cocktail clinical DDI study in cancer patients to further evaluate the impact of abemaciclib and its metabolites on the catalytic activity of the following selected CYPs (substrates): CYP1A2 (substrate: caffeine); CYP2C9 (substrate: warfarin); CYP2D6 (substrate: dextromethorphan); CYP3A (substrate: midazolam).

  If no interactions are observed with the above 4 CYPs, the sponsor proposes that no additional clinical DDI studies are required to evaluate the impact on CYP2B6 and CYP2C8. Furthermore, the sponsor proposes that no clinical DDI study is required using oral contraceptives (substrates of CYP3A) if no interaction is observed with CYP3A substrate, midazolam.
- The sponsor plans to conduct a clinical DDI study of abemaciclib with an orally administered probe-P-gp substrate in healthy subjects.

- The sponsor does not plan to conduct *in vivo* DDI studies with sensitive substrates of OCT1, OATP1B1, and OATP1B3. *In vivo* interactions of abemaciclib and its metabolites with substrates of hepatic transporters are unlikely as abemaciclib, M2 and M20 inhibited the hepatic uptake transporters OCT1, OATP1B1, and OATP1B3 with estimated R-values <1.25.
- The sponsor does not plan to conduct *in vivo* DDI studies with sensitive substrates of OCT2, OAT1, and OAT3, as abemaciclib, M2, and M20 inhibited renal transporter OCT2, OAT1 and OAT3, however the estimated unbound C_{max}/IC_{50} value was <0.1.
- Establishing the exposure-response relationships for efficacy and safety

  Preliminary analyses suggested that treatment with abemaciclib led to a decrease in pRb and topoIIα expression across the entire patient population, without apparent difference in the magnitude of the decrease in pRb and topoIIα expression between the 150-mg and 200-mg dose groups.

  A population PK/PD analysis will be used to characterize any relationship between abemaciclib exposure (e.g., $C_{min,ss}$) and outcome (e.g., response rate or survival) in patients with mBC in Study JPBN, and Phase 3 studies in patients with mBC (Phase 3 Studies JPBL and JPBM) [redacted] (b) (4)
- Characterizing any effects of abemaciclib exposure on QTc interval

  The effects of abemaciclib on QTc interval will be evaluated using (a) time-matched PK and ECG data from clinical studies conducted in healthy subjects (Study JPBS) and patients with advanced cancer (Studies JPBN and JPBC), and (b) completion of a single-dose, fixed-sequence, dose escalation study to evaluate the effect of abemaciclib exposure on QT/QTc interval in healthy subjects.
- Justifying dose selection:

  The dose of 200 mg administered Q12H has been recommended as the starting dose for further assessment of abemaciclib as a single agent in cancer patients. The PK assessments in Study JPBA indicated that the Q12H schedule was most suitable to maximize abemaciclib exposure in plasma, yielding mean steady-state trough plasma levels of 197 ng/mL (in line with the plasma concentrations shown to optimize CDK4/6 inhibition and cell cycle arrest in skin biopsies and in tumor xenografts).

  In some cases where individual patients do not tolerate a dose of 200 mg Q12H, dose reductions to as low as 50 mg Q12H may be required. Given the high inter-individual variability in abemaciclib PK, there is considerable overlap in the range of exposures achieved with 100 -, 150-, or 200-mg dosing Q12H.

  Given a mean half-life of approximately 21 hours, clinically relevant differences are not expected between the specific Q12H and the general twice daily dosing intervals. Therefore, the sponsor proposes labeling concepts in the target product profile (TPP) that specifies a twice daily dosing interval.
- Evaluating the final commercial formulation strengths

  The proposed commercial formulation for abemaciclib will be available [redacted] (b) (4) The 50-mg strength capsule is being used in the

registration-directed studies in patients with mBC (Phase 2 study JPBN, Phase 3 Studies JPBL and JPBM). (b) (4) At the time of initial registration, clinical data for the 100 mg capsule will not be available. The sponsor plans to submit a request for waiver (with NDA submission) for an RBA or BE study for the 100-mg capsule strength by demonstrating that the capsules are proportionally-similar. FDA agreed (November 14, 2014 meeting minutes).

- Evaluating food effect

  Results of a Phase 1 food-effect Study JPBG showed that in the presence of food, C_{max} increased approximately 24%-25% while AUC remained unchanged. Because food had no clinically relevant effect on the overall exposure to abemaciclib and its metabolites following single dose administration of abemaciclib using the 50% w/w formulation, which has a higher drug concentration compared to the proposed commercial formulation (abemaciclib drug concentration 25% w/w), and formulation does not appear to affect the PK of abemaciclib, the sponsor proposes in the TPP that abemaciclib may be given without regard to food, and that an additional food effect study using a proposed commercial formulation is not required.

FDA sent Preliminary Comments to Eli Lilly and Company on February 25, 2015.

2.0 DISCUSSION

2.1. Nonclinical

Question 1: Does FDA agree that the package of completed and proposed nonclinical safety pharmacology, ADME, and toxicology studies is adequate to support the registration of abemaciclib?

FDA Response: No. While we agree that the completed and proposed nonclinical studies conducted with abemaciclib that were outlined in the meeting briefing package appear appropriate to support submission of an NDA for the proposed indication, additional studies conducted with metabolites of abemaciclib are needed. See our Response to Question 2. The adequacy of the resulting nonclinical data to support approval of abemaciclib for the proposed indication will be determined following review of all data included in the NDA submission.

Question 2: Does FDA agree that no further nonclinical assessment of toxicity of metabolites LSN2839567 (M2) and LSN3106726 (M20) is warranted?

Teleconference Discussion: None

FDA Response: No, we do not agree. The potential genotoxicity of metabolites LSN2839567 (M2) and LSN3106726 (M20) should be evaluated in an in vitro assay that detects point mutations and in another assay that detects chromosomal aberrations to support an NDA submission for abemaciclib.

Lilly Response [submitted February 27, 2015]:
As noted in our suggested clarifications above, we do not believe that human exposure to M2 is disproportionate to animal exposure. In the 3-month rat study, exposure to M2 was approximately equal to human exposure to M2 at 200 mg Q12H (Table 5.2 of Briefing Document). Abemaciclib was tested in a bacterial mutagenicity (Ames) study, in which the test conditions included the addition of rat S9 mix (supplemented liver fraction) to increase the number of metabolites of abemaciclib tested in this assay (Study 962562). Based on the exposure observed in the 3-month rat repeat-dose study, we believe that the S9 fraction test conditions would include adequate levels of M2 for assessment of genotoxicity. In addition, abemaciclib was tested in a rat micronucleus assay at dose levels up to 300 mg/kg (Study 962564). While exposure was not measured in this study, it would be reasonable to assume that exposure to M2 would be higher than human exposure at 200 mg Q12H, based on rat exposure in the 3-month study. In addition, we would expect significant exposure to M20 in this study for the same reason. Abemaciclib was negative for mutagenicity and genotoxicity in these two studies. In addition, in silico mutagenicity analysis predicted that M2 would be non-mutagenic (see below). Based on this, Lilly believes that the risk that M2 is genotoxic is low.

Since receiving FDA's preliminary meeting comments, we have evaluated both M2 and M20 for mutagenicity in silico using Derek Nexus version 4.0.6, Nexus 1.7.6, Knowledgebase 2014 1.0 and Leadscope version 1.8.3 using both the E coli - Sal 102 A-T Mut and Salmonella Mut models. In addition both metabolite structures were evaluated using an internal QSAR model, were reviewed by a chemist and a toxicologist for alerting structures and a consensus call was made. Both structures were judged to be non-mutagenic according to this process. This process is similar to the process described in ICH M7 for the genotoxicity assessment of impurities. Given that the parent molecule (abemaciclib) was negative in an Ames study (Study 962562), an in vitro chromosomal aberration study (Study 962563) and a rat micronucleus study (Study 962564), Lilly believes that there is a very low likelihood that M2 or M20 are genotoxic.

While Lilly believes that the above discussion demonstrates that the risk to patients is low, we recognize that it does not completely alleviate the risk; thus, Lilly intends to conduct the requested studies to support the NDA.

Teleconference Discussion: None

2.2. Clinical

Question 3: Does FDA agree to proposed early access to PK and the population PK analysis plan (proposed analysis plan in Appendix 8) to assess factors that affect PK based upon data across multiple studies?

FDA Response: The proposed early access to PK from Study JPBN is acceptable. The overall population PK analysis plan is acceptable. We encourage you to include the PK of major active metabolites in your population PK analysis if the clinical impact of the active metabolites is not negligible (see Response to Question 9).

Teleconference Discussion: None

Question 4: Does FDA agree with the use of population PK and covariate analysis (proposed analysis plan in Appendix 8) to support dosing recommendations for patients with mild-to-moderate renal impairment, ad that a dedicated study in subjects with severe renal impairment or end stage renal disease is not required to support registration?

FDA Response: The population PK approach to supporting dosing recommendation for patients with mild-to-moderate renal impairment is acceptable if your population PK datasets include sufficient number of patients with mild-to-moderate renal impairment. However, whether a dedicated study in subjects with severe renal impairment or ESRD is needed to support registration will be a review issue.

Teleconference Discussion: None

Question 5: Does FDA agree that if the exploratory cortisol assessment for CYP3A activity is negative in Study JPBN, no additional clinical drug-drug interaction (DDI) studies are needed to investigate the effect on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A substrate drugs and oral contraceptives?

FDA Response: Your plan appears reasonable. The final decision will be an NDA review issue.

Teleconference Discussion: None

Question 6: Does FDA agree that if exploratory cortisol assessment for CYP3A activity is positive in Study JPBN, a clinical DDI study using a cocktail approach would be acceptable to evaluate the effect of abemaciclib on the catalytic activity of selected CYPs, CYP1A2 (substrate: caffeine), CYP2C9 (substrate: warfarin), CYP2D6 (substrate: dextromethorphan), and CYP3A (substrate: midazolam), and that separate clinical study is not needed to evaluate the effect on oral contraceptives?

FDA Response: Your plan appears reasonable. Please submit your protocol for review before initiating the clinical study.

Teleconference Discussion: None

Question 7: Does FDA agree that clinical DDI studies are not required with sensitive substrates of OCT1, OATP1B1 and OATP1B3?

FDA Response: Your proposal appears reasonable. The final decision will be an NDA review issue.

Teleconference Discussion: None

Question 8: Does FDA agree that clinical DDI studies are not required with sensitive substrates of OCT2, OAT1, and OAT3?

FDA Response: **Your proposal appears reasonable. The final decision will be an NDA review issue.**

Teleconference Discussion: None

Question 9: Does FDA agree to the proposed population PK/PD analysis plan to assess exposure-response in patients with mBC (Study JPBN), and to similar approach that is planned for subsequent submissions of additional registrations studies?

FDA Response: **The planned population PK/PD analysis to evaluate exposure-response (E-R) relationship is acceptable. We encourage you to include exposure to active metabolites in your E-R analysis if your data suggests that the active metabolites have significant effect on clinical efficacy and safety.**

Teleconference Discussion: None

Question 10: Does FDA agree with Lilly's approach for assessing abemaciclib's concentration-QTc relationship from clinical studies conducted in healthy subjects and patients with cancer to support initial registration and the labeling concepts in the TPP?

FDA Response: **It is likely your concentration-QTc analysis based on studies conducted in healthy subjects and patients with cancer will be sufficient to rule out large QT prolongation (i.e., >20 ms) for abemaciclib. The results might be able to support your proposed labeling concepts in the TPP. However, a thorough QT (TQT) study in healthy subjects may be feasible for abemaciclib, allowing thorough QT assessment that is able to rule out small QT prolongation (i.e., 10 ms).**

Teleconference Discussion: None

Question 11: Does FDA agree that the proposed single-dose, fixed-sequence, dose escalation study to evaluate the effect of abemaciclib exposure on QT/QTc interval in healthy subjects will constitute a robust assessment of QT?

FDA Response: **You proposed approach might be reasonable. However, we cannot make our decision based on currently available information. Currently, we consider a well-designed and well-conducted QTc assessment based on concentration-QTc analysis may be an alternative approach for a TQT study. However, the adequacy of the QTc assessment will depend on your trial design (the inclusion of the placebo control, number of subjects tested, the tested supratherapeutic exposure compared to the potential maximum therapeutic exposure at the steady state, the PK/ECG collection, etc.), the ECG quality, the concentration-QTc relationship, etc. We recommend that you submit a detailed clinical QTc assessment plan to us for more informative feedback.**

Teleconference Discussion: None

Question 12: Does FDA agree that an additional clinical food effect study with a commercial formulation is not required?

FDA Response: No. You should conduct a trial to confirm the lack of food effect with your commercial formulation before the NDA submission. Please submit your protocol for FDA review.

Lilly response [submitted February 27, 2015]:
Lilly would like to further discuss this question at the teleconference on Monday, 2 March 2015.

Does FDA agree with Lilly's conclusion from the food effect study conducted (Study JPBG see Appendix 11 of Briefing Document) that there was no clinically relevant effect of food on abemaciclib AUC or Cmax?

Other than not utilizing the commercial formulation, did FDA have any other issues with Study JPBG as conducted?

As described in Appendix 8 (Tables App.8.1 and App.8.3) of the briefing document, Lilly plans to evaluate formulation as a covariate in PopPK analysis. Data will be included from studies using drug in capsule, the 50% w/w formulation, and the 25% w/w commercial formulation. If formulation is not a significant covariate in this analysis, would FDA accept this approach (that is, utilization of Study JPBG as the only food effect study in the NDA) to support the dosing and administration labeling concepts as described in the TPP (Appendix 6) for the NDA submission?

Teleconference Discussion:
The sponsor agreed to conduct a formal food effect study with the final formulation and will submit the protocol for FDA review. The FDA indicated that this would likely not be a refuse to file issue but recommended that the sponsor readdress specific timelines for data submission during the NDA review at a pre-NDA meeting.

3.0 ADDITIONAL INFORMATION

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).

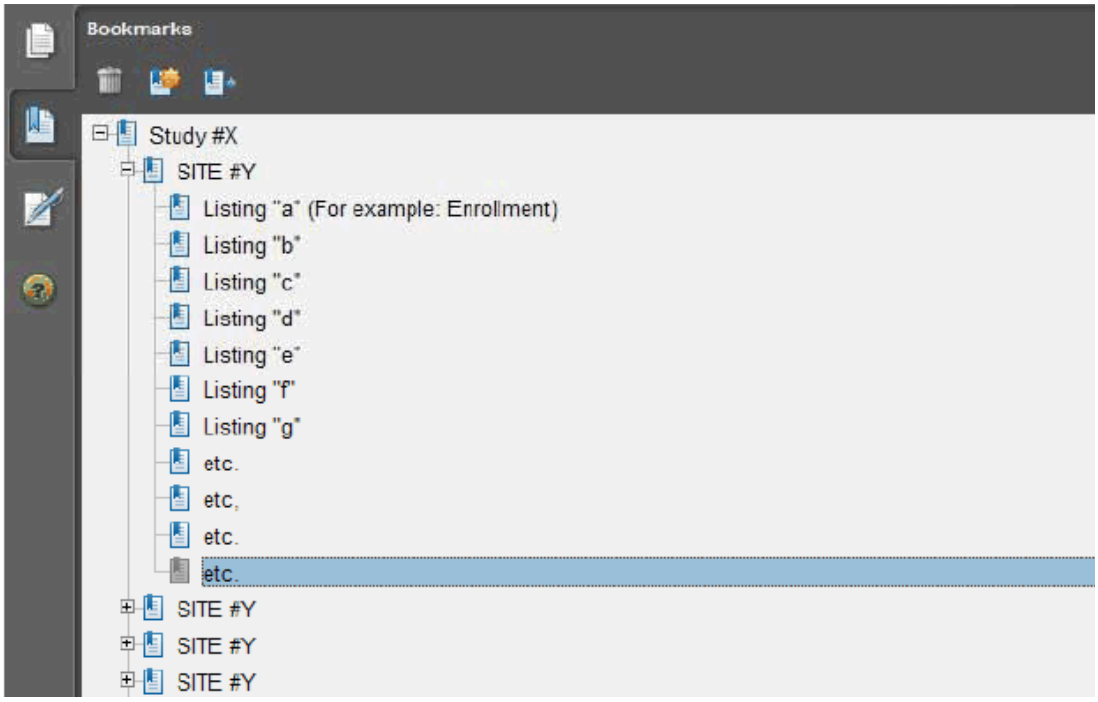
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

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.

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

/s/

JEANNETTE L O'DONNELL
03/18/2015

QI LIU
03/18/2015

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, Pharm.D., 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 LY2835219.

We also refer to the meeting between representatives of your firm and the FDA on December 18, 2013. The purpose of this meeting is to discuss the clinical development plan of LY2835219 in mBC with the United States Food and Drug Administration (FDA) and to ultimately establish agreement between FDA and the sponsor (Eli Lilly and Company [Lilly]) on issues pertinent to the development plan.

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 Frank Cross, Jr., Senior Regulatory Health Project Manager at (301) 796-0876.

Sincerely,

{See appended electronic signature page}

Frank Cross, Jr, M.A., MT (ASCP)
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Amy McKee, M.D.
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
Meeting Date and Time:	December 18, 2013
Meeting Location:	White Oak Building 22, Room 1311
Application Number:	106100
Product Name:	LY2835219
Indication:	LY2835219 in combination with fulvestrant is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC)
Sponsor/Applicant Name:	Eli Lilly and Company
Meeting Chair:	Amy McKee, Clinical Team Leader, DOP1
Meeting Recorder:	Frank Cross, Jr., Senior Regulatory Health Project Manager, DOP1

FDA ATTENDEES

Anthony J. Murgo, M.D., M.S., FACP, Director, DOP1, Associate Office Director for Regulatory Science, OHOP
Jonathan Jarow, M.D., Clinical Reviewer, DOP1
Amna Ibrahim, M.D., Deputy Division Director, DOP1
Amy McKee, M.D., Clinical Team Leader, DOP1
Geoffrey Kim, M.D., Clinical Reviewer, DOP1
Suparna Wedam, M.D., Clinical Reviewer, DOP1
Todd Palmby, Ph.D., Supervisory Pharmacologist/Toxicologist, DHOT
Qi Liu, Ph.D., Clinical Pharmacology Team Leader, DCPV
Pengfei Song, Ph.D., Clinical Pharmacology Reviewer, DCPV
Kun He, Ph.D., Biostatistics Team Leader, DBV
Erik Bloomquist, Ph.D., Biometrics Reviewer, DBV
Karen Boyd, M.S., Regulatory Health Project Manager, DOP2
Frank Cross, Jr., M.A., MT (ASCP), Senior Regulatory Health Project Manager, DOP1

SPONSOR ATTENDEES

Richard Gaynor, M.D., VP, Oncology Clinical & Product Development
Colleen Mockbee, R.Ph., Global Product Team Leader, Oncology
Donald Thornton, M.D., Sr. Medical Director, Oncology
William John, M.D., Sr. Medical Fellow, Oncology
Edward Chan, M.D., Ph.D., Sr. Medical Advisor, Oncology
Jonathan Denne, Ph.D., Sr. Director, Statistics

Martin Frenzel, Ph.D., Research Scientist, Statistics
Peipei Shi, Ph.D., Sr. Research Scientist, Statistics
Damien Cronier, Ph.D., Sr. Research Scientist, Drug Disposition
(b) (4)
Katherine P. Sugarman, M.D., Sr. Director, Global Regulatory Affairs – US
(b) (4)
Guy Ruble, Pharm.D., Director, Global Regulatory Affairs - US

1.0 BACKGROUND

LY2835219 is an oral, selective, and potent small molecule cyclin-dependent kinases (CDKs) 4 and 6 (CDK4/6) dual inhibitor with antitumor activity within multiple preclinical pharmacology models. Preliminary data from the ongoing Study JPBA, in patients with advanced or metastatic cancer and for women with hormone receptor positive (HR+) metastatic breast cancer (mBC), shows an unconfirmed objective response rate of 25% and an estimated disease control rate (DCR) of 80.6%.

The purpose of this meeting is to discuss the clinical development plan of LY2835219 in mBC with the United States Food and Drug Administration (FDA) and to ultimately establish agreement between FDA and the sponsor (Lilly) on issues pertinent to the development plan. Based on the interim analysis results from an ongoing Phase 1 trial in mBC, Lilly intends to initiate a single-arm, Phase 2 study (Study I3Y-MC-JPBN [JPBN]) of single-agent LY2835219 in hormone receptor-positive, (HR+) mBC (irrespective of human epidermal growth factor receptor 2 [HER2] status) who have received at least three regimens for their metastatic disease, including endocrine therapy and chemotherapy. Lilly also is proposing to conduct a Phase 3 study in patients with HR+, HER2- advanced or mBC to demonstrate superiority of LY2835219 plus fulvestrant over placebo plus fulvestrant in investigator-assessed progression-free survival (PFS) (Study I3Y-MC-JPBL [JPBL]). Guidance from FDA will facilitate the planning of clinical programs for LY2835219 in this tumor type.

2. DISCUSSION

2.1. Breakthrough Therapy Designation:

Question 1: Given the current safety and efficacy profile of single-agent LY2835219 in a heavily pretreated HR+ mBC population, would FDA consider there to be sufficient evidence of substantial clinical efficacy over existing therapies to support filing a request for Breakthrough Therapy Designation?

FDA Response: **No. The preliminary clinical evidence, namely the 25% unconfirmed response rate seen in the HR+ breast cancer population of JPBA, does not indicate that the drug may demonstrate substantial improvement over available therapies on one or more clinically significant endpoints.**

Lilly Response: *The data in the breast cancer cohort for Study JPBA continues to mature. In the most recent update of the data, the confirmed response rate is 22% (8/36)*

in HR+ patients and overall response rate is 31% (11 patients). Of the 3 patients whose response has not been confirmed, the patients remain on treatment and have the potential to be confirmed on the next visit. The duration of treatment in the responding patients ranges from 160 to 470 days, with 9 of 11 remaining on treatment at this time. In addition to the patients with response (per RECIST criteria), there is an overall stable disease rate in the HR+ patients of 81% with 17/36 patients remaining on treatment. The patients have tolerated the treatment well with a 2% discontinuation rate across all patients treated on JPBA suggesting the potential for safety advantages relative to available treatments. Patients who responded to treatment in this study had received a median number of 6 prior therapies. Lilly believes this is an important new class of agents, with LY2835219 having significant single-agent activity in a heavily pre-treated mBC population that has not yet been reported with other agents in this class. Lilly will continue to update the FDA on the progress of this development program. Lilly does intend to submit the updated data to the 2014 AACR meeting for presentation.

Discussion: **The Agency stated that once the Sponsor believes the data from this single-arm trial is mature, a breakthrough therapy designation request may be submitted. The Agency noted that important components of such a request include justification for why this is an improvement over available therapy, duration of response and updated safety information. The Agency also noted that patient narratives may be helpful in such a submission.**

2.2 Accelerated Approval – Single-Agent LY2835219:

Question 2: Does FDA agree that the Study JPBN population is a well-defined population (b) (4) ?

FDA Response: **No.** (b) (4)

Lilly Response: (b) (4) (b) (4)

Discussion: **The Agency clarified that the comment regarding prior therapy was to request more detailed inclusion/exclusion criteria such as time of progression since last anthracycline or taxane therapy.**

Question 3: If the single-arm Phase 2 study demonstrates a sufficient level of single-agent activity as described in the study outline, does FDA agree the study could support accelerated approval for use in HR+ mBC after prior endocrine therapy and failure of 1 to 2 prior systemic chemotherapies for metastatic disease?

FDA Response: It is unclear what you mean by "sufficient level of single-agent activity". Accelerated approval requires the demonstration of "meaningful therapeutic benefit to patients over existing treatments (21CFR314.500)" and that marketing approval may be granted if the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. In the proposed clinical setting, there is still a number of available agents that are commonly used in clinical practice, and the magnitude of improvement in response rate that is "sufficient" to predict improvement in patient survival is unknown.

In order to assess the benefit-risk profile of LY2835219 in this clinical setting, we recommend performing a randomized clinical trial of LY2835219 against an active comparator. We recommend that you use overall survival as the primary efficacy outcome measure of this trial. Alternatively, you may wish to design a trial using progression-free survival as the primary efficacy outcome measure, as a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for regulatory decision. However, you should be aware that PFS is subject to ascertainment bias, and the results of the analysis may be influenced by any imbalance in assessment dates or missing data between treatment arms. Also, note that a statistically significant difference in PFS may not necessarily demonstrate a clinically meaningful difference.

Lilly Response: *Lilly believes that a well-designed single-arm study with ORR as the primary endpoint supported by durability of response and tolerability should be an acceptable basis for accelerated approval. FDA has previously accepted ORR as the basis of accelerated approval in mBC (capecitabine, docetaxel) suggesting that this endpoint has a reasonable likelihood of predicting clinical benefit in this setting. A goal remains to bring new promising agents to patients at the earliest possible time, in particular, in a setting where treatment options are limited.*

Lilly will consider a randomized Phase 2 study. In the design of such a study, we are interested if FDA would agree that a significant improvement in ORR with durability of response and good tolerability could support an accelerated approval?

Additionally, in such a study, would FDA consider gemcitabine or vinorelbine as an acceptable control arm?

Discussion: The Agency stated that the ability to interpret the results of a single-arm study in terms of benefit-risk is often difficult. The Agency is not able to give a definitive number in terms of response rate that would garner an approval in this disease setting. The Agency recommends a randomized trial with a time-to-event endpoint, but, ultimately, the decision rests with the Sponsor.

Question 4: Does FDA agree an appropriately designed Phase 3 study in first-or second-line HR+, HER2- mBC would be adequate to confirm the benefit of LY2835219 treatment to convert the accelerated approval to a regular approval?

FDA Response: See response to question 3.

Lilly Response: *No comment.*

2.3 Phase 3 Study JPBL – LY2835219 in Combination with Fulvestrant:

Question 5: Does FDA agree that, for the proposed indication, demonstrating superior investigator-assessed PFS for LY2835219 plus fulvestrant over placebo plus fulvestrant for women with HR+, HER2- mBC in the Phase 3 study (JPBL) would be sufficient for filing a New Drug Application (NDA) for full approval?

FDA Response: We reiterate that a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for regulatory decision. Please refer to our response to question 3 for caveats regarding using PFS as the primary endpoint.

Lilly Response: *Lilly acknowledges FDA comments.*

2.4 Study JPBL – Pivotal Study Design:

Question 6: Does FDA agree that the inclusion/exclusion criteria are acceptable and identify a well-defined patient population that could support labeling for the proposed indication?

FDA Response: Overall, we are in agreement that the HR+, HER2- mBC population is a well defined population; however, there are concerns regarding some of the definitions that are presented in the clinical trial worksheet. For example, given your definition of post-menopausal, all patients who are under the age of 60 will begin therapy with goserelin irrespective of amenorrhea or FSH/Estradiol status. Additionally, it appears that concomitant therapy with zoledronic acid or

denosumab is permitted, which may be problematic in assessing the clinical activity of LY2835219 in patients with bone-only disease who may or may not be receiving concurrent treatment with a bisphosphonate on RANKL inhibitor. We recommend that you submit a finalized protocol and statistical analysis plan to the Agency for review prior to initiating this study.

Lilly Response: *Lilly agrees to modify the inclusion criteria for post-menopausal status to include age <60 years with amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and estradiol level in the post-menopausal range.*

Regarding the patients with bone-only disease, Lilly believes that the inclusion of these patients is important so that the drug can be evaluated in this clinically relevant patient population. Lilly will summarize the usage of concomitant therapies such as zoledronic acid or denosumab and assumes use will be similar across study arms.
Lilly does plan to submit the final protocol prior to study initiation. Does this address FDA concerns?

Discussion: **The Agency agrees that the Sponsor's plan appears acceptable. However, we cannot agree at this time until a full protocol is submitted for review.**

Question 7: Does FDA agree with reliance on documentation in the patient records of HR+, HER2- status?

FDA Response: Yes. However, the HER2- status must have been confirmed from a metastatic biopsy, given the conversion of some patients who are HER2- at initial diagnosis but HER2+ in metastatic sites.

Lilly Response: *Lilly will collect the results from the most recently available biopsy to confirm HR and HER2 status but will not require confirmation with a new metastatic biopsy. The conversion rate of HER2+ in metastatic sites is low and Lilly believes re-biopsy of metastatic sites for all patients enrolled in the study is not consistent with current clinical practice and would put patients at risk given the most common sites of metastatic disease (bone, brain, liver, lung) are difficult to biopsy.*

Discussion: **The Agency reiterated that knowing HER2 status at time of metastatic diagnosis is important but would be open to proposals from the Sponsor as to how to handle patients who do not have metastatic biopsies.**

2.5 Study JPBL Endpoints and Statistical Considerations:

Question 8: Does FDA agree PFS is an appropriate primary endpoint to assess the clinical benefit of LY2835219 in the proposed patient population?

FDA Response: See response to questions 3 and 5.

Lilly Response: *No comment.*

Question 9: Lilly intends to perform an interim analysis on PFS (using a minimal alpha spend 0.0082) to determine if patients are receiving overwhelming benefit from LY2835219. Does FDA agree that a successful outcome of an interim analysis demonstrating overwhelming superiority of LY2835219 plus fulvestrant versus placebo plus fulvestrant in PFS is sufficient for filing an NDA for full approval?

FDA Response: No. FDA discourages interim analysis on PFS and would recommend you perform the final analysis of PFS prior to submitting an NDA.

Lilly Response: *Lilly believes the interim PFS is robust by conducting the interim analysis at 234 PFS events, or 70% of total needed events. The median follow-up time is about 12 months. Based on simulation, under the alternative hypothesis where the true HR is 0.68, less than 2% of simulations with a positive interim outcome turn out to be negative by the final analysis.*

Question 10: For patients with "bone only" disease that is not considered measurable, does FDA agree with the proposed definition of disease progression for these patients?

FDA Response: We would prefer that you do not allow entry of patients with "bone only" disease; however, the proposed definition of disease progression based on the appearance of 1 or more new lytic lesions in bone, unequivocal progression of existing bone lesions, or the appearance of 1 or more new lesions outside bone appears acceptable.

Lilly Response: *Lilly thanks FDA for their comments, however, Lilly does plan to enroll patients with bone-only disease as outlined in the briefing document.*

Question 11: Given the randomized, double-blind, placebo-controlled study design, does FDA agree that a random sample-based independent review committee (IRC) audit is adequate to support the primary analysis of investigator-assessed PFS?

FDA Response: Possibly. In the final version of your protocol, please provide a detailed auditing plan that includes a strategy to detect potential assessment bias for our review. This auditing plan should include the percentage of patients to be audited, the method used to identify the subset of images to be

audited, the method for comparing the investigator-assessed PFS results to the sample-based IRC PFS results, and the criteria for determining whether all images will need to be audited.

Lilly Response: *Lilly acknowledges FDA response and intends to submit a pre-specified plan for auditing by blinded independent review committee for tumor-based endpoints.*

Question 12: Does FDA agree that the proposed strategy for analyzing overall survival (OS) is appropriate?

FDA Response: No, see response to question 9 regarding an interim PFS analysis. Note that if you intended to make labeling claims based upon your secondary endpoints, type I error must be controlled appropriately.

Lilly Response: *Regarding the opportunity to test OS following a positive interim analysis of PFS, please see Lilly's response to Question 9. Regarding the control of Type I error rate, Lilly is controlling the Type I error rate for both the primary endpoint of PFS and the secondary endpoint of OS, by applying the methodology described in the paper by Glimm and colleagues (Glimm et al, Statistics in Medicine, 2010).*

Discussion: The Agency stated that the disagreement with OS is related to the advice regarding performing an interim analysis of PFS. The Agency recommends O'Brien-Fleming type of spending function for an interim OS analysis. The Agency recommends that the Sponsor submit a detailed plan for review.

The Agency stated that at this time landmark analyses of time to event endpoints are discouraged; we would prefer analyses based on Kaplan Meir curves.

2.6 Study JPBL Patient-Reported Outcomes:

Question 13: Lilly included a secondary endpoint to measure the proportion of patients in each treatment arm with a ≥2 point increase in "worst pain" via the Brief Pain Inventory (BPI). BPI data will be collected on paper at baseline, Day 1 of each cycle, and at the follow-up visit. Eligible patients include those with a baseline "worst pain" score of 0 to 6, inclusive, and at least 1 on-therapy score (Cycle 2 Day 1 or later). For patients with multiple on-therapy visits, ≥65% of all "worst pain" scores must be reported. Analgesic use (including dose, unit, frequency, route) and bone agent consumption will be collected at baseline and changes recorded at each following visit. Does FDA agree (b) (4)

FDA Response: **There is insufficient information provided in this briefing package to fully address this question. Some of the issues that we have identified include:**

a. **The evaluation of pain in this patient population may be problematic as arthralgias are a well known adverse reaction associated with the use of aromatase inhibitors. The pharmacokinetic interaction between LY2835219 and fulvestrant is unknown as are the effects of LY2835219 on fulvestrant mediated arthralgias. If there is a positive effect on the proportion of patients experiencing increases in their "worst pain", it will be difficult ascertain whether this is a true prevention of cancer related pain or reduction of fulvestrant related arthralgia via a drug-drug interaction.**

b. **The protocol appears to allow concurrent treatment with either zoledronic acid or denosumab. As presented in a study published in Cancer by Cleeland et al. (epub Sept 2012), pain outcomes may vary in patients who are treated with denosumab as compared to zoledronic acid. This study appears to be similarly designed to your proposed methods of assessment of pain, and there does not appear to be any stratification factors for these treatments.**

c. **The use of a single time point to capture the patient's worst pain each cycle. We would recommend that you use the average worst pain over a 7 day period each cycle.**

d. **The clinical benefit of a reduced proportion of patients with a ≥ 2 point increase in worst pain has not been established, especially if value of the patient's worst pain fluctuates over the course of treatment. You may wish to conduct a time to worsening pain analysis as a supportive measure.**

e. **Please provide justification as to why eligible patients will be restricted to those with a baseline pain score of 0 to 6 inclusive.**

f. **It is unclear at this point whether the toxicity profile of LY2835219 will allow for a truly blinded study.**

(b) (4)

Lilly Response: *Lilly thanks the FDA for their comments. Lilly does not believe it is technically feasible to determine the mechanism of pain relief of the investigational drug*

alone versus the combination with a PRO instrument. Lilly plans to continue to collect the pain data and acknowledges FDA concerns.

2.7 Phase 3 Study JPBM - LY2835219 in Combination with Aromatase Inhibitors:

Question 14: Can FDA comment on the prospectively planned statistical approach being proposed for the pooled OS analysis across Studies JPBL and I3Y-MC-JPBM [redacted (b) (4)] [redacted (b) (4)]?

FDA Response: Your proposed pooled OS analysis will be considered as exploratory since the p-values are difficult to interpret.

Lilly Response: *Lilly acknowledges FDA response but believes this pooled analysis could help inform the risk-benefit of LY2835219. Lilly believes this approach is consistent with FDA guidance on Integrated Summary of Effectiveness, for pre-specified analysis plans of pooled analysis.*

Discussion: The Sponsor will submit a detailed statistical plan for Agency review.

ADDITIONAL COMMENT:

We remind you that results from repeat-dose toxicology studies of 3 months duration should be submitted to your IND prior to initiating Phase 3 clinical trials in patients with advanced cancer as discussed in the ICH S9 Guidance for Industry: Nonclinical Evaluation for Anticancer Pharmaceuticals [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085389.pdf].

CLINICAL PHARMACOLOGY COMMENTS:

1. **We noticed that you pooled data for two doses (150 mg Q12H and 200 mg Q12H) of LY2835219 for the efficacy and safety analyses. We are not sure if you've selected the optimal dose for future trials. We strongly recommend that you evaluate the dose-response or exposure-response relationship for LY2835219 using available data to support your dose selection and include such analyses in your proposed protocols for future trials. We also encourage you to consider conducting the proposed randomized phase 2 monotherapy trial JPBN with more than one dose level of LY2835219.**

2. **Due to the lack of the human experience of LY2835219 and fulvestrant combination therapy, a randomized Phase 2 combination therapy trial is recommended to evaluate the safety, efficacy, and drug interaction potential between LY2835219 and fulvestrant**

before initiating the proposed Phase 3 trial JPBL.

3. **It is unclear whether you have conducted study to evaluate the food effect on the bioavailability of LY2835219. We remind you that food-effect bioavailability studies should be conducted early in the drug development to guide the decisions to administer the drug with or without food, and select formulations for further development. Food-effect bioavailability information should be available to design clinical safety and efficacy studies. Conduct a food effect trial per Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070241.pdf.**

4. **Adequately address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development. Please submit an ECG evaluation plan for review. For more information, please refer to http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf.**

5. **If the study drug is developed in combination with other drugs as a combination therapy, evaluate the potential for PK interactions between the study drug and the drugs in the combination during the development of this combination therapy.**

Lilly Response: *Lilly plans to meet with FDA in 2014 to discuss the nonclinical and clinical pharmacology plan.*

3.0 OTHER

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. 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 Pediatric and Maternal Health Staff 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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

No Action Items.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

AMY E MCKEE
12/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208716

INFORMATION REQUEST

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

Dear Dr. Ruble:

Please refer to your New Drug Application (NDA) submitted May 5, 2017, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abemaciclib tablet.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Biopharmaceutics:

1. We are unable to locate the report on (b) (4) (b) (4) report (page 25) regarding (b) (4) (b) (4) If available, submit the modeling report, which provides an overview of the modeling strategy, and details of the modeling procedures including model development, model verification/modification, and model application in a step-wise manner. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity. Please provide the following:

   i. Detailed information on the inputs used in the construction and validation of the model(s) and simulations. All the physiological and physicochemical parameters as well as their sources should be clearly specified. It is understandable that some input parameters are estimated (optimized). However, when the parameters are optimized, the data source selection, the estimation method, the justification for the optimization algorithm, and the assumption used should be provided.
   ii. Although the FDA does not require the use of a specific software, due to substantive differences in software/versions, clear identification of software parameters is critical, which should include: name and version of the software, and (for custom modeling software) schematics of model structure and differential equations.

iii. The methodological approach to model verification, model verification results, and sensitivity analyses to interrogate the robustness of the model should be clearly presented. Note that it is expected that any PK data will also contribute to establish confidence in the appropriateness of the model in addressing the study question(s).

iv. The results of using the verified model to address the study question(s) should be presented using tables, figures and text where appropriate.

2. Please confirm if you plan to seek BCS Class III designation for abemaciclib. If yes, submit the BCS Class III designation request with data per the BCS guidance for evaluation by FDA's BCS Committee.

Drug Substance:

3. In lieu of missing details in the Description of Manufacturing Process (3.2.S.2.2), provide an executed batch record from the manufacture of the drug substance primary stability batches that adequately describes the following:

. (b) (4)

.

4. (b) (4)

Drug Product:

5. The package insert section 16 indicates that the (b) (4) blister configuration will be marketed. (b) (4)

(b) (4)

6. The analytical method description file for dissolution (G1928) in section 3.2.P.5.2 is corrupted on page 5 of 8. Resubmit this file such that the standard concentration calculation is clear.

7. Include references in sections 3.2.P.5.2 and 3.2.P.5.3 to the appropriate sections within the NDA describing the (b) (4)

(b) (4)

If you have any questions, please contact me, Kristine Leahy, RPh., Regulatory Business Process Manager, at (240) 402-5834. Please respond by June 28, 2017.

Sincerely,

Kristine Leahy, RPh.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208716

LATE CYCLE MEETING
BACKGROUND PACKAGE

Eli Lilly and Company
Attention: Guy Ruble, PharmD
Director, Global Regulatory Affairs, Oncology, North America
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Ruble:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Verzenio (abemaciclib), 50 mg, 100 mg, 150 mg, and 200 mg tablets.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 11, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at janice.kim@fda.hhs.gov, at your earliest convenience.

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

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Acting Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: September 11, 2017; 2:00 PM – 3:00 PM
Meeting Location: Teleconference

Application Number: NDA 208716
Product Name: Verzenio (abemaciclib)
Indication: In combination with fulvestrant for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−) metastatic breast cancer in women whose disease has progressed following endocrine therapy and for use (b) (4) in the treatment of HR+, HER2− metastatic breast cancer (b) (4) whose disease has progressed following endocrine therapy and (b) (4) prior chemotherapy (b) (4) in the metastatic setting.

Applicant Name: Eli Lilly

FDA ATTENDEES (tentative)
Julia Beaver, MD, Acting Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Laleh Amiri-Kordestani, MD, Clinical Team Leader, DOP1
Lynn Howie, MD, Clinical Reviewer, DOP1
Katherine Fedenko, MS, CRNP, Deputy Director (Safety), DOP1
William Pierce, PharmD, Associate Director for Labeling/Clinical Reviewer, DOP1
Jeanne Fourie Zirkelbach, PhD, Clinical Pharmacology Team Leader, OCP, DCPV
Vadryn Pierre, PhD, Clinical Pharmacology Reviewer, OCP, DCPV
Okpo Eradiri, PhD, Biopharmaceutics Reviewer, OPQ/ONDP/DB/BBI
Shenghui Tang, PhD, Biostatistics Team Leader, OTS/OB/DBV
Erik Bloomquist, PhD, Biostatistics Reviewer, OTS/OCP/DCPV
Carolyn McCloskey, PhD, Epidemiology Reviewer, OSE, DEPII
Todd Palmby, PhD, Pharmacology Toxicology Team Leader, DHOT
Tiffany Ricks, PhD, Pharmacology Toxicology Reviewer, DHOT
Xiao Chen, PhD, Chemistry Lead, OPQ, ONDP
Sithamalli Chandramouli, PhD, Chemistry Reviewer, OPQ, ONDP
Krishnakali Ghosh, PhD, Facility Reviewer, OPQ/OPF/DIA/IABIII
Janice Kim, PharmD, Regulatory Project Manager, DOP1

APPLICANT ATTENDEES
TBD

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

DISCIPLINE REVIEW LETTERS

No Discipline Review letters have been issued to date.

SUBSTANTIVE REVIEW ISSUES

There are no substantive review issues at this time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (Janice Kim/Laleh Amiri-Kordestani)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

   You have been notified of a postmarketing requirement:

   - To submit a final report and datasets from an ongoing or new clinical trial to evaluate the incidence of dose reductions and dose interruptions due to severe diarrhea when abemaciclib is administered with a meal, compared to abemaciclib taken in the modified fasted condition, and when it is administered without regard to food in patients.

   We have also asked that you commit to the following postmarketing commitments:

   - Conduct PBPK analysis to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of abemaciclib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. If the results from the PBPK analysis are inconclusive, conduct a pharmacokinetic trial to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of abemaciclib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations." Submit final report and data sets.

   - Submit the overall survival (OS) data and final report from clinical trial MONARCH 2: Entitled "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer."

3. Major Labeling Issues – 20 minutes

4. Review Plans – 5 minutes

   Complete labeling negotiations.

5. Wrap-up and Action Items – 5 minutes

   To be determined following Late Cycle Meeting.

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

/s/

JULIA A BEAVER
09/07/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208716

LATE-CYCLE MEETING MINUTES

Eli Lilly and Company
Attention: Guy Ruble, PharmD
Director, Global Regulatory Affairs, Oncology, North America
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Ruble:

Please refer to your New Drug Application (NDA) dated May 5, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Verzenio (abemaciclib) tablets; 50 mg, 100 mg, 150 mg, and 200 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 11, 2017.

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

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

Sincerely,

{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:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 11, 2017; 2:00 pm – 3:00 pm
Meeting Location: TCON

Application Number: NDA 208716
Product Name: abemaciclib
Applicant Name: Eli Lilly

Meeting Chair: Laleh Amiri-Kordestani, MD
Meeting Recorder: Janice Kim, PharmD

FDA ATTENDEES

Julia Beaver, MD, Acting Director, DOP1
Laleh Amiri-Kordestani, MD, Clinical Team Leader, DOP1
Lynn Howie, MD, Clinical Reviewer, DOP1
Jeanne Fourie Zirkelbach, PhD, Clinical Pharmacology Team Leader, OCP, DCPV
Vadryn Pierre, PhD, Clinical Pharmacology Reviewer, OCP, DCPV
Erik Bloomquist, PhD, Biostatistics Reviewer, OTS/OCP/DCPV
Todd Palmby, PhD, Pharmacology Toxicology Team Leader, DHOT
Tiffany Ricks, PhD, Pharmacology Toxicology Reviewer, DHOT
Xiao Chen, PhD, Chemistry Lead, OPQ, ONDP
Christina Marshall, Safety Regulatory Project Manager, DOP1
Alice Kacuba, RN, MSN, GWCPM, RAC, Chief Project Management Staff, DOP1
Janice Kim, PharmD, Regulatory Project Manager, DOP1

APPLICANT ATTENDEES

Allen Melemed, MD, Sr. Director, Global Regulatory Affairs
Guy Ruble, PharmD, RAC, Director, Global Regulatory Affairs
Jole Rodriguez, MS, Sr. Research Scientist, Global Regulatory Affairs - CMC
Colleen Mockbee, RPh, Global Product Team Leader, Oncology
Ian Smith, MD, Sr. Medical Director
Nawel Bourayou, MD, Clinical Research Advisor
Yanping Wang, PhD, Sr. Director, Statistics
Martin Frenzel, PhD, Sr. Research Scientist, Statistics
Shivani Nanda, MS, Assoc. Director, Statistics
Yong Lin, PhD, Sr. Research Scientist, Statistics
Tammy Forrester, MS, Research Scientist, Statistics
Joanne Cox, MD, Sr. Medical Advisor, Global Patient Safety
Paul Cornwell, PhD, DABT, Principal Research Scientist, Toxicology
Jill Chappell, PharmD, Principal Research Scientist, Clinical Pharmacology
Kellie Turner, PharmD, PhD, Sr. Research Scientist, PK/PD

Lan Ni, PhD, Sr. Director, PK/PD
Steve Hall, PhD, Sr. Research Fellow, Drug Disposition
Susan Holsmer-Brand, MS, Manager, Global Regulatory Affairs – N. America
Leanne Hickman, VP Global Quality
Graciela Romero, Director Quality Puerto Rico
Patrice Bradley, Sr. Advisor, Pharmaceutical Project Management
Levi Garraway, MD, Sr. VP Oncology Global Product Development and Medical Affairs

1.0 BACKGROUND

NDA 208716 was submitted on May 5, 2017, for Verzenio (abemaciclib).

Proposed indication(s): In combination with fulvestrant for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−) metastatic breast cancer in women whose disease has progressed following endocrine therapy and for use (b) (4) in the treatment of HR+, HER2− metastatic breast cancer (b) (4) whose disease has progressed following endocrine therapy and (b) (4) prior chemotherapy (b) (4) in the metastatic setting.

PDUFA goal date: January 5, 2018

FDA issued a Background Package in preparation for this meeting on September 7, 2017.

2.0 DISCUSSION

1. Introductory Comments

   Welcome, Introductions, Ground rules, Objectives of the meeting

   Discussion: **No discussion needed.**

2. Postmarketing Requirements/Postmarketing Commitments

   There is one postmarketing requirement and two commitments that have been discussed and agreed upon.

   Discussion: **No discussion needed.**

3. Major Labeling Issues

   Discussion: **Discussed acceptability of proposed text in Section 12.1.**

4. Review Plans

   Complete labeling negotiations

   Discussion: **No discussion needed.**

5. Wrap-up and Action Items

   Discussion: The **Applicant inquired about their PLAIR withdrawal. FDA will follow up with CDER-OC-PLAIR. The Applicant inquired if a Sponsor Site Inspection was going to be performed. FDA will follow up with Applicant.**

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

LALEH AMIRI KORDESTANI
09/21/2017