

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207103Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207103

SUPPL #

HFD # 150

Trade Name IBRANCE[®]

Generic Name palbociclib

Applicant Name Pfizer Inc.

Approval Date, If Known

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)

c) 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:

d) 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

e) 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: Amy Tilley
Title: Regulatory Project Manager
Date: January 20, 2015

Name of Office/Division Director signing form: Amna Ibrahim, M.D.
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/

AMY R TILLEY
01/20/2015

AMNA IBRAHIM
02/03/2015

207103

Palbociclib (PD-0332991)

DEBARMENT CERTIFICATION

[FD&C Act 306(k)(1)]

Pfizer 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.

Michelle Yu
Kite

Digitally signed by Michelle Yu Kite
DN: c=US, o=Pfizer, ou=5091327a-7d2c-4b42-
aba6-f4bed6fa10a4, cn=Michelle Yu Kite
Reason: I attest to the accuracy and integrity
of this document
Date: 2014.06.20 10:17:45 -07'00'

20-June-2014

Signature of Company Representative

Date

PFIZER CONFIDENTIAL

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207103 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Ibrance® Established/Proper Name: palbociclib Dosage Form: Capsules 75 mg 100 mg 125 mg		Applicant: Pfizer Inc. Agent for Applicant (if applicable):
RPM: Amy Tilley		Division: DOP1
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action February 3, 2015 User Fee Goal Date is <u>May 13, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> 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 <u>Per OPDP Rev Pfizer to send 1-16-15</u>		<input checked="" type="checkbox"/> Received
❖ 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): NME
 (*confirm chemical classification at time of approval*)

- | | |
|--|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input checked="" type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> 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	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> 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 (<i>approvals only</i>) Both DRAFTED	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) 2-3-15
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included 1-30-15
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 8-13-14
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included 1-30-15
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 8-13-14
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included 8-13-14
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> Review(s) <i>(indicate date(s))</i> 	9-11-14 Acceptability Letter 9-5-14 PN Review
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> 10-7-14 DMEPA: <input checked="" type="checkbox"/> 1-12-15 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> 1-26-15 OPDP: <input checked="" type="checkbox"/> 1-14-15; 1-27-15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> MPH 1-21-15
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	9-15-14
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included 2-3-15
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>Feb 4, 2015</u> If PeRC review not necessary, explain: _____ 	
❖ 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, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	Included
❖ 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)	Included
❖ Minutes of Meetings <ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) EOP2 meeting (<i>indicate date of mtg</i>) Mid-cycle Communication (<i>indicate date of mtg</i>) Late-cycle Meeting (<i>indicate date of mtg</i>) Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A or no mtg <input checked="" type="checkbox"/> 5-17-13; 12-17-13; 2-28-14; 5-6-14; 6-5-14 <input checked="" type="checkbox"/> 10-2-12; 7-11-13; 7-23-13; 5-28-14; 12-5-14 <input checked="" type="checkbox"/> 12-4-14 <input type="checkbox"/> N/A Sponsor declined LCM CMC Prelims 4-19-13; Clin Pharm Prelims 5-20-13; 5-16-14; BTT 11-14-13; CMC 1-23-14
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 2-3-15
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 2-3-15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 2-2-15
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> 2 PMRs & 2 PMCs
Clinical	
❖ Clinical Reviews <ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) Clinical review(s) (<i>indicate date for each review</i>) Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review 9-15-14 (Filing); 1-22-15 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Included in Clin Review 1-22-15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A N/A 1-15-15
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 9-30-14; 12-9-14; 12-12-14; 1-13-15; 1-21-15
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 9-15-14 (Filing); 11-5-14; 1-15-15; 1-27-15
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 9-12-14 (Filing); 10-22-14; 1-15-15; 1-27-15
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 1-23-15
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 1-22-15; 1-23-15
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 9-11-14 (Filing); 1-17-15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 1-22-15
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 9-17-14 (Filing); 1-14-15 (3); 1-17-15
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 9-11-14 (Filing); 12-8-14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC DP Review 1-14-15
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input checked="" type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	See CMC DP Review 1-14-15
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 10-8-14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done 2-3-15
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done 2-3-15
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Sent email to DARRTS to have the Product Names updated on 2-3-15.
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Sent 2-3-15

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/s/

AMY R TILLEY
02/03/2015

ALICE KACUBA
02/03/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Fedenko, Katherine](#); [Jenney, Susan](#); [Cortazar, Patricia](#); [Beaver, Julia](#); [Liu, Qi \(CDER\)](#); [Fourie Zirkelbach, Jeanne](#)
Subject: Final PMR-PMC Descriptions and Milestones re NDA 207103 Ibrance
Date: Thursday, January 29, 2015 3:49:00 PM
Attachments: [PMR-PMC language and milestones sent 1-29-15.pdf](#)
Importance: High

Ashok,

Attached are the cleared PMR-PMCs regarding NDA 207103 Ibrance.

Please note that any further revisions to the PMC descriptions or PMR/PMC milestones will cause a delay in our review process.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

PMR-2860-1 Submit the progression free survival (PFS) and overall survival (OS) data and results from the ongoing Trial A5481008, PALOMA-2, “A Randomized, Multicenter, Double-blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women with ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti-Cancer Treatment For Advanced Disease” when supplemental application for regular approval is submitted. In addition, submit OS data and results at trial completion.

Trial Completion: 12/2016

Final PFS Report Submission: 06/2017

Final OS Report Submission: 11/2020

PMR-2860-2 Submit the final report for your clinical trial A5481013 entitled, “A phase 1, open-label, single dose, parallel-group study to evaluate the pharmacokinetics of palbociclib (PD-0332991) in subjects with impaired hepatic function,” to assess the effect of moderate and severe hepatic impairment on the pharmacokinetics of palbociclib.

Trial Completion: 06/2017

Final Report Submission: 12/2017

PMC-2860-3 Submit the final report for your ongoing drug interaction trial (A5481039) entitled, “A phase 1, open-label, fixed-sequence, 2-cohort, 2-period study to investigate the effect of modafinil and pioglitazone given as multiple doses on single dose pharmacokinetics of palbociclib (PD-0332991) in healthy volunteers”, to assess the effect of modafinil (a moderate CYP3A inducer) on the pharmacokinetics of palbociclib in healthy volunteers.

Trial Completion: 04/2015

Final Report Submission: 10/2015

PMC-2860-4 Conduct analysis from the ongoing Trial A5481008, PALOMA-2, “A Randomized, Multicenter, Double-blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women with ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti-Cancer Treatment For Advanced Disease” to determine the prognostic or predictive significance of genetic alterations in the Cyclin D1/CDK4/6/p16/retinoblastoma pathway in ER (+), HER2 (-) breast cancer, specifically the prognostic/predictive significance of the genetic alteration to the safety and efficacy of palbociclib.

Trial Completion: 12/2016

Final Report Submission: 06/2017

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/s/

AMY R TILLEY
01/29/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok(Ashok.Didolkar@pfizer.com))
Subject: Time Sensitive re NDA 207103 Ibrance - FDA Revised PI/PI
Date: Thursday, January 29, 2015 2:27:00 PM
Attachments: [FDA revised PI-PPI 1-29-15.doc](#)

Ashok,

Below is the revised FDA PI/PPI from today's label meeting. We request your response **by 1 pm January 30, 2015.**

Please note that any further revisions to the PI/PPI will cause a delay in the review process.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/29/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: January 27, 2015
Application Number: NDA 207103
Product Name: Ibrance (palbociclib)
Sponsor/Applicant Name: Pfizer, Inc.

Subject: Labeling discussion regarding the rational for excluding the [REDACTED] (b) (4) from the PI.

FDA Participants :

Amna, Ibrahim, M.D., Acting Director, DOP1
Geoffrey Kim, M.D., Acting Deputy Director, DOP1
Patricia Cortazar, M.D., Clinical Team Leader
Julia Beaver, M.D., Clinical Reviewer
Katherine Fedenko, M.S., CRNP, Deputy Director Safety, DOP1
Shenghui Tang, Ph.D., Biostatistics Team Leader
Eric Bloomquist, Ph.D., Biostatistics Reviewer
Rosane Charlab Orbach, Ph.D., Genomics Team Leader, Genomics Group, OCP
Qi Liu, Ph.D., Clinical Pharmacology Team Leader
Jeanne Fourie-Zirkelbach, Ph.D., Clinical Pharmacology Reviewer
Haripada Sarker, Ph.D., CMC Lead, Branch II, ONDQA
Todd Palmby, Ph.D., Pharmacology Toxicology Supervisor, DHOT
Marybeth Toscano, PharmD, RAC, Regulatory Review Officer, OPDP
Frances Fahnbulleh, RPh, PharmD, Safety Regulatory Project Manager, OSE
Susan Jenney, M.S., Safety Regulatory Health Project Manager
Amy Tilley, Regulatory Project Manager

Sponsor/Applicant Participants:

Ramzi Dagher, M.D., Vice President and Head of Regulatory Strategy Oncology
Ashok Didolkar, Ph.D., US Regulatory Lead
Erling Donnelly, Ph.D., Submissions Asset Team Lead
Xin Huang, Ph.D., Statistical Lead
Albert Kraus, Ph.D., Global Regulatory Portfolio Lead
Sophia Randolph, M.D., Ph.D., Global Clinical Lead
Mace Rothenberg, M.D., Chief Medical Officer and Senior Vice President, Clinical Development and Medical Affairs
Patrizia Salmoiraghi, Global Regulatory Lead
Enayet Talukder, Ph.D., Vice President, Head of Statistics, Pfizer Oncology

1.0 BACKGROUND:

Pfizer wanted to use this meeting to discuss the substantially complete PI/PPI specifically why the Agency does not want to include (b) (4).

2.0 DISCUSSION:

FDA discussed how (b) (4) and continued to recommend not inclusion in the labeling. FDA also discussed how the inclusion of (b) (4) would not be appropriate, owing to the (b) (4). Pfizer and FDA reached an understanding on leaving the (b) (4) and any words which imply (b) (4) out of the labeling.

3.0 ACTION ITEMS:

None

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/s/

AMY R TILLEY
01/28/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Subject: TIME SENSITIVE re NDA 207103 Ibrance - FDA revised PI and PPI
Date: Tuesday, January 27, 2015 12:04:00 PM
Attachments: [FDA revised PI-PPI - 1-27-15.doc](#)
Importance: High

Ashok,

Below is the FDA revised PI and PPI for Pfizer's review. The Review Team wants to know whether or not Pfizer would like to keep the tcon scheduled for today to discuss any labeling questions. At this time we do not have any labeling questions to discuss.

We respectfully request your response to the PI and PPI below **no later than 12 noon tomorrow Jan 28th**.

Please let us know as soon as possible whether Pfizer wants to keep the tcon scheduled for 3 pm today.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/27/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok(Ashok.Didolkar@pfizer.com))
Bcc: [Cortazar, Patricia](#)
Subject: Time Sensitive NDA 207103 Ibrance - FDA revised PI
Date: Thursday, January 22, 2015 2:54:00 PM
Attachments: [FDA rev label 1-22-15.doc](#)
Importance: High

Ashok,

Below is the FDA revised PI only. The PPI is still grayed out as it is still under review. We request that you send your response **no later than 3 pm tomorrow Jan 23rd**.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/22/2015

From: Tilley, Amy
To: "[Didolkar, Ashok](mailto:Didolkar.Ashok)"; Katherine.Fedenko@fda.hhs.gov
Bcc: [Cortazar, Patricia](mailto:Cortazar.Patricia); [Beaver, Julia](mailto:Beaver.Julia); [Fedenko, Katherine](mailto:Fedenko.Katherine); [Jenney, Susan](mailto:Jenney.Susan)
Subject: URGENT Revision re Clin PMR/PMC Document re NDA 207103 Ibrance
Date: Wednesday, January 21, 2015 5:44:00 PM
Attachments: [PMC and PMR Clinical final.doc](#)

Ashok,

Thank you for your revisions to the Clinical PMR/PMC for palbociclib. However, for PMR/PMCs Milestone negotiations you must send back our original document with Pfizer's revisions in Track Changes via email. Once we are in agreement with all the Milestone dates please officially submit them to the NDA.

Please use the attached original *PMC and PMR Clinical final* document to make your track revisions on and then send it back to us via email **no later than 12:00 pm on Jan 22, 2015.**

Kindly confirm receipt of this email.

Regards.

Amy Tilley

From: Didolkar, Ashok [<mailto:Ashok.Didolkar@pfizer.com>]
Sent: Wednesday, January 21, 2015 3:10 PM
To: Tilley, Amy
Subject: RE: TIME SENSITIVE NDA 207103 Ibrance - Clinical PMC-PMR Milestones needed

Amy,

In addition to milestone dates, Pfizer clarification/responses are included in the attachment. Please note that Pfizer is proposing revised (earlier) milestone dates for one of Clin Pharm PMRs (Submit the final study report for your ongoing drug interaction trial -A5481039).

This response will be officially submitted to NDA later.

Should you have a question, please let me know. I will be in a telecon from 3.30 PM EST until rest of the day. Best way to contact me would be via e-mail.

Thanks

Ashok

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Tuesday, January 20, 2015 3:55 PM
To: Didolkar, Ashok
Subject: TIME SENSITIVE NDA 207103 Ibrance - Clinical PMC-PMR Milestones needed

Ashok.

Below are the Clinical PMC/PMR for which we are requesting Pfizer's Milestone dates.

We request your response via email no later than 4 pm Jan 21, 2014. Please also officially submit your request to the NDA.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD
20993

📞 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 207103
Product Name: Ibrance (palbociclib)

PMR Description: Submit the progression free survival (PFS) and Overall survival (OS) data and results from the ongoing Trial A5481008, PALOMA-2, “A Randomized, Multicenter, Double-blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women with ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti-Cancer Treatment For Advanced Disease” when supplemental application for regular approval is submitted. In addition, submit OS data and results at study completion.

PMR Schedule Milestones:	Interim Report:	<u>MM/YYYY</u>
	Trial Completion:	<u>MM/YYYY</u>
	Final PFS Report Submission:	<u>MM/YYYY</u>
	Final OS Report Submission:	<u>MM/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The final PFS results of Trial A5481008, PALOMA-2 will if statistically significant and clinically meaningful, confirm the clinical benefits of palbociclib treatment in combination with letrozole and will fulfill the requirement for the recommended accelerated approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

As the drug is being approved under accelerated approval a subsequent study is required to confirm the efficacy of palbociclib in this indication.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Clinical Trial A5481008 is a Randomized, Double-Blinded, Multicenter Phase 3 Trial in the same population as the pivotal trial A5481003 supporting accelerated approval. The study has already fully accrued.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 207103
Product Name: Ibrance (palbociclib)

PMC Description: Conduct a clinical trial to determine the prognostic or predictive significance of genetic alterations in the Cyclin D1/CDK4/6/p16/retinoblastoma pathway in ER (+), HER2 (-) breast cancer, specifically the prognostic/predictive significance of the genetic alteration to the safety and efficacy of palbociclib.

PMC Schedule Milestones:	Final Protocol Submission	<u>MM/YYYY</u>
	Trial Completion:	<u>MM/YYYY</u>
	Final Report Submission:	<u>MM/YYYY</u>
	Other: _____	<u>MM/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Further biomarker exploration is needed given that the pivotal study PALOMA-1 did not identify a biomarker for prediction or prognosis, but did indicate the potential that patients with *CDKN2A* loss might benefit less from palbociclib. These findings are preliminary in a small sample size and would require confirmation in a future study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Further biomarker exploration is needed given that the pivotal study PALOMA-1 did not identify a biomarker for prediction or prognosis, but did indicate the potential that patients with *CDKN2A* loss might benefit less from palbociclib.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An ongoing or new clinical trial will be required to test the prognostic and or predictive value of relevant biomarkers.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Exploratory clinical pharmacogenetic trial
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

AMY R TILLEY
01/21/2015

From: Tilley, Amy
To: "Didolkar, Ashok"
Subject: RE: Question re next printing of Container labels re NDA 207103 Ibrance
Date: Wednesday, January 21, 2015 3:57:00 PM

Ashok,

I just wanted to let you know that DMEPA has confirmed that your proposal below regarding the next printing of the container labels is acceptable

Regards

Amy

From: Didolkar, Ashok [mailto:Ashok.Didolkar@pfizer.com]
Sent: Tuesday, January 20, 2015 6:55 PM
To: Tilley, Amy
Subject: RE: Question re next printing of labels re NDA 207103 Ibrance Carton - Container question - R or TM

Amy,

Pfizer will implement the bottle label revisions approximately 2 months after NDA approval (b) (4)

Thanks

Ashok

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Tuesday, January 20, 2015 2:50 PM
To: Didolkar, Ashok
Subject: RE: Question re next printing of labels re NDA 207103 Ibrance Carton - Container question - R or TM

We need to know *when* after the launch, i.e. number of weeks/months/years, etc

Amy

From: Didolkar, Ashok [mailto:Ashok.Didolkar@pfizer.com]
Sent: Tuesday, January 20, 2015 2:48 PM
To: Tilley, Amy
Subject: RE: Question re next printing of labels re NDA 207103 Ibrance Carton - Container question - R or TM

Amy,

Thanks for your responses to both questions below. The next printing will be after the launch

Best regards,

Ashok

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Tuesday, January 20, 2015 2:39 PM
To: Didolkar, Ashok
Subject: Question re next printing of labels re NDA 207103 Ibrance Carton - Container question - R or TM

Ashok, when will your next printing of the labels be after the launch?

Amy

From: Tilley, Amy
Sent: Tuesday, January 20, 2015 2:26 PM
To: Didolkar, Ashok (Ashok.Didolkar@pfizer.com)
Subject: FW: TIME SENSITIVE NDA 207103 Ibrance Carton - Container question - R or TM

Ashok,

Yes we can confirm the 24 month shelf life for palbociclib and your responses to the container labels for initial launch below are acceptable

Amy

From: Didolkar, Ashok [mailto:Ashok.Didolkar@pfizer.com]
Sent: Sunday, January 18, 2015 7:33 AM
To: Tilley, Amy
Subject: RE: TIME SENSITIVE NDA 207103 Ibrance Carton - Container question - R or TM

Amy,

As discussed on 15 January during End of Cycle telecon, did you get confirmation from Dr Olen Stephens (Branch Chief, Division of New Drug Quality Assessment I) regarding 24 month shelf life for palbociclib? Also, could you please confirm that the below clarifications provided to you are acceptable and we can proceed with printing of the container labels for initial launch?

Thanks

Ashok

Amy,

Pfizer's responses to the Agency requested revisions received on 12 January 2015 related to container label are provided below. We would like to clarify that carton labels were not included in the NDA 207103 as we do not currently intend to use them. For ease of your review the Agency's requested revision is stated in bold followed by Pfizer's response

Request 1 for revision:

Please confirm which version of the carton and container labels will be used for the marketed product? The version (b) (4) and the Pfizer logo (submitted June 30, 2014) or (b) (4) (submitted August 13, 2014)?

Response:

The version (b) (4) will be used for launch. The version (b) (4) will be phased in after launch.

Request 2 for revision:

Which name is correct “Ibrance ®” or “Ibrance ™”? The PI has “Ibrance ®” while the carton and container labels have “Ibrance ™”.

Response:

Ibrance ™ on the container label (b) (4)

DMEPA requests for revisions to the Carton and Container labels:

1 **Remove the statement “For Oncology Use Only” on the principle display panel. This proposed statement is not specific and may mislead the end users to think the proposed drug product is for all oncology indications.**

Response:

Pfizer would like to leave the statement “For Oncology Use Only” on the container label at the initial launch and (b) (4)

2 **Currently the blacked out area on the side panel appears to be a placeholder for the lot number and expiration dates. Ensure that the lot number and the expiration date are presented on the side panel.**

Response:

Please be assured that the lot number and expiration date will appear in white on the black background located on the side panel of the label.

These responses will be officially submitted to NDA later.

Best regards,

Ashok

Ashok K. Didolkar, Ph.D.
Director
Worldwide Safety & Regulatory- Oncology Regulatory
Worldwide Research & Development
Pfizer Inc
235 East 42nd Street Mail Stop 219/09/S10
New York, NY 10017
Tel. (212) 733 8574
Fax (646) 441 4319
Cell (b) (6)
E-mail: ashok.didolkar@pfizer.com

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Monday, January 12, 2015 2:45 PM
To: Didolkar, Ashok
Subject: TIME SENSITIVE NDA 207103 Ibrance Carton - Container question - R or TM
Importance: High

Ashok,

Regarding both sets of the carton and container labels received June 30th and August 13th, 2014, we have 2 questions.

Please confirm which version of the carton and container labels will be used for the marketed product? The version (b) (4) and the Pfizer logo (submitted June 30, 2014) or (b) (4) (submitted August 13, 2014)?

Which name is correct “Ibrance ®” or “Ibrance ™”? The PI has “Ibrance ®” while the carton and container labels have “Ibrance ™”.

We request your response **by Noon, January 13, 2015.**

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/21/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Cc: [Kacuba, Alice](#)
Bcc: [Cortazar, Patricia](#); [Beaver, Julia](#); [Palmby, Todd](#); [Chen, Wei](#)
Subject: URGENT NDA 207103 Ibrance - FDA Revisions to PI sent 1-21-15
Date: Wednesday, January 21, 2015 1:55:00 PM
Attachments: [FDA Working Label palbociclib 1-21-15.doc](#)
Importance: High

Ashok,

Please see the revised PI for your review. Please keep in mind we have grayed out the PPI as it is still under review.

We respectfully request your emailed response to the revised PI **by Jan 22nd at 11:00 am.** Please confirm your response date/time as we have a label meeting tomorrow to review your revisions.

When responding please "Reply to All".

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/21/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: January 15, 2015

Application Number: NDA 207103

Product Name: Ibrance (palbociclib)

Sponsor/Applicant Name: Pfizer Inc.

Subject: End of Review Cycle Teleconference

FDA Participants : Richard Pazdur, M.D., Director, OHOP
Amna Ibrahim, M.D., Acting Director, DOP1
Geoffrey Kim, M.D., Acting Deputy Director, DOP1
Patricia Cortazar, M.D., Clinical Team Leader
Julia Beaver, M.D., Clinical Reviewer
Olen Stephens, Ph.D., Branch Chief, DNDQAIH
Rajeshwari Sridhara, Ph.D., Biostatistics Division Director, OB/DBV
Eric Bloomquist, Ph.D., Biostatistics Reviewer
Alice Kacuba, RN, MSN, RAC, CPMS, DOP1
Amy Tilley, Regulatory Project Manager

Sponsor/Applicant Participants

Susan Berlam, Global Regulatory CMC
Ramzi Dagher, M.D., Vice President and Head of Regulatory Strategy
Oncology
Ashok Didolkar, Ph.D., US Regulatory Lead
Erling Donnelly, Ph.D., Submissions Asset Team Lead
Kieran Fitzpatrick, M.B.A., Global Launch Operations Lead
John Groskoph, Ph.D., Senior Director, Global CMC
Xin Huang, Ph.D., Statistical Lead
Sindy Kim, PALOMA-1 Clinical Lead
Albert Kraus, Ph.D., Global Regulatory Portfolio Lead
Macci Kristy, Project Manager, Clinical Research Unit
Sophia Randolph, M.D., Ph.D., Global Clinical Lead
Mace Rothenberg, M.D., Chief Medical Officer and Senior Vice
President,
Clinical Development and Medical Affairs
Allan Z. Safferman, M.D., Safety & Surveillance Oncology Group Lead
Patrizia Salmoiraghi, Global Regulatory Lead
Patrick Schnell, M.D., Safety Risk Lead
Enayet Talukder, Ph.D., Vice President, Head of Statistics, Pfizer
Oncology

1.0 BACKGROUND:

The purpose of this teleconference was to discuss the end of the review cycle and the launch status of the product.

2.0 DISCUSSION:

Dr. Richard Pazdur stated the purpose of this teleconference was to alert the sponsor to an early action to occur the first week in February 2015. The Agency noted there would be 1 PMC and 1 PMR from the Clinical Team. The sponsor stated they are well positioned for the launch from the Puerto Rico Site. Pfizer also stated they received a safe to proceed and a customs release.

3.0 ACTION ITEMS:

Agency to send the Clinical PMC/PMRs to the sponsor.

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/s/

AMY R TILLEY
01/20/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 14, 2015

TO: NDA 207103

FROM: Amy Tilley

SUBJECT: NDA PDUFA V Late-Cycle Meeting Cancellation

APPLICATION/DRUG: NDA 207103 Ibrance (palbociclib)

The purpose of this memo is to indicate that a Late-Cycle Meeting between the Agency and Applicant for NDA 207103 Ibrance (palbociclib) for January 27, 2014, was canceled as per the Applicant's request.

On January 8, 2015, the Applicant communicated to the Agency (see attached email) that they do not have any item for discussion during the Late Cycle Meeting but would like to keep the date and time on calendars so as to discuss labeling if needed.

We discussed the Applicant's decision to decline the Late-Cycle Meeting with the Office of New Drugs Immediate Office (OND IO) and the OND IO decided that the Late-Cycle Meeting with the Applicant is not needed but that we will keep this date available to discuss labeling if needed.

From: [Didolkar, Ashok](#)
To: [Tilley, Amy](#)
Subject: RE: NDA 207103 Ibrance - Need copy of Pfizer PR and Statement no Late Cycle is needed
Date: Thursday, January 08, 2015 3:23:30 PM
Attachments: [FINAL PFE ODAC Release 1-8-2015.pdf](#)

Amy,

Here is a copy of the press release. As mentioned to you Drs. Mace Rothenberg and Ramzi Dagher from Pfizer had a brief conversation with Dr. Pazdur on Tuesday, 6 January 2015 regarding the press release.

Also, I would like to confirm that Pfizer does not have any item for discussion during the Late Cycle Meeting but would like to keep date and time on calendars so as to discuss labeling if needed.

Best regards,

Ashok

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Thursday, January 8, 2015 3:00 PM
To: Didolkar, Ashok
Subject: NDA 207103 Ibrance - Need copy of Pfizer PR and Statement no Late Cycle is needed
Importance: High

Ashok,

As discussed today via telephone please send me a copy of the Press Release (PR) Pfizer sent out stating there would be no ODAC for this application.

We also need you to confirm in writing that Pfizer does not want to keep the Late Cycle Meeting but would prefer to keep the date/time on our calendars to discuss labeling if needed.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD
20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/20/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Cortazar, Patricia](mailto:Cortazar.Patricia); [Beaver, Julia](mailto:Beaver.Julia); [Ibrahim, Amna \(Amna.Ibrahim@fda.hhs.gov\)](mailto:Ibrahim.Amna@fda.hhs.gov); [Kim, Geoffrey \(Geoffrey.Kim@fda.hhs.gov\)](mailto:Kim.Geoffrey@fda.hhs.gov); [Tang, Shenghui](mailto:Tang.Shenghui); [Bloomquist, Erik](mailto:Bloomquist.Erik); [Fedenko, Katherine](mailto:Fedenko.Katherine)
Subject: TIME SENSITIVE NDA 207103 Ibrance - Clinical PMC-PMR Milestones needed
Date: Tuesday, January 20, 2015 3:55:00 PM
Attachments: [PMC and PMR Clinical final.doc](#)

Ashok.

Below are the Clinical PMC/PMR for which we are requesting Pfizer's Milestone dates.

We request your response via email no later than 4 pm Jan 21, 2014. Please also officially submit your request to the NDA.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 207103
Product Name: Ibrance (palbociclib)

PMR Description: Submit the progression free survival (PFS) and Overall survival (OS) data and results from the ongoing Trial A5481008, PALOMA-2, “A Randomized, Multicenter, Double-blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women with ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti-Cancer Treatment For Advanced Disease” when supplemental application for regular approval is submitted. In addition, submit OS data and results at study completion.

PMR Schedule Milestones:	Interim Report:	<u>MM/YYYY</u>
	Trial Completion:	<u>MM/YYYY</u>
	Final PFS Report Submission:	<u>MM/YYYY</u>
	Final OS Report Submission:	<u>MM/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The final PFS results of Trial A5481008, PALOMA-2 will if statistically significant and clinically meaningful, confirm the clinical benefits of palbociclib treatment in combination with letrozole and will fulfill the requirement for the recommended accelerated approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

As the drug is being approved under accelerated approval a subsequent study is required to confirm the efficacy of palbociclib in this indication.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Clinical Trial A5481008 is a Randomized, Double-Blinded, Multicenter Phase 3 Trial in the same population as the pivotal trial A5481003 supporting accelerated approval. The study has already fully accrued.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 207103
Product Name: Ibrance (palbociclib)

PMC Description: Conduct a clinical trial to determine the prognostic or predictive significance of genetic alterations in the Cyclin D1/CDK4/6/p16/retinoblastoma pathway in ER (+), HER2 (-) breast cancer, specifically the prognostic/predictive significance of the genetic alteration to the safety and efficacy of palbociclib.

PMC Schedule Milestones:	Final Protocol Submission	<u>MM/YYYY</u>
	Trial Completion:	<u>MM/YYYY</u>
	Final Report Submission:	<u>MM/YYYY</u>
	Other: _____	<u>MM/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Further biomarker exploration is needed given that the pivotal study PALOMA-1 did not identify a biomarker for prediction or prognosis, but did indicate the potential that patients with *CDKN2A* loss might benefit less from palbociclib. These findings are preliminary in a small sample size and would require confirmation in a future study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Further biomarker exploration is needed given that the pivotal study PALOMA-1 did not identify a biomarker for prediction or prognosis, but did indicate the potential that patients with *CDKN2A* loss might benefit less from palbociclib.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An ongoing or new clinical trial will be required to test the prognostic and or predictive value of relevant biomarkers.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Exploratory clinical pharmacogenetic trial
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

AMY R TILLEY
01/20/2015

From: Tilley, Amy
To: [Didolkar_Ashok \(Ashok Didolkar@pfizer.com\)](mailto:Didolkar_Ashok (Ashok Didolkar@pfizer.com))
Bcc: [Al-Hakim, Ali H](#); [Sarker, Haripada](#); [Chen, Xiao H](#); [Crich, Joyce](#); [Stephens, Olen](#); [Tu, Chi-Ming \(Alice\)](#); [Mathew, Davis](#); [Kacuba, Alice](#)
Subject: FW: TIME SENSITIVE NDA 207103 Ibrance Carton - Container question - R or TM
Date: Tuesday, January 20, 2015 2:25:00 PM

Ashok,

Yes we can confirm the 24 month shelf life for palbociclib and your responses to the container labels for initial launch below are acceptable

Amy

From: Didolkar, Ashok [mailto:Ashok.Didolkar@pfizer.com]
Sent: Sunday, January 18, 2015 7:33 AM
To: Tilley, Amy
Subject: RE: TIME SENSITIVE NDA 207103 Ibrance Carton - Container question - R or TM

Amy,

As discussed on 15 January during End of Cycle telecon, did you get confirmation from Dr. Olen Stephens (Branch Chief, Division of New Drug Quality Assessment I) regarding 24 month shelf life for palbociclib? Also, could you please confirm that the below clarifications provided to you are acceptable and we can proceed with printing of the container labels for initial launch?

Thanks

Ashok

Amy,

Pfizer's responses to the Agency requested revisions received on 12 January 2015 related to container label are provided below. We would like to clarify that carton labels were not included in the NDA 207103 as we do not currently intend to use them. For ease of your review the Agency's requested revision is stated in bold followed by Pfizer's response.

Request 1 for revision:

Please confirm which version of the carton and container labels will be used for the marketed product? The version (b) (4) and the Pfizer logo (submitted June 30, 2014) or (b) (4) (submitted August 13, 2014)?

Response:

The version (b) (4) will be used for launch. The version (b) (4) will be phased in after launch.

Request 2 for revision:

Which name is correct "Ibrance ®" or "Ibrance ™"? The PI has "Ibrance ®" while the carton and container labels have "Ibrance ™".

Response:

Ibrance ™ on the container label (b) (4)

DMEPA requests for revisions to the Carton and Container labels:

1 Remove the statement "For Oncology Use Only" on the principle display panel. This proposed statement is not specific and may mislead the end users to think the proposed drug product is for all oncology indications.

Response:

Pfizer would like to leave the statement "For Oncology Use Only" on the container label at the initial launch and (b) (4)

2 Currently the blacked out area on the side panel appears to be a placeholder for the lot number and expiration dates. Ensure that the lot number and the expiration date are presented on the side panel.

Response:

Please be assured that the lot number and expiration date will appear in white on the black background located on the side panel of the label.

These responses will be officially submitted to NDA later.

Best regards,

Ashok

Ashok K. Didolkar, Ph.D.
Director
Worldwide Safety & Regulatory- Oncology Regulatory
Worldwide Research & Development
Pfizer Inc
235 East 42nd Street Mail Stop 219/09/S10
New York, NY 10017
Tel. (212) 733 8574
Fax (646) 441 4319
Cell (b) (6)
E-mail: ashok.didolkar@pfizer.com

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Monday, January 12, 2015 2:45 PM
To: Didolkar, Ashok
Subject: TIME SENSITIVE NDA 207103 Ibrance Carton - Container question - R or TM
Importance: High

Ashok,

Regarding both sets of the carton and container labels received June 30th and August 13th, 2014, we have 2 questions.

Please confirm which version of the carton and container labels will be used for the marketed product? The version (b) (4)

(b) (4) and the Pfizer logo (submitted June 30, 2014) or (b) (4) (submitted August 13, 2014)?
Which name is correct “Ibrance ®” or “Ibrance ™”? The PI has “Ibrance ®” while the carton and container labels have “Ibrance ™”.

We request your response **by Noon, January 13, 2015**.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/20/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Cortazar, Patricia](mailto:Cortazar.Patricia@fda.hhs.gov); [Ibrahim, Amna \(Amna.Ibrahim@fda.hhs.gov\)](mailto:Ibrahim.Amna@fda.hhs.gov)
Subject: TIME SENSITIVE NDA 207103 Ibrance - PI Revisions
Date: Thursday, January 15, 2015 4:56:00 PM
Attachments: [FDA rev label 1-14-15.doc](#)

Ashok,

Please see the attached PI with our partial revisions. We have grayed out the sections we ***do not*** want you to review at this time.

Also, if Pfizer agrees with our revisions please “Accept” them within the Word document instead of entering a comment that Pfizer agrees.

We request your emailed response **by COB 1-19-15.**

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/15/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Cortazar, Patricia](#); [Beaver, Julia](#)
Subject: URGENT NDA 207103 Ibrance - Clinical IR
Date: Thursday, January 15, 2015 11:53:00 AM
Importance: High

Ashok,

Please propose a plan to provide the OS data from PALOMA 2 in the event that you submit an application based on the interim analysis of PFS.

We request your response **no later than 12 pm Friday, January 16, 2015.**

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/15/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Cortazar, Patricia](#); [Beaver, Julia](#)
Subject: URGENT NDA 207103 Ibrance - FDA addtl revs Sect 14 sent 1-12-15
Date: Monday, January 12, 2015 4:07:00 PM
Attachments: [Addt revs to sect 14 FDA rev label 1-12-15.doc](#)
Importance: High

Ashok,

Attached is the Word document containing our additional revisions to Section 14.

We request your response **no later than 4 pm on Thursday, January 15, 2015.**

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/12/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Tu, Chi-Ming \(Alice\)](#); [Mathew, Davis](#); [Al Hakim, Ali H](#); [Stephens, Olen](#); [Sarker, Haripada](#); [Crich, Joyce](#); [Chen, Xiao H](#)
Subject: TIME SENSITIVE NDA 207103 Ibrance - DMEPA C&C IR
Date: Monday, January 12, 2015 3:15:00 PM
Importance: High

Ashok,

Below are the DMEPA requests for revisions to the Carton and Container labels:

1. Remove the statement “For Oncology Use Only” on the principle display panel. This proposed statement is not specific and may mislead the end users to think the proposed drug product is for all oncology indications.
2. Currently the blacked out area on the side panel appears to be a placeholder for the lot number and expiration dates. Ensure that the lot number and the expiration date are presented on the side panel.

We respectfully request your response to this email **no later than 1 pm on Wednesday, January 14 2015.**

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/12/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Ashok.Didolkar@pfizer.com)
CC: [Al-Ha'im, Ali H.](#); [Sis-hens, Olen](#); [Sar-er, Hari-ada](#); [Crich, Joyce](#); [Chen, Xiao H.](#); [T. Chi-Ming \(Alice\)](#); [Mathe, Da-Is](#)
Subject: TIME SENSITIVE NDA 207103 Ibrance Carton - Container question - R or TM
Date: Monday, January 12, 2015 2:44:00 PM
Importance: High

Ashok,

Regarding both sets of the carton and container labels received June 30th and August 13th, 2014, we have 2 questions.

1. Please confirm which version of the carton and container labels will be used for the marketed product? The version (b) (4) and the Pfizer logo (submitted June 30, 2014) or (b) (4) (submitted August 13, 2014)?
2. Which name is correct "Ibrance ®" or "Ibrance ™"? The PI has "Ibrance ®" while the carton and container labels have "Ibrance ™".

We request your response **by Noon, January 13, 2015.**

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/12/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok(Ashok.Didolkar@pfizer.com))
Bcc: [Beaver, Julia](#); [Cortazar, Patricia](#)
Subject: Addtl revs to Sect 14 TBD URGENT NDA 207103 Ibrance - FDA Revised Label Sects 5-6 and 14 only
Date: Friday, January 09, 2015 1:07:00 PM

Ashok, I was just informed that we will have additional changes to Sect 14 which we hope we will be ready to send to you today. Our suggestion is that you hold off on sending us any revisions to Sect 14 until we can send you our addtl revisions.

Thanks.

Amy

From: Tilley, Amy
Sent: Friday, January 09, 2015 9:56 AM
To: Didolkar, Ashok (Ashok.Didolkar@pfizer.com)
Subject: URGENT NDA 207103 Ibrance - FDA Revised Label Sects 5-6 and 14 only
Importance: High

Ashok,

Attached are two Word Documents with FDA's revisions to the Ibrance label Sections 5, 6, and 14 only.

The first document contains revisions to Sections 5 & 6 and the second document contains revisions to Section 14.

We respectfully request your emailed response as soon as possible. As always, please follow up with an official submission to the NDA.

Kindly confirm receipt of this IR.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/09/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Cortazar, Patricia](mailto:Cortazar.Patricia); [Ibrahim, Amna \(Amna.Ibrahim@fda.hhs.gov\)](mailto:Ibrahim.Amna@fda.hhs.gov); [Kim, Geoffrey \(Geoffrey.Kim@fda.hhs.gov\)](mailto:Kim.Geoffrey@fda.hhs.gov); [Beaver, Julia](mailto:Beaver.Julia)
Subject: URGENT NDA 207103 Ibrance - FDA Revised Label Sects 5-6 and 14 only
Date: Friday, January 09, 2015 9:55:00 AM
Attachments: [Ibrance FDA rev label sects 5 and 6 only 1-8-15.doc](#)
[Ibrance FDA rev label Sect 14 only 1-9-15.doc](#)
Importance: High

Ashok,

Attached are two Word Documents with FDA's revisions to the Ibrance label Sections 5, 6, and 14 only.

The first document contains revisions to Sections 5 & 6 and the second document contains revisions to Section 14.

We respectfully request your emailed response as soon as possible. As always, please follow up with an official submission to the NDA.

Kindly confirm receipt of this IR.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/09/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207103

GENERAL ADVICE

Pfizer Inc.
Attention: Ashok K. Didolkar, Ph.D.
Director, Worldwide Safety & Regulatory- Oncology Regulatory
235 East 42nd Street Mail Stop 219/09/S10
New York, NY 10017

Dear Dr. Didolkar:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ibrance (palbociclib) Capsules 75mg, 100mg and 125mg.

We also refer to information request sent on January 5, 2015 and teleconference on January 6, 2015. The reasoning for not reporting impurities to the hundredths place is reasonable and is consistent with ICH Q3B. A response is not necessary to the information request sent on January 5, 2015.

If you have any questions, call Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Acting Branch Chief, Branch I
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Olen
Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Olen Stephens -S,
0.9.2342.19200300.100.1.1=2000558
826
Date: 2015.01.09 14:07:20 -05'00'

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Cortazar, Patricia](#)
Subject: NDA 207103 Ibrance - Need copy of Pfizer PR and Statement no Late Cycle is needed
Date: Thursday, January 08, 2015 2:59:00 PM
Importance: High

Ashok,

As discussed today via telephone please send me a copy of the Press Release (PR) Pfizer sent out stating there would be no ODAC for this application.

We also need you to confirm in writing that Pfizer does not want to keep the Late Cycle Meeting but would prefer to keep the date/time on our calendars to discuss labeling if needed.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/08/2015

Tilley, Amy

From: Tilley, Amy
Sent: Wednesday, January 07, 2015 4:47 PM
To: Didolkar, Ashok (Ashok.Didolkar@pfizer.com)
Subject: Request Prompt Response re NDA 207103 Ibrance - Need Clin Pharm PMR proposed Milestone dates

Importance: High

Ashok,

To expedite our review we will be sending you the PMRs or PMCs as they are cleared. Below are the Clinical Pharmacology PMRs for this application for Pfizer's review. The only items negotiable are the Milestone Dates.

We request Pfizer's prompt response regarding their proposal of the PMR Schedule Milestone dates.

PMR Description: Submit the final study report for your clinical trial A5481013 entitled, "A phase 1, open-label, single dose, parallel-group study to evaluate the pharmacokinetics of palbociclib (PD-0332991) in subjects with impaired hepatic function", to assess the effect of moderate and severe hepatic impairment on the pharmacokinetics of palbociclib.

PMR Schedule Milestones:	Final Protocol Submission:	<u>12/01/2014</u>
	Trial Completion:	<u>MM/YYYY</u>
	Final Report Submission:	<u>MM/YYYY</u>

PMR Description: Submit the final study report for your ongoing drug interaction trial (A5481039) entitled, "A phase 1, open-label, fixed-sequence, 2-cohort, 2-period study to investigate the effect of modafinil and pioglitazone given as multiple doses on single dose pharmacokinetics of palbociclib (PD-0332991) in healthy volunteers", to assess the effect of modafinil (a moderate CYP3A inducer) on the pharmacokinetics of palbociclib in healthy volunteers.

PMR Schedule Milestones:	Final Protocol Submission:	<u>08/08/2014</u>
	Trial Completion:	<u>MM/YYYY</u>
	Final Report Submission:	<u>MM/YYYY</u>

Please note that as additional PMRs or PMCs are cleared they will be sent to you expeditiously.

Regards.
Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,

CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/07/2015

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Beaver, Julia](#); [Cortazar, Patricia](#)
Subject: URGENT NDA 207103 Ibrance - Clin IR sent 1-6-15
Date: Tuesday, January 06, 2015 12:28:00 PM
Importance: High

Ashok,

Below is a Clinical IR which we request your response to by 4 pm on Wednesday, Jan 7, 2015.

In section 6.1 of the label only 3 cases of Pulmonary Embolus are included as serious adverse reactions when it appears there should be 4 cases (SID 10312001, 10562001, 10482001, and 10332007). We believe it is SID 10332007 which is omitted, but this case although not initially deemed serious by the investigator was a Grade 4 PE. Please explain your rationale for including only three cases in the label.

Please confirm receipt of this IR.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/06/2015

From: Agosto, Teicher
To: Ashok.Didolkar@pfizer.com
Cc: [Tilley, Amy](#)
Subject: NDA 207103 Information Request
Date: Monday, January 05, 2015 1:23:00 PM

Dear Dr. Didolkar,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palbociclib capsules.

We are requesting additional information. We request a prompt written response by Wednesday, January 7, 2015, in order to continue our evaluation of your NDA.

1. Revise the drug product palbociclib specification for the following: Express the acceptance criteria to the hundredths (two decimals) for all degradation products (unspecified, specified, and total).

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

Teicher
N.
Agosto -S

Digitally signed by
Teicher N. Agosto -S
DN: c=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1
.1=2001299714,
cn=Teicher N. Agosto -S
Date: 2015.01.05
13:28:35 -05'00'

From: Agosto, Teicher
To: Ashok.Didolkar@pfizer.com
Subject: Information Request NDA 207103
Date: Friday, December 19, 2014 1:36:00 PM
Attachments: [NDA 207103 Information Request \(19 December 2014 update\).pdf](#)
Importance: High

Dear Dr. Didolkar,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palbociclib capsules.

We are requesting additional information (Please see attached letter) . We request a prompt written response by Monday, December 22, 2014, in order to continue our evaluation of your NDA.

1. The acceptance criteria for (b) (4) are wider than process capabilities supported during the development process. From the data for the four registration batches included in the NDA (0000) and the nine new validation batches submitted in the Amendment (0048) of 26-Nov-2014, the reported relative standard deviation (RSD) was less than 2.0% and within +/-5% from the mean. Please revise the (b) (4) acceptance to be representative based on process knowledge.
2. Perform (b) (4) capsule content uniformity assay test and dissolution test across all throughput (in kilograms and # Caps). We recommend, designing the sampling plan at appropriate intervals throughout the whole (b) (4) process, from (b) (4)% by weight as previously reported in the NDA section 3.2. P.2.3 and in the Amendment (0053) titled "response2dp-to-fda-cmc-02-dec-2014".
3. Place one batch from each strength of 75 mg, 100 mg, and 125 mg on long-term stability, with the test time points of 0, 3, 6, 9, 12, 18, 24, and 36 months.

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,
Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777



NDA 207103

MID-CYCLE COMMUNICATION

Pfizer Inc.
Attention: Ashok Didolkar, Ph.D.
Director
235 East 42nd Street
New York, NY 10017

Dear Dr. Didolkar:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ibrance[®] (palbociclib) Capsules, 125 mg, 100 mg, and 75 mg.

We also refer to the teleconference between representatives of your firm and the FDA on December 4, 2014. 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, contact me at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Amy R. Tilley
Regulatory Project Manager
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: December 4, 2014, 3:00 pm – 4:00 pm

Application Number: NDA 207103
Product Name: Ibrance[®] (palbociclib) Capsules
Indication: Advanced Breast Cancer
Applicant Name: Pfizer, Inc.

Meeting Chair: Patricia Cortazar, M.D., Clinical Team Leader
Meeting Recorder: Amy Tilley, Regulatory Project Manager

FDA ATTENDEES

Richard Pazdur, M.D., Director, OHOP
Amna Ibrahim, M.D., Acting Director, DOP1
Geoffrey Kim, M.D., Acting Deputy Director, DOP1
Patricia Cortazar, M.D., Clinical Team Leader, DOP1
Julia Beaver, M.D., Clinical Reviewer, DOP1
Laleh Kordestani-Amiri, M.D., Clinical Reviewer, DOP1
Sanjeeve Balasubramaniam, M.D., Clinical Reviewer, DOP1
Shenghui Tang, Ph.D., Biostatistics Team Leader
Erik Bloomquist, Ph.D., Biostatistics Reviewer
Qi Liu, Ph.D., Clinical Pharmacology Team Leader
Liang Zhao, Ph.D., Clinical Pharmacology Team Leader
Jeanne Fourie-Zirkelbach, Ph.D., Clinical Pharmacology Reviewer
Jingyu (Jerry) Yu, Ph.D., Clinical Pharmacology Reviewer
Ali H Al Hakim, Ph.D., Branch Chief, ONDQA
Haripada Sarker, Ph.D., CMC Lead, Branch II, ONDQA
Joyce Crich, Ph.D., Chemistry Reviewer, ONDQA
Xiao Hong Chen, Ph.D., Chemistry Reviewer, ONDQA
Rosane Charlab Orbach, Ph.D., Genomics Team Leader, Genomics Group, OCP
Todd Palmby, Ph.D., Pharmacology Toxicology Supervisor, DHOT
Wei Chen, Ph.D., Pharmacology Toxicology Reviewer, DHOT
Mona Patel, Ph.D., DRISK Reviewer
Susan Jenney, M.S., Safety Regulatory Health Project Manager
Amy Tilley, Regulatory Project Manager

APPLICANT ATTENDEES

Susan Berlam, Global Regulatory CMC
Ramzi Dagher, M.D., Vice President and Head of Regulatory Strategy Oncology
Susan Decoteau, Global Regulatory CMC

Ashok Didolkar, Ph.D., US Regulatory Lead
Erling Donnelly, Ph.D., Submissions Asset Team Lead
Rebecca Hintze, Oncology Programming Lead
Xin Huang, Ph.D., Statistical Lead
Yuqiu (John) Jiang, Ph.D., Translation Oncology Lead
Sindy Kim, PALOMA-1 Clinical Lead
Eric Kowack, MS, MBA, Asset Team Lead
Albert Kraus, Ph.D., Global Regulatory Portfolio Lead
Norihiko Oharu, Palbociclib Programming Lead
Sophia Randolph, M.D., Ph.D., Global Clinical Lead
Mace Rothenberg, M.D., Chief Medical Officer and Senior Vice President, Clinical Development and Medical Affairs
Aida Sacaan, Ph.D., Nonclinical Drug Safety Research and Development
Allan Z. Safferman, M.D., Safety & Surveillance Oncology Group Lead
Patrizia Salmoiraghi, Global Regulatory Lead
Patrick Schnell, M.D., Safety Risk Lead
Diane Wang, Ph.D., Clinical Pharmacology Lead
Jenny Zheng, Pharmacometrician

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

FDA conveyed to the sponsor that many challenges were encountered during the review of this application. It was discussed that the pivotal study was small and not initially planned to support marketing approval which resulted in data-driven changes. In addition, there was a high level of censoring and disagreements between investigator assessments and central review assessments.

Discussion also revolved around study conduct violations found at site 1001 which resulted in a preliminary classification of official action indicated. FDA stated these findings were concerning an OSI recommendation to remove patients from this site from the final analysis.

3.0 INFORMATION REQUESTS

FDA asked the sponsor to provide a corrective action plan to prevent further conduct issues in study A5481008 (Phase 3 trial).

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

FDA stated there was no need for an ODAC for this application.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late-Cycle Meeting is currently scheduled for January 27, 2015. The briefing package will be sent approximately 2 days in advance of the meeting. Any updates to the timeline will be communicated.

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/s/

AMY R TILLEY
12/19/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com); Patricia.Cortazar@fda.hhs.gov
Bcc: [Cortazar, Patricia](#); [Beaver, Julia](#); [Amiri Kordestani, Laleh \(FDA\)](#)
Subject: Time Sensitive NDA 207103 Ibrance - FDA Revised Label Sects 5 & 6 only sent 12-16-14
Date: Tuesday, December 16, 2014 5:52:00 PM
Attachments: [FDA rev label 12-16-14 Sects 5 and 6 except 5.4 and 5.5.doc](#)

Ashok,

Below are the FDA's revisions to-date of the Ibrance label Sections 5 and 6 only. **However, please note we have not yet finalized our revisions to subsections 5.4 Fertility and 5.5 Embryo-Fetal Toxicity.**

We request your response by Dec 29, 2014.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
12/17/2014

From: Tilley, Amy
To: [Didolkar_Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar_Ashok@pfizer.com)
Bcc: [Cortazar_Patricia](#); [Amiri Kordestani_Laleh \(FDA\)](#); [Beaver_Julia](#)
Subject: URGENT NDA 207103 Ibrance - Clin IR sent 12-5-14
Date: Friday, December 05, 2014 10:31:00 AM
Importance: High

Ashok,

Please respond by 12/8/14 8 a.m.

System Organ Class	IBRANCE + Letrozole (N=83)			Letrozole Alone (N=77)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Adverse Reaction	%	%	%	%	%	%
Infections and infestations						(b) (4)
URI ^a	31.3	1.2	0	18.2	0	0 (b) (4)

- Please provide the cut off point for inclusion of adverse reactions in Table 4 of the label.
- Please provide your rationale not including (b) (4) in Table 4 of the label.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
 CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD 20993
 ☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
12/05/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Liu, Qi \(CDER\)](#); [Fourie Zirkelbach, Jeanne](#)
Subject: Time Sensitive - NDA 207103 Ibrance - Clin Pharm IR sent 12-4-14
Date: Thursday, December 04, 2014 4:31:00 PM
Importance: High

Ashok,

We note that on November 14, 2014 you submitted to your IND 69324 a description of results from your trial 1016 evaluating the effect of itraconazole on palbociclib exposure.

Please submit the final study report for review as well as your proposed labeling language of the sections affected no later than **2 pm on December 8, 2014.**

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
12/04/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Beaver, Julia](#); [Amiri Kordestani, Laleh \(FDA\)](#)
Subject: NDA 207103 Ibrance - Financial Disclosure Section 1.3.4
Date: Thursday, December 04, 2014 4:21:00 PM

Ashok,

For your information, and as discussed during today's Mid-Cycle Communication Meeting, see the financial information table below which will be incorporated into the medical officer clinical review. If you feel edits should be made please respond no later than close of business on December 15th.

Clinical Site Number	Investigator Name (PI or SI)	Phase 2 Patient Enrollment at Site	Disclosure
[REDACTED]	[REDACTED]	(b) (6)	Honorariums totaling \$29,630.50
			Advisory board, scientific grants and individual services totaling \$92,500
			Consulting, honorarium, symposia speaker totaling \$53,233
			Equity in Pfizer totaling \$254,865.70
			Miscellaneous payments totaling \$35,712.28
			Miscellaneous payments totaling \$212,124.37
			Miscellaneous payments totaling \$41,147.09
			Miscellaneous payments and consulting totaling \$133,316.55

PI: Principle Investigator; SI: Sub-investigator. Source: NDA 207103 Section 1.3.4, Financial Disclosure

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
12/04/2014

From: Tilley, Amy
To: [Didolkar_Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar_Ashok (Ashok.Didolkar@pfizer.com))
Bcc: [Amiri_Kordestani_Laleh \(FDA\)](#)
Subject: URGENT NDA 207103 Ibrance - Clinical IR sent 12-3-14
Date: Wednesday, December 03, 2014 2:24:00 PM
Importance: High

Ashok,

There are some discrepancies between the rate of some of the adverse drug reactions (shown below). **Please explain the differences by 8 a.m. Eastern time 12/4/14.**

Applicant Table

System Organ Class	IBRANCE + Letrozole (N=83)			Letrozole Alone (N=77)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any Adverse Drug Reaction	%	%	%	%	%	%
Stomatitis	25.3	0	0	6.5	1.3	0
Nausea	25.3	2.4	0	13.0	1.3	0
Diarrhea	20.5	3.6	0	10.4	0	0
Vomiting	14.5	0	0	3.9	1.3	0
Pyrexia	8.4	0	0	2.6	0	0

FDA Table generated from advers.xpt database

System Organ Class	IBRANCE + Letrozole (N=83)			Letrozole Alone (N=77)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any Adverse Drug Reaction	%	%	%	%	%	%
Stomatitis	33.7	0	0	7.8	1.3	0
Nausea	26.5	2.4	0	14.3	1.3	0
Diarrhea	20.5	3.6	0	11.8	0	0
Vomiting	15.7	0	0	3.9	1.3	0
Pyrexia	9.6	0	0	2.6	0	0

Stomatitis includes the following preferred terms: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
12/03/2014

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/s/

AMY R TILLEY
12/02/2014

Panorama
copy



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207103

INFORMATION REQUEST

Pfizer Inc.
Attention: Ashok K. Didolkar, Ph.D.
Director, Worldwide Safety & Regulatory- Oncology Regulatory
235 East 42nd Street Mail Stop 219/09/S10
New York, NY 10017

Dear Dr. Didolkar:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palbociclib capsules.

We reviewed the preliminary response for the information request and have the following comments. We request a prompt written response by December 8, 2014, in order to continue our evaluation of your NDA.

Drug Substance:

Query 1: No further comment.

Query 2: The response is acceptable.

Query 3: No further comment.

Query 4: The proposed acceptance limit (NMT ^{(b) (4)} ppm) is calculated using the ICH Q3D guidelines option 2a and the maximum daily dose of 125 mg. Pd offers no therapeutic benefit. Therefore, tighten the acceptance criterion for Pd based on batch analysis data and manufacturing capability in the event that higher doses will be used for other indications or as combination use with other drug products.

Query 5: Provide a description of the method used and related test data to support your justification of "*Omission of Tests are the reporting limits of the method. No detectable levels of these solvents were observed in the final drug substance.*"

Query 6: No further comment.

Query 7: No further comment.

Query 8: No further comment.

Drug Product:

Query 1: FDA will review the Master Batch Records.

Query 2:

To assess adequacy of your (b) (4) control and to verify if there is any impact on the content uniformity by the (b) (4) process and (b) (4) and their modifications, we need to review the related (b) (4) (b) (4) data as listed below, considering the last (b) (4) (b) (4) of the registration batches have not been used in clinical studies. To facilitate our review, please provide the following information in a tabular format:



3. Manufacturing information for the new nine validation batches (J54976, J54978, J55109, J54977, J54979, J55106, J53342, J53343, and J53344) since these batches were not included in the NDA. This should include:

- manufacturing date
- name of the site
- strength,
- batch size

- (b) (4) procedure
- (b) (4)
- the clinical usage (with or without (b) (4)% clinical cut off control)
- (b) (4) data
- any other changes made to the manufacturing process which was used for the nine registration batches in the NDA.
- If the (b) (4)% clinical cut off control was applied to those nine batches, resubmit (b) (4) (b) (4) sample assay data by listing the data separately before and after the (b) (4)% clinical cutoff.

Query 3: FDA will assess the (b) (4)

Query 4: No further comment.

Query 5: No further comment.

Query 6: No further comment.

Query 7: No further comment.

Query 8: No further comment.

If you have any questions, call Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.

Sincerely,

{See appended electronic signature page.}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Ali H. Al-
Hakim -S

Digitally signed by Ali H. Al- Hakim
-S
DN: c=US, o=U.S. Government,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=13000
93815, cn=Ali H. Al- Hakim -S
Date: 2014.12.01 18:13:56 -0500

From: Tilley, Amy
To: "[Didolkar, Ashok](#)"
Bcc: [Palmby, Todd](#); [Chen, Wei](#)
Subject: RE: URGENT NDA 207103 Ibrance - Pharm Tox Information Request sent 11-24-14
Date: Monday, November 24, 2014 12:38:00 PM

Ashok, I just spoke with the PT Team Leader regarding the timeframe for you to submit your response.

It is acceptable for you to submit the Tox Reports tomorrow, Nov 25th. As for the assessment part of your response, it is acceptable for you to submit your response on Tues, Dec 2nd.

Regards.

Amy

From: Didolkar, Ashok [<mailto:Ashok.Didolkar@pfizer.com>]
Sent: Monday, November 24, 2014 12:20 PM
To: Tilley, Amy
Subject: RE: URGENT NDA 207103 Ibrance - Pharm Tox Information Request sent 11-21-14

Amy,

I tried to recall that message as there are some new developments. Therefore, I just left you a voicemail message. I would like to speak with you regarding the response strategy for this Pharm Tox IR. Could you please give me a call at (b) (6) (preferred) or 212 733 8574.

Thanks

Ashok

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Monday, November 24, 2014 12:17 PM
To: Didolkar, Ashok
Subject: RE: URGENT NDA 207103 Ibrance - Pharm Tox Information Request sent 11-21-14

Ashok, yes it is acceptable to provide us your response to the Pharm Tox IR below on Nov 25, 2014.

Please send your response no later than 4 pm.

Amy

From: Didolkar, Ashok [<mailto:Ashok.Didolkar@pfizer.com>]
Sent: Friday, November 21, 2014 6:52 PM
To: Tilley, Amy
Subject: RE: URGENT NDA 207103 Ibrance - Pharm Tox Information Request sent 11-21-14

Amy,

We would be able to provide the response to this Pharm Tox IR by end of business on Tuesday, 25 November 2014.

Best regards,

Ashok

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Friday, November 21, 2014 5:35 PM
To: Didolkar, Ashok
Subject: URGENT NDA 207103 Ibrance - Pharm Tox Information Request sent 11-21-14
Importance: High

Ashok,

We reviewed the report for the 27-week rat study submitted to IND 69324 with your 2-year rat carcinogenicity study SPA. Given the significant palbociclib-related toxicities observed in the 27-week rat study, please submit the final reports for the 27-week rat study (# 8282224) and 39-week dog study (# 8282225) to NDA 207103. In addition, submit your risk assessment and the clinical relevance of the findings in those studies to NDA 207103, primarily the pancreatic islet vacuolation, hyperglycemia and associated toxicities in multiple tissues and organs observed in the 13-week and 27-week repeat-dose rat studies.

We respectfully request your response as soon as possible.

Please confirm receipt of this email.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/24/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Ashok.Didolkar@pfizer.com)
Bcc: [Palmy, Todd](#); [Chen, Wei](#); [Cortazar, Patricia](#); [Beaver, Julia](#)
Subject: URGENT NDA 207103 Ibrance - Pharm Tox Information Request sent 11-21-14
Date: Friday, November 21, 2014 5:35:00 PM
Importance: High

Ashok,

We reviewed the report for the 27-week rat study submitted to IND 69324 with your 2-year rat carcinogenicity study SPA. Given the significant palbociclib-related toxicities observed in the 27-week rat study, please submit the final reports for the 27-week rat study (# 8282224) and 39-week dog study (# 8282225) to NDA 207103. In addition, submit your risk assessment and the clinical relevance of the findings in those studies to NDA 207103, primarily the pancreatic islet vacuolation, hyperglycemia and associated toxicities in multiple tissues and organs observed in the 13-week and 27-week repeat-dose rat studies.

We respectfully request your response as soon as possible.

Please confirm receipt of this email.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/21/2014

From: Tilley, Amy
To: "Didolkar, Ashok"
Bcc: Cole, Jessica
Subject: RE: Time Sensitive NDA 207103 Ibrance - Micro IR
Date: Friday, November 21, 2014 11:41:00 AM

Ashok,

Upon conferring with the Micro Reviewer, please officially submit your response for review regarding the initial Micro Information Request sent November 19, 2014.

Regards.

Amy

From: Didolkar, Ashok [mailto:Ashok.Didolkar@pfizer.com]
Sent: Wednesday, November 19, 2014 4:33 PM
To: Tilley, Amy
Subject: RE: Time Sensitive NDA 207103 Ibrance - Micro IR sent 11-19-14

Amy,

Thank your for your review and comment on the microbiological query responses provided on 23 October 2014 (Sequence 0027). We are providing a draft query response to your question raised today by e-mail to facilitate your review in a timely manner. We kindly request a quick response from the Agency to confirm this approach is acceptable.

-
CMC Response:

All ^{(b) (4)} validation/commercial lots were tested for *E.coli* at release and shown to be negative per USP <62>. This test was not shown on the stability protocol described in Table 3.2.P.8.2-1 Stability Testing Protocol to Confirm Proposed Shelf Life. We agree to amend the protocol to show that this test was performed at the initial time point. As these lots demonstrated absence of *E. coli* at the initial time point, there will be no subsequent testing for *E.coli* in the stability program.

To summarize, Pfizer previously provided justification to eliminate all microbiological testing (USP <61> and <62>) at release and for the annual batch commitment. However, Pfizer will perform microbiological testing on the ^{(b) (4)} commercial batches of each strength as described in the amended Table 3.2.P.8.2-1 (pasted below for ease of review) which adds USP <62> absence of *E. coli* only at the initial time point.

Table 3.2.P.8.2-1 Stability Testing Protocol to Confirm Proposed Shelf Life

Storage Condition	Interval ^(a) (Months)							
	Initial	3	6	9	12	18	24	36
Initial	A							
40 °C/75% RH		B	B					
30 °C/75% RH		B	B	B	C	B	C	C

(a) The expiry interval is based on the manufacturing date. All other intervals are determined from the date stability studies are placed under the specified storage conditions. Additional intervals may be added for the purpose of extending shelf-life.

The following tests will be applied to the protocol above:

A: Appearance, Assay, Degradation Products, Dissolution, (b) (4) and Microbiological Quality (absence of *E. coli*, total aerobic microbial count and total combined yeasts and molds count)

B: Appearance, Assay, Degradation Products, Dissolution and (b) (4)

C: Appearance, Assay, Degradation Products, Dissolution, (b) (4) and Microbiological Quality (total aerobic microbial count and total combined yeasts and molds count)

If this approach is acceptable, Pfizer will provide the formal query response, including the updated 3.2.P.8.2 section, by November 26, 2014 with the other CMC responses.

Thanks

Ashok

Ashok K. Didolkar, Ph.D.
Director
Worldwide Safety & Regulatory- Oncology Regulatory
Worldwide Research & Development
Pfizer Inc
235 East 42nd Street Mail Stop 219/09/S10
New York, NY 10017
Tel. (212) 733 8574
Fax (646) 441 4319
Cell (b) (6)
E-mail: ashok.didolkar@pfizer.com

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Wednesday, November 19, 2014 1:17 PM
To: Didolkar, Ashok
Subject: Time Sensitive NDA 207103 Ibrance - Micro IR sent 11-19-14

Ashok,

We refer to your Oct 23, 2014, response to microbiology question 2 from the Sept 11, 2014, information request. In that response, the absence of USP<62> testing on stability is justified due to the conduct of USP<62> testing for *Escherichia coli* at release. However, the Oct 23, 2014, response to Question 1 removes microbiological release testing from the specification. Module 3.2.P.8.2 states that microbiological testing on stability will only include total aerobic microbial count and total yeast and mold count. USP<62> testing for the absence of *E. coli* should be included on stability.

We request your response as soon as possible.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/21/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok(Ashok.Didolkar@pfizer.com))
Bcc: [Cole, Jessica](#)
Subject: Time Sensitive NDA 207103 Ibrance - Micro IR sent 11-19-14
Date: Wednesday, November 19, 2014 1:16:00 PM

Ashok,

We refer to your Oct 23, 2014, response to microbiology question 2 from the Sept 11, 2014, information request. In that response, the absence of USP<62> testing on stability is justified due to the conduct of USP<62> testing for *Escherichia coli* at release. However, the Oct 23, 2014, response to Question 1 removes microbiological release testing from the specification. Module 3.2.P.8.2 states that microbiological testing on stability will only include total aerobic microbial count and total yeast and mold count. USP<62> testing for the absence of *E. coli* should be included on stability.

We request your response as soon as possible.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/19/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok(Ashok.Didolkar@pfizer.com))
Subject: *URGENT* re NDA 207103 Ibrance - Clin IR sent 11-19-14
Date: Wednesday, November 19, 2014 10:09:00 AM

Ashok,

Where in the datasets can we locate the information regarding the name of the investigator who treated each patient? If this information is coded where is the location of the code?

Please respond to this email by **Noon today, Nov 19th, 2014.**

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/19/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar_Ashok_(Ashok.Didolkar@pfizer.com))
Bcc: [Beaver, Julia](#)
Subject: TIME SENSITIVE re NDA 207103 Palbociclib - Clinical IR sent 11-18-14
Date: Tuesday, November 18, 2014 4:46:00 PM

Ashok,

Please respond to the Clinical IR below **by close of business on November 24th**.

Regarding financial disclosures:

1. Please provide the number of investigators screened for financial information in study 1003.
2. Please provide the number of investigators in study 1003.
3. In study 1003, how many patients in the ITT population (n=165) did each investigator with financial information to disclosure (shown below) enroll

Site	Investigator	Patients Enrolled on study 1003
(b) (6)		

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/18/2014

From: [Didolkar, Ashok](#)
To: [Agosto, Teicher](#)
Cc: [Tilley, Amy](#)
Subject: RE: Information Request NDA 207103
Date: Monday, November 17, 2014 5:42:56 PM
Attachments: [Palbociclib NDA DRAFT CMC Query Responses.pdf](#)

Hi Teicher,

Thank you for the productive teleconference last Friday. As per agreement during the meeting, at this time we are providing preliminary responses to the queries from the Chemistry Review Team in the Attachment. Please note that these responses are draft and for responses containing data, the responses are still undergoing QC to verify correct data transcription. Pfizer would like to confirm if the approaches included in the preliminary responses are acceptable to Chemistry Review Team. As agreed, Pfizer will provide the final responses and updated NDA sections by November 26.

These preliminary responses will be officially submitted to NDA later.

Best regards,

Ashok

Ashok K. Didolkar, Ph.D.
Director
Worldwide Safety & Regulatory- Oncology Regulatory
Worldwide Research & Development
Pfizer Inc
235 East 42nd Street Mail Stop 219/09/S10
New York, NY 10017
Tel. (212) 733 8574
Fax (646) 441 4319
Cell (b) (6)
E-mail: ashok.didolkar@pfizer.com

From: Agosto, Teicher [mailto:Teicher.Agosto@fda.hhs.gov]
Sent: Wednesday, November 12, 2014 7:14 AM
To: Didolkar, Ashok
Cc: Tilley, Amy
Subject: Information Request NDA 207103

Dear Dr. Didolkar,

We are requesting the following information concerning your New Drug Application- NDA 207103. We request a prompt response to this IR request no later than Wednesday COB

November 26, 2014.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response by November 26, 2014, in order to continue our evaluation of your NDA.

Drug Substance :

1. Submit validation data for the LC method (TM-1855A) to determine the impurity of (b) (4).
2. It is recommended that you change the acceptance criterion for Total Organic Impurities from “NMT (b) (4)%” to “NMT (b) (4)%”.
3. Tighten the acceptance criteria for (b) (4) and (b) (4) based on batch analysis data and manufacturing capability since they are potential genotoxic impurities.
4. Tighten the proposed acceptance limit for Pd based on batch analysis data and manufacturing capability.
5. The provided justification for not to test (b) (4) at drug substance release is not acceptable. They are used in the (b) (4) of the drug substance manufacturing process, and are present in the drug substance at the levels of (b) (4) ppm to (b) (4) ppm. These residual solvents should be monitored at drug substance release testing.
6. Include particle size testing in the stability testing program. Submit available stability data for particles size testing.
7. Stability commitment for the (b) (4) commercial batches should be tested for assay, particle size, (b) (4) and solid state form ((b) (4) or other appropriate method) in addition to the proposed appearance and purity. Testing frequency should be every three month for the first year, every six month for the second year and annually thereafter. (Refer to ICH Q1A guidelines.)
8. Stability testing for annual batch should also include testing for assay, particle size, (b) (4) and solid state form ((b) (4) or other appropriate method) in addition to the proposed appearance and purity. Testing frequency for annual batch should be every three month for the first year, every six month for the second year and annually thereafter.

Drug Product:

1. Your manufacturing process description in Section P.3.3 is inadequate and does not provide a complete understanding of the drug product manufacturing process and in-process controls. Adequate information should be provided to describe all the manufacturing steps and in-process controls, including the non-critical process parameters. Thus, in accordance with 21CFR 314.50(d)(ii)(c), either provide a master batch record to any section of Module 3, with a reference/link to the master batch record in the process description (Section P.3.3) OR provide a process description to Section P.3.3 that is comparably detailed to the master batch record.
2. Provide in-process control specifications including a proposed test method and acceptance criterion for (b) (4) during the manufacturing process for palbociclib capsules. The proposed (b) (4) as the only in-

process control is not sufficient.

3. We cannot comment on your proposal to submit (b) (4) (b) (4) since this would be a post-approval issue.
4. Correct the discrepancy of the relative response factor (FR) for degradation product (b) (4) in the procedure of analytical method for Identity, Assay, and Purity (TM-1876A), and revise the relative response factor from (b) (4) to (b) (4) in the procedure, refer to Table 3.2.P.5.3-6 Specificity of TM-1876A ((b) (4) nm).
5. As indicated in 3.2.P.5.5, degradation product (b) (4) is derived from (b) (4) to (b) (4) of (b) (4) under certain conditions (temperature and humidity). Provide information on the source of (b) (4) and the control of (b) (4) in drug product.
6. Proposed acceptance limit for degradation product (b) (4) as NMT (b) (4) % seems much higher than that in all batch data, including the level ((b) (4) %) under accelerated conditions, either tighten or provide justification for the proposed level. Also express the acceptance limit to the hundredths.
7. Since Palbociclib capsules are for US market, please use the following compendia storage condition for the proposed drug products: Stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).
8. The proposed (b) (4) (b) (4) are not acceptable based on ICH Q1A (R2). Revise accordingly for the followings

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

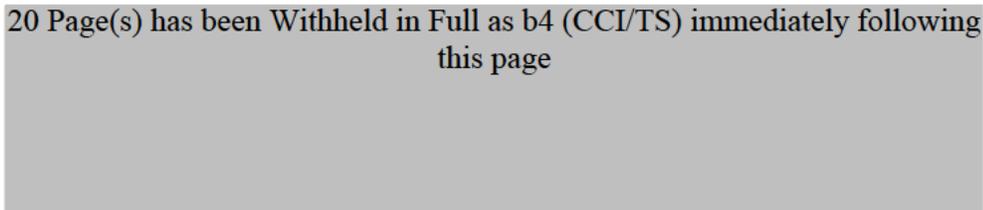
Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Teicher Agosto, Pharm D, RPh

Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

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



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/s/

AMY R TILLEY
11/18/2014

From: [CDER-OC-PLAIR](#)
To: "[Ashok Didolkar@pfizer.com](mailto:Ashok.Didolkar@pfizer.com)"
Cc: [CDER-OC-PLAIR; Tilley, Amy](#)
Subject: FW: NDA 207103 for palbociclib: Follow up on Pre-Launch Activities Importation Request (PLAIR)
Date: Monday, November 17, 2014 9:03:25 AM

Dear Ashok

We understand that this drug has been designated a Breakthrough Therapy NDA and FDA will work with the circumstances of the approval process. Therefore, you may submit the PLAIR request 60 days prior to the anticipated target action date. To further assist you, we have provided the following link on the necessary information for a PLAIR submission:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ImportsandExportsCompliance/UCM365538.pdf>

In your email you mentioned the importation of [REDACTED] (b) (4). Please note that the unapproved new drug product labeling must comply with 21 CFR 201 Labeling, otherwise it is considered to be misbranded under FD&C Act Section 801(a)(3) in violation of 502.

If you have any future PLAIR related questions, please email CDER-OC-PLAIR@fda.hhs.gov. For questions regarding imports and exports, please email: CDERImportsExports@fda.hhs.gov.

Thank you,
CDER-OC-PLAIR

From: Didolkar, Ashok [<mailto:Ashok.Didolkar@pfizer.com>]
Sent: Wednesday, November 12, 2014 4:53 AM
To: Tilley, Amy
Subject: NDA 207103 for palbociclib: Follow up on Pre-Launch Activities Importation Request (PLAIR)

Amy,

I would like to follow up on the discussion during the CMC pre-NDA meeting that was held on 23 January 2014. Pfizer asked the following question:

Question 5: In order to ensure launch supplies are available at the time of approval, the Applicant plans to use the Pre-Launch Activities Importation Request (PLAIR) to import supplies prior to NDA approval. The Applicant requests specific guidance on how to apply for early importation when the NDA approval is expected to be in advance of the PDUFA date.

FDA response to Question 5:

A PLAIR only applies to unapproved finished dosage form drug products based on anticipated approval of a pending original application. The PLAIR is submitted within 60 days of expecting approval. For further information regarding a PLAIR submission, the following link includes the PLAIR process which may be provided to the firm.

With the knowledge that the user fee goal date is April 13, 2015, we would like to supply palbociclib as quickly as possible to patients after approval of the pending NDA 207103 for palbociclib. Would it be acceptable to the Agency if we submit the PLAIR in December 2014 seeking authorization to import launch supplies in January 2015, greater than 60 days from the April 13, 2015 PDUFA user fee goal date with the following understanding?

- The PLAIR will request authorization to import [REDACTED] (b) (4) from the Pfizer manufacturing site in Freiburg, Germany into the Pfizer site in Vega Baja, Puerto Rico prior to NDA approval.
- Importation greater than 60 days from the PDUFA date will allow sufficient time for US Customs and FDA clearance of the imported shipment, and for Pfizer to perform secondary packaging, labeling, and shipment to the Pfizer Distribution Center if approval is granted earlier than the April 13, 2015 user fee goal date.
- All products will remain under quarantine at Pfizer until the NDA is approved.

Additionally, because of the following reasons we would like to know if the proposed shelf life of 24 months could be confirmed in January 2015.

- The lot expiry date is printed on the bottle label during secondary packaging and labeling.
- Confirmation of the product shelf life will allow us to secondary package and label some of the launch supplies prior to receiving the NDA approval.

We would really appreciate receiving the Agency responses to the above questions if possible by 28 November 2014.

Thank you very much for your help.

Best regards,

Ashok

Ashok K. Didolkar, Ph.D.
Director

Worldwide Safety & Regulatory- Oncology Regulatory
Worldwide Research & Development
Pfizer Inc
235 East 42nd Street Mail Stop 219/09/510
New York, NY 10017
Tel. (212) 733 8574
Fax (646) 441 4319
Cell (b) (6)
E-mail: ashok.didolkar@pfizer.com

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/s/

AMY R TILLEY
11/17/2014

From: Tilley, Amy
To: "[Didolkar, Ashok](#)"
Bcc: [Wittorf, Robert](#); [Al Hakim, Ali H](#); [Dillahunt, Michelle](#); [Lopez, Marybet](#); [CDER-OC-PLAIR](#)
Subject: RE: NDA 207103 for palbociclib: Follow up on Pre-Launch Activities Importation Request (PLAIR)
Date: Thursday, November 13, 2014 12:55:00 PM

Ashok, you should be hearing shortly from the Office of Compliance Imports group with respect to your request below.

Thanks.

Amy

From: Didolkar, Ashok [mailto:Ashok.Didolkar@pfizer.com]
Sent: Wednesday, November 12, 2014 4:53 AM
To: Tilley, Amy
Subject: NDA 207103 for palbociclib: Follow up on Pre-Launch Activities Importation Request (PLAIR)

Amy,

I would like to follow up on the discussion during the CMC pre-NDA meeting that was held on 23 January 2014. Pfizer asked the following question:

Question 5: In order to ensure launch supplies are available at the time of approval, the Applicant plans to use the Pre-Launch Activities Importation Request (PLAIR) to import supplies prior to NDA approval. The Applicant requests specific guidance on how to apply for early importation when the NDA approval is expected to be in advance of the PDUFA date.

FDA response to Question 5:

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With the knowledge that the user fee goal date is April 13, 2015, we would like to supply palbociclib as quickly as possible to patients after approval of the pending NDA 207103 for palbociclib. Would it be acceptable to the Agency if we submit the PLAIR in December 2014 seeking authorization to import launch supplies in January 2015, greater than 60 days from the April 13, 2015 PDUFA user fee goal date with the following understanding?

- The PLAIR will request authorization to import (b) (4) from the Pfizer manufacturing site in Freiburg, Germany into the Pfizer site in Vega Baja, Puerto Rico prior to NDA approval.
- Importation greater than 60 days from the PDUFA date will allow sufficient time for US Customs and FDA clearance of the imported shipment, and for Pfizer to perform secondary packaging, labeling, and shipment to the Pfizer Distribution Center if approval is granted earlier than the April 13, 2015 user fee goal date.
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Additionally, because of the following reasons we would like to know if the proposed shelf life of 24 months could be confirmed in January 2015.

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- Confirmation of the product shelf life will allow us to secondary package and label some of the launch supplies prior to receiving the NDA approval.

We would really appreciate receiving the Agency responses to the above questions if possible by 28 November 2014.

Thank you very much for your help.

Best regards,

Ashok

Ashok K. Didolkar, Ph.D.

Director

Worldwide Safety & Regulatory- Oncology Regulatory

Worldwide Research & Development

Pfizer Inc

235 East 42nd Street Mail Stop 219/09/S10

New York, NY 10017

Tel. (212) 733 8574

Fax (646) 441 4319

Cell (b) (6)

E-mail: ashok.didolkar@pfizer.com

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/s/

AMY R TILLEY
11/13/2014



NDA 207103

INFORMATION REQUEST

Pfizer Inc.
Attention: Ashok K. Didolkar, Ph.D.
Director, Worldwide Safety & Regulatory- Oncology Regulatory
235 East 42nd Street Mail Stop 219/09/S10
New York, NY 10017

Dear Dr. Didolkar:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palbociclib capsules.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response by November 26, 2014, in order to continue our evaluation of your NDA.

Drug Substance :

1. Submit validation data for the LC method (TM-1855A) to determine the impurity of (b) (4) (b) (4)
2. It is recommended that you change the acceptance criterion for Total Organic Impurities from "NMT (b) (4)%" to "NMT (b) (4)%".
3. Tighten the acceptance criteria for (b) (4) based on batch analysis data and manufacturing capability since they are potential genotoxic impurities.
4. Tighten the proposed acceptance limit for Pd based on batch analysis data and manufacturing capability.
5. The provided justification for not to test (b) (4) and (b) (4) at drug substance release is not acceptable. They are used in the (b) (4) of the drug substance manufacturing process, and are present in the drug substance at the levels of (b) (4) ppm to (b) (4) ppm. These residual solvents should be monitored at drug substance release testing.
6. Include particle size testing in the stability testing program. Submit available stability data for particles size testing.
7. Stability commitment for the (b) (4) commercial batches should be tested for assay, particle size, (b) (4) and solid state form ((b) (4) or other appropriate method) in addition to the proposed appearance and purity. Testing frequency should be every three

month for the first year, every six month for the second year and annually thereafter. (Refer to ICH Q1A guidelines.)

8. Stability testing for annual batch should also include testing for assay, particle size, (b) (4) (b) (4) and solid state form (b) (4) or other appropriate method) in addition to the proposed appearance and purity. Testing frequency for annual batch should be every three month for the first year, every six month for the second year and annually thereafter.

Drug Product:

1. Your manufacturing process description in Section P.3.3 is inadequate and does not provide a complete understanding of the drug product manufacturing process and in-process controls. Adequate information should be provided to describe all the manufacturing steps and in-process controls, including the non-critical process parameters. Thus, in accordance with 21CFR 314.50(d)(ii)(c), either provide a master batch record to any section of Module 3, with a reference/link to the master batch record in the process description (Section P.3.3) OR provide a process description to Section P.3.3 that is comparably detailed to the master batch record.
2. Provide in-process control specifications including a proposed test method and acceptance criterion for (b) (4) during the manufacturing process for palbociclib capsules. The proposed (b) (4) testing as the only in-process control is not sufficient.
3. We cannot comment on your proposal to submit (b) (4) (b) (4) since this would be a post-approval issue.
4. Correct the discrepancy of the relative response factor (FR) for degradation product (b) (4) (b) (4) in the procedure of analytical method for Identity, Assay, and Purity (TM-1876A), and revise the relative response factor from (b) (4) in the procedure, refer to Table 3.2.P.5.3-6 Specificity of TM-1876A ((b) (4) nm).
5. As indicated in 3.2.P.5.5, degradation product (b) (4) is derived from (b) (4) to trace levels of (b) (4) under certain conditions (temperature and humidity). Provide information on the source of (b) (4) and the control of (b) (4) in drug product.
6. Proposed acceptance limit for degradation product (b) (4) as NMT (b) (4) % seems much higher than that in all batch data, including the level ((b) (4) %) under accelerated conditions, either tighten or provide justification for the proposed level. Also express the acceptance limit to the hundredths.
7. Since Palbociclib capsules are for US market, please use the following compendia storage condition for the proposed drug products: Stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

8. The proposed [REDACTED] (b) (4)

[REDACTED]

If you have any questions, call Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.

Sincerely, **Ali H. Al-Hakim -S**
Digitally signed by Ali H. Al-Hakim -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300093815, cn=Ali H. Al-Hakim -S
Date: 2014.11.10 17:08:52 -05'00'

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Charlab Orbach, Rosane](#)
Subject: Time Sensitive NDA 207103 Ibrance - Clin Pharm/Genomics IR sent 11-7-14
Date: Friday, November 07, 2014 1:52:00 PM
Importance: High

Ashok,

Based on published articles assessing CCND1 amplification by FISH, the cutoff selected to define the presence of CCND1 amplification in the A5481003 (PALOMA-1) study appears to be low. Please clarify why the CCND1/CEP11 ratio ≥ 1.5 was selected to define CCND1 amplification positivity. Also, please clarify whether you assessed if the tumors with loss of CDKN2A/p16INK4A gene (CDKN2A/CEP9 ratio < 0.8) showed p16 homozygous or heterozygous deletion.

Please respond to this email **no later than 10 am November 12, 2014.**

Note: please remember to follow up all Information Requests with an official submission to the NDA.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/07/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Amiri Kordestani, Laleh \(FDA\)](#)
Subject: Time Sensitive NDA 207103 Ibrance - Clin IR sent 11-6-14
Date: Thursday, November 06, 2014 5:12:00 PM
Importance: High

Ashok,

We have noted an increase in the rate of pulmonary embolism in the Palbociclib arm of the PALOMA-1 study.

- Please provide the summary of all cases that have developed arterial and venous thromboembolic events in all of the Pfizer- sponsored and investigator initiated research studies with palbociclib.
- Please provide a review of what the possible mechanism for this toxicity is.

We request your response **no later than 3 pm on November 11, 2014.**

Please confirm receipt fo this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/06/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Beaver, Julia](#)
Subject: *TIME SENSITIVE* NDA 207103 Ibrance - Clinical IR sent 11-5-14
Date: Wednesday, November 05, 2014 4:00:00 PM
Importance: High

Ashok,

Please provide the number of patients screened for each Part of the Phase 2 Trial as well as the reasons (with numbers) for screen failure (or direct us to where this information is located in the EDR).

We respectfully request your response to this IR **no later than 3 pm on Friday, November 7, 2014.**

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/05/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Subject: NDA 207103 Ibrance - Response to SAP Amendment
Date: Tuesday, November 04, 2014 4:24:00 PM

Ashok,

Below is the Agency's response regarding your September 23, 2014, response to FDA request for information regarding the magnitude of effect in the PALOMA 2 trial.

The Agency agrees with the proposed amendment to the SAP and would like to meet with Pfizer when the results of the interim PFS analysis are available prior to stopping the study. Please let us know what your plans are for demonstrating efficacy in the proposed prescribed population (fed condition with no PPI) at the time of the interim analysis.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/04/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Subject: **TIME SENSITIVE** NDA 207103 Palbociclib - Clinical IR sent 10-30-14
Date: Thursday, October 30, 2014 3:05:00 PM
Importance: High

Ashok,

Please provide narratives regarding the radiation therapy for the 10 patients receiving “some” radiation (according to FRAD.xpt dataset) on study. Specifically provide details regarding dates of therapy and sites radiated.

Please query the sites for the 57 patients for whom there is no concomitant radiation information due to these patients still being on study and not having the CRF page filled out (what we understood from your 9/9/14 IR response). We would like to know if these patients received radiation or not. For any patients who received radiation while on study please provide a narrative including dates of therapy, sites of therapy and if patient was receiving study treatment or in follow-up.

We respectfully request your response to this Clinical IR **by 3:00 pm Wednesday, November 5, 2014.**

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
10/31/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Cortazar, Patricia](#); [Beaver, Julia](#)
Subject: *TIME SENSITIVE* NDA 207103 Palbociclib - Addtl Clinical IR sent 10-29-14
Date: Wednesday, October 29, 2014 4:19:00 PM
Importance: High

Ashok, below is an additional Clinical Information Request (IR) which we are requesting your response to **by 4 pm on Friday, October 31, 2014.**

10823007: Did the BICR review the CT scan from 12/21/11 and comment on new bone lesions (lumbar vertebral and pelvis)?

10823009: According to CRF this patient had one non-target lesion (a humerus bone lesion) which was followed by only X-ray. It does not appear from the CRF that any CT scan was performed at any time during the study including at screening- is this accurate? Is this why the BICR censored the patient for no disease at baseline? This patient should have been censored at baseline if no appropriate imaging studies were performed.

10823017: According to the narrative and CRF, progression was noted on 9/13/12 CT scan, however in the dataset the date is listed as 9/14/12 according to BICR. Can you confirm this is an error?

10833001: Please clarify why BICR did not think the mediastinal lymph nodes and axillary lymph node were not considered disease at baseline. Were these lesions biopsied? Was an adjudicator involved to clarify if the imaging appeared not to represent disease? Please clarify if this patient did or did not have metastatic disease at baseline.

10833003: According to the narrative BICR thought the patient progressed on 11/30/11 however in the dataset it is recorded that the progression was on 12/15/11. Please explain, is this an error?

10833004: According to the narrative there was a CT scan on 5/29/12 showing a new liver lesion as assessed by BICR. However also according to the narrative it states the patient did not allow for further imaging to identify progressive disease and so was censored as global deterioration of health by the investigator. This patient should have been marked as progression event according to the narrative. Please explain the discrepancy.

10833005: Why was the patient not willing to continue treatment? Why is the censor date different for the Investigator and BICR (the patient withdrew consent on 1/2/2013 with the last assessment prior on 12/29/12 yet the BICR censor date is 12/18/2012 and the investigator censor date is 12/19/2012)?

10833006: Did the BICR look at the CT scan from 4/17/12?

10913003: Did the BICR review the brain MRI from 9/23/13?

10923004: Did the BICR review the hip xray from 12/11/12?

10933007: Did the BICR review the CT scan from 9/25/12 and comment on the liver lesion?

11023013: Did the BICR review the CT scan from 2/21/13 and comment on paratracheal lymph nodes?

11183019: Did the investigator comment on a new pancreatic lesion on 7/25/2012 as identified by the BICR?

11203016: Did the BICR review the scan from 7/23/13 demonstrating impending cord compression? Why was the date of censoring 6/25/2013 by BICR a month ahead of the last assessment?

11233001: Did the BICR review the scan from 11/1/11?

11413001: BICR thought progression almost one year earlier than the investigator by detection of new bone lesions and a rib fracture. Did investigator note this fracture?

11413001: BICR thought progression almost one year earlier than the investigator by new bone lesions. Did the investigator note this new bone lesion?

11433004: Did the BICR review the scan from 8/23/12?

11433005: Did the BICR review the scan from 9/13/2012 (which showed 66% increase in liver lesion according to investigator)?

11453002: Please clarify how pleural effusion was deemed progression if cytology was not performed and according to BICR the patient had baseline pleural cavity involvement.

11653001: Did the BICR review the scan from 3/15/2012?

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
10/29/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Ashok.Didolkar@pfizer.com)
Bcc: [Cortazar, Patricia](#); [Beaver, Julia](#)
Subject: *TIME SENSITIVE* NDA 207103 Palbociclib - Clinical IR
Date: Wednesday, October 29, 2014 9:43:00 AM
Importance: High

Ashok,

Below are the Clinical Information Requests regarding NDA 207103 Palbociclib.

We request your emailed response **no later than 4 pm on Friday, October 31, 2014.**

Please follow up with an official submission to the NDA.

The following questions relate to specific patients and imaging or BICR review. The patient ID(s) will be given first followed by the questions.

- 1. 10012005, 10013010, 10262002, 10332005, 10333002, 10522001, 10793003, 10523005, 11023002, 11023003, 11023017:** Per protocol bone scans were required at baseline and lesions were to be followed and bone scans were to be repeated at 12-week intervals. According to the CRFs these patients with bone only disease did not have baseline or follow-up bone scans. Why were these not reported as protocol violations? Disease progression in bone cannot be assessed accurately without appropriate baseline and follow-up bone scans.
- 2. 10202002:** Per protocol bone scans were required at baseline. According to the CRFs this patients with bone only disease did not have baseline bone scans. Why was this not reported as a protocol violation? Disease progression in bone cannot be assessed accurately without appropriate baseline bone scans.
- 3. 10012002:** Why are the censoring dates different for the investigator (8/26/10) and the BICR (7/23/10)?
- 4. 10202001:** How many BICR reviewers reviewed the scans. Did all reviewers report bone scan from 6/2/10 as “probable flair”?
- 5. 10202002:** Did BICR review the bone scan on 4/24/12? Why was the progression date on 4/23/12 when the scan showing progression according to the investigator was on 4/24/12?
- 6. 10332003:** Did BICR review the CT scan from 5/31/11 that was retrospectively called a progression by Investigator? Why was the patient censored and not called Progression Event by investigator?
- 7. 10332007:** It is not clear from the narrative or the ONN dataset why the new bone

lesion and new pathologic fracture were called by the BICR. Was it because prior imaging from that area was not reviewed? What was the adjudicator report?

8. 10332008: Please clarify if the pleural effusion on 1/3/2012 met the criteria for RECIST in order to call it progressive disease. The narrative and ONN dataset narrative does not answer this. Also was the patient receiving thoracenteses?

9. 10332010: Did BICR examine Brain MRIs from Feb 2011 to September 2011? In the ONN dataset the report from the MRI on 9/20/11 does not mention new multiple brain lesions but the narrative states this was the case, please clarify?

10. 10462001: The ONN dataset and Narrative do not match. One states the investigator did not think the liver lesions met criteria for progression and the other states progression but this is not PD by RECIST criteria. Please clarify. It appears the patient progressed on 6/3/11?

11. 10472001: The date of the progression CT was 11/7/13. Why is the BICR event date 11/8/13?

12. 10472002: BICR identified new supraclav node on 11/30/2010 CT scan confirming progression. Why was this not called progression by investigator?

13. 10482001: Why are the censor dates for BICR and investigator different?

14. 10513002: Why did investigator not call the two new bone lesions on 4/20/12 progressive disease?

15. 10542002: What was the assessment of the adjudicator as the investigator and BICR disagreed regarding progressive disease on CT scan from 5/5/10.

16. 10553003: Please clarify if the investigator saw the scans demonstrating progression by BICR and why they felt the increase in liver disease was not indicative of progression?

17. 10563001: Why was this patient deemed a progression event and not censored for multiple myeloma? The patient was known to have bone metastasis in the pelvis so why was she deemed progression with the finding of breast cancer in a bone marrow biopsy? As patient was diagnosed with multiple myeloma she should have been censored at the assessment date prior.

18. 10563007: please send a narrative for this patient to clarify why the dates for censoring of investigator and BICR are different. And clarify why the patient was censored by the investigator.

19. 10813006: Why did the investigator not see progressive disease as seen by

progression in the lung and a new chest lesion on the 5/15/12 CT scan?

20. 10813010: Did an adjudicator look at the scan from 9/27/2013 as this was deemed progression by Investigator but not BICR?

21. 10823004: Did an adjudicator look at the scan from 9/3/2013 as this was deemed progression by BICR but not Investigator?

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
10/29/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Ashok.Didolkar@pfizer.com)
Bcc: [Cortazar, Patricia](#); [Beaver, Julia](#)
Subject: *URGENT* NDA 207103 Palbociclib - Clinical IR
Date: Wednesday, October 29, 2014 9:38:00 AM
Importance: High

Ashok,

Below is a Clinical Information Request regarding NDA 207103 Palbociclib.

We request your emailed response **no later than 4 pm on Wednesday, October 29, 2014.**
As always, follow up with an official submission to the NDA.

In dataset ptevnt.xpt in the ADRESULT column what does ADJ_ACCEPT, ACCEPT and blank mean? Does this mean the adjudicator agrees with the BICR reading? If not please explain what adjudication was performed and for what cases?

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
10/29/2014

From: Tilley, Amy
To: "Ashok.Didolkar@pfizer.com"
Bcc: [Cortazar, Patricia](#); [Beaver, Julia](#); [Amiri Kordestani, Laleh \(FDA\)](#)
Subject: **TIME SENSITIVE** NDA 207103 Palbociclib - Clinical Information Request
Date: Monday, October 27, 2014 12:17:00 PM
Importance: High

Ashok,

Below are the Clinical Information Requests regarding NDA 207103 Palbociclib.

We request your response **no later than 4 pm on Friday, October 31, 2014.**

1. With regard to the cut off for the FISH testing of CCND1. In the CSR (page 55 and other locations) it states the cut off of ≥ 1.5 for CCND1 positivity but in the SAP (page 7) it has > 1.5 as the cut off. Which cut off was used \geq or $>$?
2. The following questions relate to specific patients and imaging or BICR review. The patient ID(s) will be given first followed by the questions.
 - a. **10012002, 10012004, 10062001, 10113001, 10162001:** Per protocol bone scans were required at baseline and lesions were to be followed and bone scans were to be repeated at 12-week intervals. According to the CRFs these patients with bone only disease did not have baseline or follow-up bone scans. Why were these not reported as protocol violations? Disease progression in bone cannot be assessed accurately without appropriate baseline and follow-up bone scans.
 - b. **10062004, 10113006:** Per protocol bone scans were required at baseline. According to the CRFs these patients with bone only disease did not have baseline bone scans. Why were these not reported as protocol violations? Disease progression in bone cannot be assessed accurately without appropriate baseline bone scans.
 - c. **10022001:** Did the BICR review the bone scan from 4/5/2010?
 - d. **10062001:** According to the CRF, the patient was terminated from the study secondary to MD decision and "Other" is listed in the reason for censoring. What was the specific reason for censoring for this patient?
 - e. **10062002:** Did the BICR review the Bone Scan from 9/6/2011 and PET from 9/22/2011?
 - f. **10062004:** Did the BICR review the Bone Scan from 2/23/11?
 - g. **10082001:** Did the BICR review the Bone Scan from 4/4/11?

- h. 10082006:** Clarify why the BICR stop date was 4/5/11 since progressive disease was seen by BICR on 3/31/11 according to narrative.
- i. 10083005:** Did BICR review the Bone Scan from 1/16/12?
- j. 10112001:** Did BICR review the MRI from 9/14/10?
- k. 10112003:** Did BICR identify a new right axillary node on CT scan from 8/28/10?
- l. 10112008:** Did BICR review the MRI from 9/9/13 and why did BICR censor date occur on 7/15/13 (two months before INV progression event as assessed by MRI)?
- m. 10113006:** Did BICR review the bone scan from 4/15/13?
- n. 10163004:** Did BICR review the bone scan from 11/28/13? If progression was noted by Investigator on 11/28/13 why was progression event date listed as 11/18/13?
- o. 10192001:** Did BICR assess CT scan from 8/22/12?
- p. 10193004:** According to the narrative, target lesion in the breast was removed by bilateral mastectomy. When was the date of surgery? Why was this patient not included in the list of patients undergoing surgery on study (Page 130 of CSR)? Are there additional patients not listed in the CSR who had surgery on study? Progressive disease cannot be assessed accurately if a metastatic site is removed.

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
10/27/2014



NDA 207103

**METHODS VALIDATION
MATERIALS RECEIVED**

Pfizer Inc.
Attention: Ashok K. Didolkar, Ph.D.
Director Worldwide Safety & Regulatory- Oncology Regulatory
235 East 42nd Street
Mail Stop 219/09/S10
New York, NY 10017
E-mail: ashok.didolkar@pfizer.com

Dear Dr. Didolkar:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ibrance (Palbociclib Capsule 70, 100 and 125 mg to our September 17, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on September 24, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
10/20/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Ashok.Didolkar@pfizer.com); Caleb.Briggs@fda.hhs.gov
Bcc: [Briggs, Caleb](#)
Subject: NDA 207103 Palbociclib - Tentative ODAC Dates and Mid-Cycle Info
Date: Wednesday, October 15, 2014 3:42:00 PM

Ashok,

This email serves as a follow up to our telephone discussion earlier today regarding possible ODAC Dates and Mid-Cycle information.

The actual ODAC date has not yet been determined. However, it could potentially be on either February 11th or 12th, 2015.

You can expect a formal letter from my colleague Caleb Briggs which will include preparation timelines, later this month. Caleb will be in touch with you regarding further details as our preparations continue and he will be your primary contact for ODAC meeting-related questions.

Regarding feedback after our Mid-Cycle Meeting this is done via the Mid-Cycle Communication for the PDUFA V "Program" Applications. Our Mid-Cycle Communication for the Palbociclib application will be during our Teleconference currently scheduled and confirmed by you to occur on Dec 4th 2014, from 3:00 pm – 4:00 pm, Washington, D.C. time.

The Agenda for the Mid-Cycle Communication Teleconference is as follows:

- Any significant issues identified by the review team to date
- Any new information requests
- Information regarding major safety concerns
- Preliminary review team thinking regarding risk management
- Proposed date(s) for the late-cycle meeting
- Updates regarding plans for the ODAC meeting (if an ODAC meeting is anticipated)
- Other projected milestones dates for the remainder of the review cycle

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
10/15/2014



NDA 207103

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED
PRIORITY REVIEW DESIGNATION**

Pfizer Inc.
Attention: Ashok Didolkar, Ph.D.
Director
235 East 42nd Street
New York, NY 10017

Dear Dr. Didolkar:

Please refer to your New Drug Application (NDA) dated August 13, 2014, received August 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Ibrance[®] (palbociclib) Capsules, 125 mg, 100 mg, and 75 mg.

We also refer to your amendments dated June 30 (2); July 7; August 12, 13 (2), 14 (2), 15, 29; September 9 (2), 12, 15, 16 (2), 18, 19 (2), 23, 24, 25, 26; and October, 3, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is April 13, 2015.

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 February 10, 2015.

In addition, the planned date for our internal mid-cycle review meeting is November 13, 2014. We are currently planning to hold an advisory committee meeting to discuss this application. At this time, we are notifying you that, we have not identified any potential review issues. Please 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](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

1. In the Highlights Section regarding the product title, you must include the route of administration after the dosage form, i.e., Ibrance® (palbociclib) capsules, for oral use.
2. Delete the periods after the numbers for the section or subsection headings throughout the Full Prescribing Information (FPI).
3. Identifying numbers must precede the heading or subheading by at least two square m's (i.e., two squares of the size of the letter "m" in 8 point type).
4. Delete the internal company study titles, (e.g., PALOMA-1).

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by October 31, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (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. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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, contact Amy Tilley, Regulatory Project Manager, at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, M.D.
Acting Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

AMNA IBRAHIM
10/09/2014

From: Tilley, Amy
To: ["Didolkar, Ashok"](mailto:Ashok.Didolkar@pfizer.com)
Subject: RE: NDA 207103 for Ibrance (palbociclib; PD 0332991) Capsules: Submission Sequence 0019
Date: Thursday, October 09, 2014 10:03:00 AM

Ashok,

Just wanted to let you know we will be having an internal discussion regarding the proposed amendment to the statistical analysis plan and that we will inform you of our response as soon as it is ready.

Amy

From: Didolkar, Ashok [mailto:Ashok.Didolkar@pfizer.com]
Sent: Tuesday, October 07, 2014 10:17 AM
To: Tilley, Amy
Subject: NDA 207103 for Ibrance (palbociclib; PD 0332991) Capsules: Submission Sequence 0019

Hi Amy,

This is to follow up on our conversation a few minutes ago.

A teleconference was held on 19 September 2014 between Dr. Pazdur, Dr. Ibrahim and clinical/statistical group at FDA and Dr. Dagher and Dr. Rothenberg of Pfizer. During that discussion Dr Pazdur and other Agency attendees were in general agreement with Pfizer plans regarding A5481008: to revise the analysis plan for the interim, and to keep the final analysis plan for the study as is. Following that discussion Pfizer submitted the general plan in writing on 23 September 2014 to NDA 207103, sequence 0019 with a request to provide the Agency's feedback, if any.

Could you please let us know if the Agency has feedback, if any on Pfizer's plan to update the interim analysis for Study A5481008 (PALOMA-2) or should Pfizer go ahead and submit the details of the proposed final protocol and SAP to the IND / NDA?

Thanks

Ashok

Ashok K. Didolkar, Ph.D.
Director
Worldwide Safety & Regulatory- Oncology Regulatory
Worldwide Research & Development
Pfizer Inc
235 East 42nd Street Mail Stop 219/09/S10
New York, NY 10017
Tel. (212) 733 8574
Fax (646) 441 4319

Cell [REDACTED] (b) (6)

E-mail: ashok.didolkar@pfizer.com

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/s/

AMY R TILLEY
10/09/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok@pfizer.com)
Bcc: [Fourie Zirkelbach, Jeanne](#)
Subject: Time Sensitive - NDA 207103 Ibrance - Clin Pharm IR
Date: Wednesday, October 01, 2014 1:43:00 PM
Importance: High

Ashok,

Please provide the molecular weight of PF-05089326 **as soon as possible or no later than 5 business days**. The clinical pharmacology reviewer was not able to locate this value.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
10/01/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar.Ashok(Ashok.Didolkar@pfizer.com))
Bcc: [Fahnbulleh, Frances](#); [Salaam, Tracy](#)
Subject: NDA 207103 Ibrance - Pharmacovigilance IR
Date: Monday, September 22, 2014 4:21:00 PM
Attachments: [FDA Guidance.E2E.PV.Planning.2005.pdf](#)
[FDA Guidance.Good.PV.Practices.and.PE.Assessment.2005.pdf](#)

Ashok,

FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with **palbociclib** following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please include it in the NDA application in the appropriate module so it can be reviewed accordingly.

We respectfully request your response **no later than October 1, 2014.**

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

44 pages of the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005) have been withheld. They can be found online at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf> and <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf>

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/s/

AMY R TILLEY
09/22/2014



NDA 207103

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Pfizer Inc.
Attention: Ashok K. Didolkar, Ph.D.
Director Worldwide Safety & Regulatory- Oncology Regulatory
235 East 42nd Street
Mail Stop 219/09/S10
New York, NY 10017
E-mail: ashok.didolkar@pfizer.com

Dear Dr. Didolkar:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ibrance (Palbociclib Capsule 70, 100, 125 mg).

We will be performing methods validation studies on Ibrance (Palbociclib Capsule 70, 100, 125 mg), as described in NDA 207103.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

- TM-1855A Particle size by (b) (4)
- TM-1855A assay by liquid chromatography
- TM-1855A organic impurities
- TM-1876A assay (LC)
- TM-1876A degradation products
- TM-1877A dissolution

Samples and Reference Standards

- (b) (4) mg palbociclib reference standard
- (b) (4) g of palbociclib drug substance
- (b) (4) Ibrance (Palbociclib Capsules) 70 mg/capsule
- Ibrance (Palbociclib Capsules) 100 mg/capsule
- Ibrance (Palbociclib Capsules) 125 mg/capsule
- mg of impurity standard (b) (4)
- mg of impurity (b) (4) if available
- mg of impurity if available
- mg of impurity if available
- mg of impurity if available

Equipment

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this e-mail. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or preferably by e-mail (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
09/17/2014

From: Tilley, Amy
To: [Didolkar, Ashok \(Ashok.Didolkar@pfizer.com\)](mailto:Didolkar_Ashok_(Ashok.Didolkar@pfizer.com))
Cc: "Yu-Kite, Michelle"
Bcc: [Cortazar, Patricia](#); [Amiri Kordestani, Laleh \(FDA\)](#); [Beaver, Julia](#)
Subject: Addtl Clarification re NDA 207,103 - Clinical/Biomarker Rapid Response due COB 9-17-14
Date: Tuesday, September 16, 2014 4:33:00 PM
Attachments: [Tables for Protocol Deviations Phase 2 1003 study \(2\).docx](#)
Importance: High

Ashok,

For clarity regarding our initial Clinical IR below, we have attached a document showing examples of the protocol deviation tables and information we are requesting.

We look forward to receiving your response **by COB Sept 17th, 2014.**

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

From: Tilley, Amy
Sent: Monday, September 15, 2014 4:32 PM
To: 'Yu-Kite, Michelle'
Subject: RE: NDA 207,103 - Clinical/Biomarker Rapid Response

Michelle,

Your response is not what we were expecting. We need the information we asked for as we already looked at the listings provided in Module 5.3.5.1. which do not have the detailed information we want, particularly the treatment arm information.

- Table 16.2.2.1.a - Protocol Deviations - Clinically Significant Deviations - Intention to Treat Set
- Table 16.2.2.1.b.p1 - Protocol Deviations - Clinically Significant Deviations - Intention to Treat Set
- Table 16.2.2.1.b.p2 - Protocol Deviations - Clinically Significant Deviations - Intention to Treat Set
- Table 16.2.2.2.a - Summary of Protocol Deviations - Intention to Treat Set
- Table 16.2.2.2.b.p1 - Summary of Protocol Deviations - Intention to Treat Set
- Table 16.2.2.2.b.p2 - Summary of Protocol Deviations - Intention to Treat Set
- Table 16.2.2.3.a - Protocol Deviations Listing - Intention to Treat Set
- Table 16.2.2.3.b.p1 - Protocol Deviations Listing - Intention to Treat Set
- Table 16.2.2.3.b.p2 - Protocol Deviations Listing - Intention to Treat Set

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Monday, September 15, 2014 11:17 AM
To: Tilley, Amy
Subject: NDA 207,103 - Clinical/Biomarker Rapid Response

Dear Amy,

Pertaining to FDA's query received on Friday, 12 September, please find enclosed our response to FDA's clinical request for information. Regarding the protocol deviation tables, we have provided locations in the NDA where the protocol deviations are separated by Phase 2 Part 1 and Phase 2 Part 2 and by Subject ID.

Can we ask FDA for clarification if this is sufficient or if FDA would still like us to provide protocol deviation information for Part 1 and Part 2 combined? If this is requested, may we ask for an extension for the response by COB 17 September?

Thanks,

Michelle Y. Kite, MS, RAC
Worldwide Safety and Regulatory

Office: (858) 526-4025
Mobile: (b) (6)
Fax: (858) 526-4402
Email: Michelle.Y.Kite@Pfizer.com

Summary of Protocol Deviations Phase 2 1003 study

Category of Deviation (any PD as well as any significant PD)	Phase 2 (Ph2P1+Ph2P2) Number (%) of Patients and number of deviations		Ph2P1 Number (%) of Patients number of deviations		Ph2P2 Number (%) of Patients number of deviations	
	Palbociclib +Letrozole	Letrozole	Palbociclib + Letrozole	Letrozole	Palbociclib + Letrozole	Letrozole

Table of subject IDs for each category of deviation

Subject ID	Phase 2 Part 1 or Part2	Treatment Arm	Category of deviation	Date	Significant	Description of Deviation(s)

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/s/

AMY R TILLEY
09/16/2014

From: Tilley, Amy
To: "Yu-Kite, Michelle"
Bcc: Cole, Jessica; Riley, Bryan S
Subject: Revised due date re TIME SENSITIVE NDA Ibrance Palbociclib - Micro IR
Date: Monday, September 15, 2014 5:50:00 PM
Importance: High

Michelle,

As discussed via telephone earlier today, the Micro Review Team would prefer that Pfizer miss our suggested deadline of Sept 25, 2014, and submit a complete answer after our deadline rather than submit a partial written response and then later submit the updated CTD section. Having one submission that contains the response and the associated CTD update simplifies the review process and is more efficient.

The new proposed deadline for your response to the Micro IR is **by COB on Oct 31, 2014.**

As discussed please check with your team regarding this new proposed deadline for your response. However, we reiterate that we must receive your response to the Micro IR in order for us to complete our Midcycle Review of this application.

Regards.

Amy Tilley

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Monday, September 15, 2014 4:21 PM
To: Tilley, Amy
Subject: RE: TIME SENSITIVE NDA Ibrance Palbociclib - Micro IR
Importance: High

Hi Amy,

In order to meet response timelines and allow efficient updating of CTD sections, Pfizer GCMC is proposing to initially include only responses to the CMC queries, and not include updated CTD sections with the initial response. If the Agency agrees with our responses, we will provide updated CTD sections at a later date, prior to approval.

If acceptable to the Agency, we propose to include the updated 2.3 QOS and Module 3 sections once CMC review is complete and prior to approval. For example, our response to this first set of CMC queries, if accepted by the Agency, will require updating of our drug product specification (3.2.P.5.1) and justification of specification (3.2.P.5.6).

We propose to include the following statement in our response to Q1 "If the Agency agrees with this approach, the Specification (3.2.P.5.1) and Justification for Specification (3.2.P.5.6) will be updated and provided prior to Approval." Does the Agency agree with this approach?

Thanks,

Michelle

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Thursday, September 11, 2014 8:38 AM
To: Yu-Kite, Michelle
Subject: TIME SENSITIVE NDA Ibrance Palbociclib - Micro IR
Importance: High

Michelle,

The Microbiology Review Team has the following Information Request (IR) and requests your emailed response **by September 25, 2014.**

Also, follow up with an official response to the NDA.

1. We refer to footnote 2 in the product specification that indicates microbial limits will comply when tested. Define the proposed testing schedule for microbiological enumeration of the final drug product.

Please note that Skip-lot testing for drug products is not allowed by regulation (21 CFR 211.165 (a) and (b).) If a drug product release specification includes tests and acceptance criteria for a given attribute, then the test must be performed on every batch. However, microbial limits testing may be omitted from the product release specification provided adequate (b) (4) microbiological controls are established and documented. If you wish to omit the microbial limits specification, more information on your process is needed. Address the following points.

- a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product. For example, a microbial specification for incoming components would provide data to support reduced testing for this (b) (4) manufacturing process.
- b. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
- c. Describe activities taken when microbiological acceptance criteria are not met at control points.

2. Justify the lack of USP<62> testing on stability.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/15/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Bcc: [Cortazar, Patricia](#); [Amiri Kordestani, Laleh \(FDA\)](#); [Beaver, Julia](#)
Subject: RE: NDA 207,103 - Clinical/Biomarker Rapid Response
Date: Monday, September 15, 2014 4:31:00 PM

Michelle,

Your response is not what we were expecting. We need the information we asked for as we already looked at the listings provided in Module 5.3.5.1. which do not have the detailed information we want, particularly the treatment arm information.

- Table 16.2.2.1.a - Protocol Deviations - Clinically Significant Deviations - Intention to Treat Set
- Table 16.2.2.1.b.p1 - Protocol Deviations - Clinically Significant Deviations - Intention to Treat Set
- Table 16.2.2.1.b.p2 - Protocol Deviations - Clinically Significant Deviations - Intention to Treat Set
- Table 16.2.2.2.a - Summary of Protocol Deviations - Intention to Treat Set
- Table 16.2.2.2.b.p1 - Summary of Protocol Deviations - Intention to Treat Set
- Table 16.2.2.2.b.p2 - Summary of Protocol Deviations - Intention to Treat Set
- Table 16.2.2.3.a - Protocol Deviations Listing - Intention to Treat Set
- Table 16.2.2.3.b.p1 - Protocol Deviations Listing - Intention to Treat Set
- Table 16.2.2.3.b.p2 - Protocol Deviations Listing - Intention to Treat Set

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Monday, September 15, 2014 11:17 AM
To: Tilley, Amy
Subject: NDA 207,103 - Clinical/Biomarker Rapid Response

Dear Amy,

Pertaining to FDA's query received on Friday, 12 September, please find enclosed our response to FDA's clinical request for information. Regarding the protocol deviation tables, we have provided locations in the NDA where the protocol deviations are separated by Phase 2 Part 1 and Phase 2 Part 2 and by Subject ID.

Can we ask FDA for clarification if this is sufficient or if FDA would still like us to provide protocol deviation information for Part 1 and Part 2 combined? If this is requested, may we ask for an extension for the response by COB 17 September?

- 1. Please provide a table of protocol deviations for the Phase 2 1003 study divided by treatment arm for the combined Part 1 and Part 2 portions as well as the separate parts by treatment arm. Also provide a separate table with subject ID for each of the categories by treatment arm. Or provide where this is located in the submission.**
- 2. Please provide the number of patients you needed to screen in order to accrue the biomarker positive patients for Part 2 of the study. Or provide where this is located in the submission.**

Please submit by email response by noon Monday, September 15, 2014. And follow with official submission.

Response:

1. Provided in Module 5.3.5.1. A5481003 CSR under Section 16.2.2 Protocol Deviations are tables separated by Phase 1 Part 2 and Phase 2 Part 2 and by subject ID. Note, “a” is Phase 1, “b.p1” is Phase 2 Part 1, and “b.p2” is Phase 2 Part 2.

- Table 16.2.2.1.a - Protocol Deviations - Clinically Significant Deviations - Intention to Treat Set
- Table 16.2.2.1.b.p1 - Protocol Deviations - Clinically Significant Deviations - Intention to Treat Set
- Table 16.2.2.1.b.p2 - Protocol Deviations - Clinically Significant Deviations - Intention to Treat Set
- Table 16.2.2.2.a - Summary of Protocol Deviations - Intention to Treat Set
- Table 16.2.2.2.b.p1 - Summary of Protocol Deviations - Intention to Treat Set
- Table 16.2.2.2.b.p2 - Summary of Protocol Deviations - Intention to Treat Set
- Table 16.2.2.3.a - Protocol Deviations Listing - Intention to Treat Set
- Table 16.2.2.3.b.p1 - Protocol Deviations Listing - Intention to Treat Set
- Table 16.2.2.3.b.p2 - Protocol Deviations Listing - Intention to Treat Set

2. In Study 1003, biomarker screen fail data/rate was not captured in the Oracle clinical database, and therefore was not included in the NDA submission. However, for Study 1003, 319 patients were screened for the 99 patients enrolled in Phase 2 Part.

REFERENCES:

[Module 5.3.5.1. CSR 1003 Section 16.2.2](#)

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/s/

AMY R TILLEY
09/15/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Bcc: [Fourie Zirkelbach, Jeanne](#); [Liu, Qi \(CDER\)](#); [Cortazar, Patricia](#); [Amiri Kordestani, Laleh \(FDA\)](#); [Beaver, Julia](#)
Subject: TIME SENSITIVE - NDA 207103 Palbociclib - Clin Pharm IR
Date: Monday, September 15, 2014 10:30:00 AM
Importance: High

Michelle,

Below is the Clinical Pharmacology IR for palbociclib which we request your response **within 30 business days**.

NDA207103-Palbociclib Information Request:

1. Provide dose recommendation for palbociclib in patients concomitantly taking a moderate CYP3A inducer.

Based on the information provided in your NDA submission, it appears that you can address above issue using a physiologically-based pharmacokinetic (PBPK) modeling approach. If you decide to use PBPK, you should submit PBPK simulation report for review. The report should include:

Purpose

Methods

- A table summarizing model input parameters, including parameter values (mean and/or variability), source of the parameter values and assumptions being made.
- Modification of the default values of the system (e.g., healthy volunteer or other virtual populations) and drug (e.g., inhibitor/inducer) models and justification, if specialized PBPK software is used.
- Development and qualification of perpetrator models.

Results

- Capability of the model in describing observed palbociclib PK in healthy volunteers and patients under different dose levels and dosing regimens
- Verification of palbociclib model with respect to quantitative CYP3A contribution to the elimination of palbociclib using results from rifampin drug-drug interaction study (A5481017), and if available, interim results from ongoing ketoconazole drug-drug interaction trial (A5481016).
- Application of palbociclib model to simulate untested drug-drug interaction scenarios, including the effect of a moderate CYP3A inducer on its PK. You

can use efavirenz as a moderate CYP3A inducer for this simulation according to the following design:

Oral administration of efavirenz 400 mg once daily for 12 days, oral administration of a single oral dose of palbociclib (125 mg) under fasted condition on day 8.

Conclusions

Besides a study report, please include relevant PBPK model files in your submission. Please submit this information **in 30 business days**. The adequacy of PBPK model to support a dose recommendation for this drug drug interaction scenario, not tested clinically, will be a review issue.

2. Justify the capability of the simulated and observed effects of CYP3A modulators in extrapolating situations when patients are taking final phase 3 formulation under fed condition. You can use PBPK simulations to support your rationale. Please submit this information in 30 business days.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/15/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Subject: RE: Palbociclib Updates
Date: Friday, September 12, 2014 3:32:00 PM

Michelle, we are in receipt of the PREA Waiver submitted in the NDA. However, it too needs to be processed/reviewed by our PeRC committee again (by law). We will let you know the final conclusion of the waiver at a later date.

I forwarded your previous email regarding your plans to submit a written response for the confirmatory study 1008 (PALOMA-2) both to Dr Pazdur and the review team. However I have not heard anything further.

Today I forwarded your email below to the clinical and clin pharm review teams as well.

If I should receive any information from the team I will forward it to you expeditiously.

Have a nice weekend.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Friday, September 12, 2014 3:15 PM
To: Tilley, Amy
Subject: Palbociclib Updates

Thank you Amy.

Just wanted to note that the request for PREA waiver was submitted within the NDA 207103 under Wave 1 on 30 June 2014 in Module 1. Please let me know if there are any questions about that request.

Also, just a heads up that as agreed in our rolling review plan, the 1038 CSR (clin pharm study) and updated proposed USPI will be submitted today officially to the NDA.

Were you able to forward my previous email about our plans to submit a written response for the confirmatory study 1008 (PALOMA-2) to Dr Pazdur/review team? Did they have any comments to us sending that in the next 2 weeks?

Thanks and have a great weekend,

Michelle

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Friday, September 12, 2014 11:34 AM
To: Yu-Kite, Michelle
Subject: IND 69324 Palbociclib - iPSP Agreed Initial letter

Michelle,

Below is the iPSP Agreed Initial letter regarding IND 69324 Palbociclib.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

📞 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/12/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Bcc: [Cortazar, Patricia](#); [Amiri Kordestani, Laleh \(FDA\)](#); [Beaver, Julia](#)
Subject: TIME SENSITIVE - NDA 207103 Ibrance - Clinical IR - prot deviations
Date: Friday, September 12, 2014 3:16:00 PM
Importance: High

Michelle,

Below is the Clinical IR regarding protocol deviations which we request your emailed response to by **COB Monday, September 15, 2014**. Please follow up with an official submission to the NDA.

Please provide a table of protocol deviations for the Phase 2 1003 study divided by treatment arm for the combined Part 1 and Part 2 portions as well as the separate parts by treatment arm. Also provide a separate table with subject ID for each of the categories by treatment arm. Or provide where this is located in the submission.

Please provide the number of patients you needed to screen in order to accrue the biomarker positive patients for Part 2 of the study. Or provide where this is located in the submission.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/12/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207103

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Pfizer Inc.
10646 Science Center Drive
San Diego, CA 92121

ATTENTION: Michelle Y. Kite
Associate Director
Worldwide Safety and Regulatory

Dear Ms. Kite:

Please refer to your New Drug Application (NDA) dated and received August 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palbociclib Capsules, 75 mg, 100 mg, and 125 mg.

We also refer to your correspondence, dated and received July 7, 2014, requesting review of your proposed proprietary name, Ibrance.

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

If any of the proposed product characteristics as stated in your July 7, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 Amy Tilley, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
09/11/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Bcc: [Cole, Jessica](#); [Riley, Bryan S](#)
Subject: TIME SENSITIVE NDA Ibrance Palbociclib - Micro IR
Date: Thursday, September 11, 2014 11:38:00 AM
Importance: High

Michelle,

The Microbiology Review Team has the following Information Request (IR) and requests your emailed response **by September 25, 2014.**

Also, follow up with an official response to the NDA.

1. We refer to footnote 2 in the product specification that indicates microbial limits will comply

when tested. Define the proposed testing schedule for microbiological enumeration of the final

drug product.

Please note that Skip-lot testing for drug products is not allowed by regulation (21 CFR 211.165 (a) and (b).) If a drug product release specification includes tests and acceptance criteria for a given attribute, then the test must be performed on every batch. However, microbial limits testing may be omitted from the product release specification provided adequate (b) (4) microbiological controls are established and documented. If you wish to omit the microbial limits specification, more information on your process is needed.

Address the following points.

a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product. For example, a microbial specification for incoming components would provide data to support reduced testing for this (b) (4) manufacturing process.

b. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your

drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.

c. Describe activities taken when microbiological acceptance criteria are not met at control points.

2. Justify the lack of USP<62> testing on stability.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/11/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Bcc: [Liu, Qi \(CDER\)](#); [Fourie Zirkelbach, Jeanne](#)
Subject: TIME SENSITIVE NDA 207103 Ibrance - Clin Pharm IR
Date: Wednesday, September 10, 2014 5:19:00 PM
Importance: High

Michelle,

Please submit both via email and as an official submission to the NDA **within 5 business days** the study design and status of your renal impairment (A5481014) and hepatic impairment (A5481013) trials.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/10/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Bcc: [Kozeli, Devi](#)
Subject: NDA 207103 Ibrance - QT IR - Submit ECG Waveforms in PDF format
Date: Tuesday, September 02, 2014 9:56:00 AM

Michelle,

The QT/IRT folks would appreciate it if you would officially submit your paper ECGs in PDF format.

Thanks.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Monday, August 25, 2014 5:24 PM
To: Tilley, Amy
Subject: RE: Addtl URGENT Time Sensitive re NDA 207103 Ibrance - QT IR - Need ECG Waveforms submitted to ECG Warehouse

Hi Amy,

Study report PMAR-287-PK-ECG included data from studies A5481001, A5481002 and 1003. At the start of each of these three studies, the ECG data were not intended to support an NDA. After further investigation about the requirements to submit to the ECG warehouse, it would be challenging to obtain and submit for these three studies because the ECG data was not collected using a central ECG reader. Therefore, it would be challenging (and may take extended time) to go to every site for the three studies, collect the ECG data, and upload to the appropriate FDA XML format of the ECG waveform.

However, the ongoing, confirmatory Phase 3 Study A5481008 (PALOMA-2) utilizes the central ECG reader and we will ensure that the ECG waveforms for Study 1008 will be submitted to the ECG warehouse upon completion of the Study 1008.

We are available to set up a teleconference with the FDA reviewer(s) to discuss this topic further to ensure we provide the needed information. I can help set up a teleconference if needed.

Thanks,

Michelle

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Monday, August 25, 2014 1:35 PM
To: Yu-Kite, Michelle
Subject: RE: Addtl URGENT Time Sensitive re NDA 207103 Ibrance - QT IR - Need ECG Waveforms submitted to ECG Warehouse

Michelle,

Our request is for the ECGs related to three studies (A5481001, A5481003 and A5481008) that were used to compile the study report PMAR-287-PK-ECG.

Regards.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]

Sent: Monday, August 25, 2014 12:53 PM

To: Tilley, Amy

Subject: RE: Addtl URGENT Time Sensitive re NDA 207103 Ibrance - QT IR - Need ECG Waveforms submitted to ECG Warehouse

Hi Amy,

Can we clarify with FDA whether the request is only for TQT studies? Currently, the only TQT study is our confirmatory Study 1008 (PALOMA-2). We will ensure that the ECG waveforms for Study 1008 will be submitted to the ECG warehouse upon completion of the Study 1008. We did not collect ECG data via central ECG reader for Study 1003 (PALOMA-1) so it would be challenging to obtain and submit as these may not have been produced in the proper format for ECG warehouse.

Thanks,

Michelle

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]

Sent: Monday, August 25, 2014 9:29 AM

To: Yu-Kite, Michelle

Subject: Addtl URGENT Time Sensitive re NDA 207103 Ibrance - QT IR - Need ECG Waveforms submitted to ECG Warehouse

Michelle,

In your attached email cover letter you stated that you have not yet submitted the related ECG waveforms to the ECG warehouse. In order to speed up our review process we will need them to be submitted to the ECG Warehouse asap.

Please let me know when the ECG Waveforms have been submitted to the ECG Warehouse.

Thanks.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]

Sent: Friday, August 15, 2014 4:34 PM

To: Tilley, Amy

Cc: Wheeler, Charlene; Cross Jr, Frank H; Venugopal, Rajesh

Subject: RE: URGENT Time Sensitive re NDA 207103 Ibrance - QT Info Request

Dear Amy,

Please find enclosed our responses. We will also formally submit to the NDA later today.

Thanks,

Michelle Y. Kite, MS, RAC
Worldwide Safety and Regulatory

Office: (858) 526-4025
Mobile: (b) (6)
Fax: (858) 526-4402
Email: Michelle.Y.Kite@Pfizer.com

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Wednesday, August 13, 2014 1:33 PM
To: Yu-Kite, Michelle
Cc: Wheeler, Charlene; Cross Jr, Frank H; Venugopal, Rajesh
Subject: URGENT Time Sensitive re NDA 207103 Ibrance - QT Info Request

Michelle,

****When responding to this email please reply to all as I will be on leave starting tomorrow.****

Please complete the attached Clin Pharm and Cardiac Safety Table and submit it to us ASAP. Also, please confirm whether or not you have submitted the related ECG waveform to the ECG warehouse. We cannot locate them.

Your prompt response to this email is greatly appreciated.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

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/s/

AMY R TILLEY
09/02/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Bcc: [Cortazar, Patricia](#); [Amiri Kordestani, Laleh \(FDA\)](#)
Subject: URGENT Time Sensitive - NDA 207103 Ibrance - Clin IR - Raw Datasets
Date: Wednesday, September 03, 2014 4:50:00 PM
Importance: High

Michelle,

The Clinical Review Team has the following questions and are requesting your response **today or asap.**

- 1) Did you submit raw datasets?**
- 2) Where is the raw dataset for CRF Page 14 Baseline disease sites? We cannot find the variables BLDSSITF.**
- 3) We note that the annotated CRF does not state at the top of the page the name of the dataset where the variables are. Please explain.**

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/03/2014

From: Tilley, Amy
To: "Yu-Kite, Michelle"
Bcc: Tang, Shenghui; Bloomquist, Erik
Subject: Request to discuss primary eff program during Orientation Meeting Sept 5 Palbociclib NDA 207103
Date: Tuesday, August 26, 2014 11:50:00 AM

Michelle, the Stats Reviewer has requested the following to be discussed during our Sept 5th dataset mtg:

Please walk us through one of your programs, i.e., the primary efficacy program [REDACTED] (b) (4)

Do let me know if this is a possibility.

Amy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Wednesday, August 20, 2014 5:27 PM
To: Tilley, Amy
Subject: Palbociclib Slides due 9-4-14 send to Christine Lincoln re NDA 207103 - Orientation Meeting Sept 5
Importance: High

Hi Amy,

Please find below a list of the Pfizer Attendees for the Sept 5, 2014 orientation meeting at 1:20-2:30pm EDT. We will have a total of 15 in-person and 2 via teleconference only.

Mace L. Rothenberg, MD	Senior Vice President, Clinical Development and Medical Affairs
Erling Donnelly, PhD	Submissions Asset Team Lead
Ramzi Dagher, MD	Head of Regulatory Strategy Oncology
Albert Kraus, PhD	Tumor Strategy Regulatory Lead
Michelle Yu Kite, MS, RAC	US Regulatory Lead
Sophia Randolph, MD, PhD	Global Clinical Lead
Sindy Kim	PALOMA-1 Clinical Lead
Xin Huang, PhD	Statistical Lead
Patrick Schnell, PhD	Safety Risk Lead
Susan Decoteau	Global Regulatory CMC
Yuqiu (John) Jiang, PhD	Translation Oncology Lead
Diane Wang, PhD	Clinical Pharmacology Lead
Aida Sacaan, PhD	Nonclinical Drug Safety Research and Development
Rebecca Hintze	Oncology Programming Lead
Norihiko Oharu	Palbociclib Programming Lead
Leena Das-Young, PharmD	Vice President, Late Phase Strategy, Development, Submission, and Lifecycle Management Group (Teleconference Only)
Eric Kowack, MS, MBA	Asset Team Lead (Teleconference Only)

Here is the teleconference information:

Teleconference [REDACTED] (b) (4) (US);
International [REDACTED] (b) (4);
participant code: [REDACTED] (b) (4) #
chair (Amy only) [REDACTED] (b) (4) #

For the dataset meeting at 2:30-3:30 here are the attendees all of whom will join in-person. In the past, for other programs FDA reviewers provided us with questions relating to the dataset. Please let me know if you think FDA reviewers will provide any questions ahead of the meeting?

Erling Donnelly, PhD	Submissions Asset Team Lead
----------------------	-----------------------------

Albert Kraus, PhD	Tumor Strategy Regulatory Lead
Michelle Yu Kite, MS, RAC	US Regulatory Lead
Sophia Randolph, MD, PhD	Global Clinical Lead
Sindy Kim	PALOMA-1 Clinical Lead
Xin Huang, PhD	Statistical Lead
Rebecca Hintze	Oncology Programming Lead
Norihiko Oharu	Palbociclib Programming Lead

We will have slides to present for both meetings. I will provide the slides to you no later than Sept 4, 4pm EDT.

Thanks,

Michelle Y. Kite, MS, RAC
Worldwide Safety and Regulatory

Office: (858) 526-4025
Mobile: (b) (6)
Fax: (858) 526-4402
Email: Michelle.Y.Kite@Pfizer.com

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/s/

AMY R TILLEY
08/26/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Bcc: [Kozeli, Devi](#); [Cortazar, Patricia](#); [Amiri Kordestani, Laleh \(FDA\)](#)
Subject: RE: Addtl URGENT Time Sensitive re NDA 207103 Ibrance - QT IR - Need ECG Waveforms submitted to ECG Warehouse
Date: Monday, August 25, 2014 4:35:00 PM

Michelle,

Our request is for the ECGs related to three studies (A5481001, A5481003 and A5481008) that were used to compile the study report PMAR-287-PK-ECG.

Regards.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Monday, August 25, 2014 12:53 PM
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Thanks,

Michelle

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Subject: Addtl URGENT Time Sensitive re NDA 207103 Ibrance - QT IR - Need ECG Waveforms submitted to ECG Warehouse

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Amy

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Sent: Friday, August 15, 2014 4:34 PM
To: Tilley, Amy
Cc: Wheeler, Charlene; Cross Jr, Frank H; Venugopal, Rajesh
Subject: RE: URGENT Time Sensitive re NDA 207103 Ibrance - QT Info Request

Dear Amy,

Please find enclosed our responses. We will also formally submit to the NDA later today.

Thanks,

Michelle Y. Kite, MS, RAC
Worldwide Safety and Regulatory

Office: (858) 526-4025
Mobile: (b) (6)
Fax: (858) 526-4402
Email: Michelle.Y.Kite@Pfizer.com

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Wednesday, August 13, 2014 1:33 PM
To: Yu-Kite, Michelle
Cc: Wheeler, Charlene; Cross Jr, Frank H; Venugopal, Rajesh
Subject: URGENT Time Sensitive re NDA 207103 Ibrance - QT Info Request

Michelle,

****When responding to this email please reply to all as I will be on leave starting tomorrow.****

Please complete the attached Clin Pharm and Cardiac Safety Table and submit it to us ASAP. Also, please confirm whether or not you have submitted the related ECG waveform to the ECG warehouse. We cannot locate them.

Your prompt response to this email is greatly appreciated.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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

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/s/

AMY R TILLEY
08/25/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Cc: [Wheeler, Charlene](#); [Cross Jr, Frank H](#); [Venugopal, Rajesh](#)
Bcc: [CDER DCRP OT](#); [Kozeli, Devi](#)
Subject: URGENT Time Sensitive re NDA 207103 Ibrance - QT Info Request
Date: Wednesday, August 13, 2014 4:32:00 PM
Attachments: [Highlights ClinPharm and Cardiac Safety.doc](#)

Michelle,

****When responding to this email please reply to all as I will be on leave starting tomorrow.****

Please complete the attached Clin Pharm and Cardiac Safety Table and submit it to us ASAP. Also, please confirm whether or not you have submitted the related ECG waveform to the ECG warehouse. We cannot locate them.

Your prompt response to this email is greatly appreciated.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C _{max} and AUC
	Multiple Dose	Mean (%CV) C _{max} and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	T _{max}	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	V _d /F or V _d	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC
	Sex	Specify mean changes in C _{max} and AUC
	Race	Specify mean changes in C _{max} and AUC
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C _{max} and AUC
	Food Effects	Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in C _{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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/s/

AMY R TILLEY
08/13/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Cc: [Smith, Patricia S](#)
Bcc: [Iacono-Connor, Lauren](#)
Subject: RE: URGENT NDA 207103 Ibrance - OSI IR/Response needs to be officially submted
Date: Tuesday, August 12, 2014 5:08:00 PM

Michelle,

You must officially submit all the information you provided below to the NDA.

Thanks.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Tuesday, August 12, 2014 4:58 PM
To: Tilley, Amy
Cc: Smith, Patricia S
Subject: RE: URGENT NDA 207103 Ibrance - OSI IR

Hi Amy,

The POC is Patricia Smith (cc-ed here) and her number is +1 [REDACTED] (b) (6)

Thanks,

Michelle

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Tuesday, August 12, 2014 1:50 PM
To: Yu-Kite, Michelle
Subject: RE: URGENT NDA 207103 Ibrance - OSI IR

Do you have a POC name and phone number?

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Tuesday, August 12, 2014 4:49 PM
To: Tilley, Amy
Subject: RE: URGENT NDA 207103 Ibrance - OSI IR

Hi Amy,

Here is the exact address:

445 Eastern Point Rd, Groton CT 06340.

Thanks,

Michelle

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]

Sent: Tuesday, August 12, 2014 1:40 PM
To: Heise, Carrie
Cc: Yu-Kite, Michelle; Robinson, Kelley E
Subject: FW: URGENT NDA 207103 Ibrance - OSI IR
Importance: High

Carrie, you are receiving this email as I received an Automatic Reply after sending the email below to Kelley Robinson.

The OSI Team needs a response to our request below asap.

Kindly confirm receipt of the emailed Information Request below.

Thanks.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

From: Tilley, Amy
Sent: Tuesday, August 12, 2014 4:34 PM
To: 'kelley.e.robinson@pfizer.com'; 'Yu-Kite, Michelle'
Subject: URGENT NDA 207103 Ibrance - OSI IR
Importance: High

Kelley and/or Michelle,

Please confirm the geographic location of the TMF for the pivotal study. FDA plans to conduct a sponsor inspection of Pfizer for the oversight, conduct and control of the pivotal study. We expect all related and supportive study documents to be made available at a single location.

We request your response to this IR **as soon as possible**.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
08/13/2014

Tilley, Amy

From: Tilley, Amy
Sent: Monday, August 11, 2014 4:16 PM
To: 'Yu-Kite, Michelle'
Cc: Cross Jr, Frank H
Subject: URGENT-Time Sensitive re NDA 207103 Ibrance - Clin/Stat IR

Importance: High

Michelle,

Shown below is a snapshot of a list taken from the file *list-of-programs.pdf*. For this table in this file, please include an additional column that lists the specific datasets used to generate each individual table, e.g. Table 14.2.1.1.b. Please respond back by email **no later than August 15, 2014**, and follow up with an official submission to the NDA.

Please respond to all when sending your emailed response as I will be out of the office, however Frank Cross will be covering for me.

(b) (4)



Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177|Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
08/11/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Bcc: [Thompson, Susan \(CDER\)](#); [Iacono-Connor, Lauren](#); [Cortazar, Patricia](#); [Amiri Kordestani, Laleh \(FDA\)](#)
Subject: NDA 207103 Ibrance - OSI IR
Date: Friday, August 08, 2014 2:33:00 PM

Michelle,

Please provide the address and point of contact, name and phone numbers and email, for the CRO who performed the BICR for the PFS endpoint for the pivotal study. In addition, please provide the PFS data listing for each subject organized by site, in pdf format. Also, please provide a copy of the BICR Charter with all amendments. If these have already been submitted to the application please provide the exact location.

If the above requested information was not already submitted to the application, please send it both via email and as an official submission to this NDA.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
08/08/2014

From: Tilley, Amy
To: "[Yu-Kite, Michelle](#)"
Bcc: [Cortazar, Patricia](#); [Amiri Kordestani, Laleh \(FDA\)](#); [Liu, Qi \(CDER\)](#); [Fourie Zirkelbach, Jeanne](#); [Al Hakim, Ali H](#); [Sarker, Haripada](#); [Crich, Joyce](#); [Chen, Xiao H](#); [Sridhara, Rajeshwari](#); [Tang, Shenghui](#); [Bloomquist, Erik](#); [Palmbly, Todd](#); [Chen, Wei](#)
Subject: Change in Time of AOM re NDA 207103 Palbociclib
Date: Wednesday, August 06, 2014 9:46:00 AM

Michelle,

Just wanted to let you know due to a scheduling conflict the Application Orientation Meeting (AOM) for Ibrance will not begin until ~ 1:20 pm on Sept 5th. Since this is an Office Meeting I have no control over the scheduling/topics discussed during this meeting.

Regards.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Thursday, June 26, 2014 2:10 PM
To: Tilley, Amy
Subject: RE: IND 69324 / NDA 207103 Palbociclib - 16 Pfizer Attendees for AOM

Hi Amy,

We would like to confirm the Sept 5 date for the two orientation meetings at 1pm and 2:30pm EDT. I am estimating about 16 Pfizer attendees for the first meeting and about 9 for the dataset meeting.

Thanks,

Michelle

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Wednesday, June 25, 2014 3:02 PM
To: Yu-Kite, Michelle
Subject: RE: IND 69324 / NDA 207103 Palbociclib - FDA Feedback re Rolling Submission

Orientation Mtg to begin around 1 pm.

Datasets Mtg to begin around 2:30 pm

Sorry I cannot be more specific but the Application Orientation is being held during our Office meeting and the start time may not be until 1:15 ish as we have a brief internal discussion prior to allowing sponsors in to the room.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Wednesday, June 25, 2014 5:59 PM
To: Tilley, Amy
Subject: RE: IND 69324 / NDA 207103 Palbociclib - FDA Feedback re Rolling Submission

I hope to give you a confirmation of the Sept 5 by the end of the week. Do you know about what time of day the meetings will be?

Michelle

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Wednesday, June 25, 2014 2:58 PM
To: Yu-Kite, Michelle
Subject: RE: IND 69324 / NDA 207103 Palbociclib - FDA Feedback re Rolling Submission

Michelle once Pfizer has reviewed our response please let me know as soon as possible regarding the Sept 5th Application Orientation meeting date.

Thanks.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Wednesday, June 25, 2014 5:52 PM
To: Tilley, Amy
Subject: RE: IND 69324 / NDA 207103 Palbociclib - FDA Feedback re Rolling Submission

Thank you Amy!

Michelle

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Wednesday, June 25, 2014 2:20 PM
To: Yu-Kite, Michelle
Subject: IND 69324 / NDA 207103 Palbociclib - FDA Feedback re Rolling Submission

Michelle,

Attached is our response to your Rolling Submission proposal.

Regards.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Thursday, June 19, 2014 2:59 PM
To: Tilley, Amy
Cc: Kacuba, Alice
Subject: RE: IND 69324 / NDA 207103 Palbociclib - Request for FDA Feedback

Hi Amy,

Thank you for the quick feedback. The team has been working diligently the past week to develop a Rolling Review proposal. Per your instructions below, a Request for Submission of Portions of an Application will be submitted under the IND 69,324, Serial Number 0363 today. For your reference, I have included a copy of the request here.

Depending on FDA's agreement with our proposal, because all the datasets will be included in Wave 1 (submission on or by 30 June), we believe the July 28 orientation meetings are still appropriate dates and would like to request keeping the meetings as scheduled. But again, I will wait to hear back from FDA about our RR proposal first.

Thanks,

Michelle Y. Kite, MS, RAC
Worldwide Safety and Regulatory

Office: (858) 526-4025
Mobile: (b) (6)
Fax: (858) 526-4402
Email: Michelle.Y.Kite@Pfizer.com

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Thursday, June 12, 2014 8:12 AM
To: Yu-Kite, Michelle
Cc: Kacuba, Alice
Subject: RE: IND 69324 / NDA 207103 Palbociclib - Request for FDA Feedback
Importance: High

Michelle,

In response to your question regarding the late submission of the efficacy narratives, please see upper management's response below.

As specified in the PDUFA V agreements, applications are expected to be complete at the time of original submission of an application. During the May 6 and 16 meetings, FDA indicated that efficacy narratives for all patients that had progressive disease need to be included in the initial NDA. This information is critical to have in order to begin the review of your application, therefore, the complete efficacy narratives need to be submitted at the time of your original submission in order for the NDA to be considered a complete application.

To facilitate review of your application, you may request to submit complete sections of your NDA for Rolling Review. If you make such a request, you should provide a proposed schedule for submission of each completed section (e.g., CMC and/or nonclinical section) of your application as soon as possible. A request for submission of portions of an application should be sent as an amendment to the IND; attach Form FDA 1571. The amendment should be clearly identified as a **REQUEST FOR SUBMISSION OF PORTIONS OF AN APPLICATION** in bold, uppercase letters.

Regards.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Tuesday, June 10, 2014 3:20 PM
To: Tilley, Amy
Cc: Kacuba, Alice
Subject: IND 69324 / NDA 207103 Palbociclib - Request for FDA Feedback
Importance: High

Hi Amy,

Yesterday, we submitted a general correspondence to IND 69324 requesting FDA feedback. During the May 6 and 16 meetings when we discussed the censoring information for PALOMA-1 study, Patricia Cortazar requested that efficacy narratives for all patients that had progressive disease be included in the initial NDA. As agreed, we will include all the efficacy narratives, however, as part of our diligence we are scheduling clinical sites visits to gather additional patient information especially for those patients where the investigator called progression but BICR did not. As you can imagine, these efforts are time and labor intense and this supplemental information will not be included in the initial NDA (June 30), so we propose to submit updated efficacy narratives to FDA by Day 45 of the 60-Day NDA Filing Determination period which will be Aug 15.

Please let me know if you have any questions. I have included a copy of our submission in this email.

Thanks,

Michelle Y. Kite, MS, RAC
Worldwide Safety and Regulatory

Office: (858) 526-4025
Mobile: (b) (6)
Fax: (858) 526-4402
Email: Michelle.Y.Kite@Pfizer.com

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/s/

AMY R TILLEY
08/06/2014

Tilley, Amy

From: Yu-Kite, Michelle <michelle.y.kite@pfizer.com>
Sent: Monday, June 30, 2014 1:49 PM
To: Tilley, Amy
Subject: NDA 207103 - palbociclib 1.14.1.1

Hi Amy,

Thank you for calling. To clarify, there are 2 sets for 75, 100 and 125 (b) (4)
(b) (4). The third 125 mg label is a Draft sample label only.

Hope that helps.

Thanks,

Michelle Y. Kite, MS, RAC
Worldwide Safety and Regulatory

Office: (858) 526-4025
Mobile: (b) (6)
Fax: (858) 526-4402
Email: Michelle.Y.Kite@Pfizer.com

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Bcc: [Al Hakim, Ali H](#); [Sarker, Haripada](#); [Crich, Joyce](#)
Subject: RE: IND 69324 / NDA 207103 Palbociclib - Rolling Submission - CMC IR
Date: Thursday, June 19, 2014 4:37:00 PM

Michelle the CMC Review Team accepts your proposal of the CMC submissions.

Amy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Thursday, June 19, 2014 4:34 PM
To: Tilley, Amy
Subject: RE: IND 69324 / NDA 207103 Palbociclib - Rolling Submission - CMC IR

Hi Amy,

On 30 June 2014 (Wave 1), 9 month stability data will be included. On 15 August 2014 (Wave 2), 12 month stability data will be included.

Thanks,

Michelle

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Thursday, June 19, 2014 1:31 PM
To: Yu-Kite, Michelle
Subject: RE: IND 69324 / NDA 207103 Palbociclib - Rolling Submission - CMC IR
Importance: High

Michelle,

According to the table below, Pfizer will provide the NDA quality section on June 30, 2014 except the 12-month stability data. Please clarify how much stability data (in months) will be provided in the initial submission on June 30 and how much additional stability data will be submitted on August 15.

Wave	Module	Item	Estimated Submission Date
1	1	All Sections Except USPI/PL	30 June 2014
	2	All Sections Except CO	30 June 2014
	3	All Quality Sections Except 12 Month Stability Data	30 June 2014
	4	All Nonclinical Sections	30 June 2014
	5	All Clinical Sections Except 1003 efficacy narratives (PALOMA-1) and Clinical Pharmacology Study 1040	30 June 2014
2	1.14	USPI documents	15 August 2014
	2.5	CO	15 August 2014
	3.2.P.8	12 Month Stability Data	15 August 2014

	5.3.5.1	1003 efficacy narratives and patient level summary (PALOMA-1) and Clinical Pharmacology Study 1040	15 August 2014
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Kindly respond to this email as soon as possible.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]

Sent: Thursday, June 19, 2014 2:59 PM

To: Tilley, Amy

Cc: Kacuba, Alice

Subject: RE: IND 69324 / NDA 207103 Palbociclib - Request for FDA Feedback

Hi Amy,

Thank you for the quick feedback. The team has been working diligently the past week to develop a Rolling Review proposal. Per your instructions below, a Request for Submission of Portions of an Application will be submitted under the IND 69,324, Serial Number 0363 today. For your reference, I have included a copy of the request here.

Depending on FDA's agreement with our proposal, because all the datasets will be included in Wave 1 (submission on or by 30 June), we believe the July 28 orientation meetings are still appropriate dates and would like to request keeping the meetings as scheduled. But again, I will wait to hear back from FDA about our RR proposal first.

Thanks,

Michelle Y. Kite, MS, RAC
Worldwide Safety and Regulatory

Office: (858) 526-4025

Mobile: (b) (6)

Fax: (858) 526-4402

Email: Michelle.Y.Kite@Pfizer.com

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]

Sent: Thursday, June 12, 2014 8:12 AM

To: Yu-Kite, Michelle

Cc: Kacuba, Alice

Subject: RE: IND 69324 / NDA 207103 Palbociclib - Request for FDA Feedback

Importance: High

Michelle,

In response to your question regarding the late submission of the efficacy narratives, please see upper management's response below.

As specified in the PDUFA V agreements, applications are expected to be complete at the time of original submission of an application. During the May 6 and 16 meetings, FDA indicated that efficacy narratives for all patients that had progressive disease need to be included in the initial NDA. This information is critical to have in order to begin the review of your application, therefore, the complete efficacy narratives need to be submitted at the time of your original submission in order for the NDA to be considered a complete application.

To facilitate review of your application, you may request to submit complete sections of your NDA for Rolling Review. If you make such a request, you should provide a proposed schedule for submission of each completed section (e.g., CMC and/or nonclinical section) of your application as soon as possible. A request for submission of portions of an application should be sent as an amendment to the IND; attach Form FDA 1571. The amendment should be clearly identified as a **REQUEST FOR SUBMISSION OF PORTIONS OF AN APPLICATION** in bold, uppercase letters.

Regards.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Tuesday, June 10, 2014 3:20 PM
To: Tilley, Amy
Cc: Kacuba, Alice
Subject: IND 69324 / NDA 207103 Palbociclib - Request for FDA Feedback
Importance: High

Hi Amy,

Yesterday, we submitted a general correspondence to IND 69324 requesting FDA feedback. During the May 6 and 16 meetings when we discussed the censoring information for PALOMA-1 study, Patricia Cortazar requested that efficacy narratives for all patients that had progressive disease be included in the initial NDA. As agreed, we will include all the efficacy narratives, however, as part of our diligence we are scheduling clinical sites visits to gather additional patient information especially for those patients where the investigator called progression but BICR did not. As you can imagine, these efforts are time and labor intense and this supplemental information will not be included in the initial NDA (June 30), so we propose to submit updated efficacy narratives to FDA by Day 45 of the 60-Day NDA Filing Determination period which will be Aug 15.

Please let me know if you have any questions. I have included a copy of our submission in this email.

Thanks,

Michelle Y. Kite, MS, RAC
Worldwide Safety and Regulatory

Office: (858) 526-4025
Mobile: (b) (6)
Fax: (858) 526-4402
Email: Michelle.Y.Kite@Pfizer.com

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/s/

AMY R TILLEY
06/19/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](mailto:Yu-Kite, Michelle); Laleh.AmiriKordestani@fda.hhs.gov
Cc: [Kacuba, Alice](#)
Bcc: [Cortazar, Patricia](#); [Amiri Kordestani, Laleh \(FDA\)](#)
Subject: RE: IND 69324 / NDA 207103 Palbociclib - Request for FDA Feedback
Date: Thursday, June 12, 2014 11:12:00 AM
Importance: High

Michelle,

In response to your question regarding the late submission of the efficacy narratives, please see upper management's response below.

As specified in the PDUFA V agreements, applications are expected to be complete at the time of original submission of an application. During the May 6 and 16 meetings, FDA indicated that efficacy narratives for all patients that had progressive disease need to be included in the initial NDA. This information is critical to have in order to begin the review of your application, therefore, the complete efficacy narratives need to be submitted at the time of your original submission in order for the NDA to be considered a complete application.

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Regards.

Amy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Tuesday, June 10, 2014 3:20 PM
To: Tilley, Amy
Cc: Kacuba, Alice
Subject: IND 69324 / NDA 207103 Palbociclib - Request for FDA Feedback
Importance: High

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Please let me know if you have any questions. I have included a copy of our submission in this email.

Thanks,

Michelle Y. Kite, MS, RAC
Worldwide Safety and Regulatory

Office: (858) 526-4025
Mobile: (b) (6)
Fax: (858) 526-4402
Email: Michelle.Y.Kite@Pfizer.com

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/s/

AMY R TILLEY
06/12/2014



IND 69324

MEETING MINUTES

Pfizer Inc.
Attention: Michelle Kite, M.S., RAC
Senior Manager, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Ms. Kite:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Palbociclib (PD-0332991).

We also refer to your February 10, 2014, correspondence, received February 10, 2014, requesting a meeting to discuss the findings from clinical pharmacology and biopharmaceutical Phase 1 studies of palbociclib in healthy volunteers investigating bioequivalence/bioavailability (Studies 1020 and 1036), food effect (Study 1021), DDI with a PPI, rabeprazole (Study 1018) and proposal on the use of palbociclib free base capsule formulation for clinical and commercial purposes.

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 Teicher Agosto, Regulatory Project Manager at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre- NDA

Meeting Date and Time: May 6, 2014, 11:00- 12:00 PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: 69324
Product Name: Palbociclib
Indication: Palbociclib in combination with letrozole is indicated for the treatment of postmenopausal women with estrogen receptor positive (ER+) and human epidermal growth factor receptor 2 (HER2) negative advanced breast cancer who has not received any prior systemic anti-cancer treatment for their advanced disease.

Sponsor/Applicant Name: Pfizer

Meeting Chair: Ali Al Hakim, Branch Chief
Meeting Recorder: Teicher Agosto, Regulatory Project Manager

FDA ATTENDEES

Ali Al Hakim, PhD, Branch Chief, ONDQA
Haripada Sarker, CMC Lead, ONDQA
Joyce Crich PhD, CMC Reviewer, ONDQA
Minerva Hughes, PhD, Biopharmaceutics Reviewer, ONDQA
Richard Pazdur, M.D., Director, OHOP
Amna Ibrahim, M.D., Deputy Division Director, DOP1
Geoffrey Kim, M.D., Acting Deputy Director, DOP1
Patricia Cortazar, M.D., Clinical Team Leader, DOP1
Laleh Amiri-Kordestani, M.D., Clinical Reviewer, DOP1
Amy McKee, M.D., Clinical Team Leader, DOP1
Tatiana Prowell, M.D., Clinical Reviewer, DOP1
Qi Liu, Ph.D., Clinical Pharmacology Team Leader, DCPV
Shenghui Tang, Ph.D., Biostatistics Team Leader
Lijun Zhang, Ph.D., Biostatistics Reviewer
Jeanne Fourie Zirkelbach, Ph.D., Clinical Pharmacology Reviewer, DCPV
Jingyu (Jerry) Yu, Ph.D., Pharmacometrics Reviewer, DPM
Liang Zhao, Ph.D., Pharmacometrics Team Leader, DPM

Alice Kacuba, Chief Regulatory Project Manager, DOP1
Amy Tilley, Regulatory Project Manager, DOP1
Teicher Agosto, PharmD, Regulatory Project Manager, ONDQA

SPONSOR ATTENDEES

Mace L. Rothenberg, MD, Senior Vice President, Clinical Development and Medical Affairs
Erling Donnelly, PhD, Palbociclib Submissions Strategy Team Leader
Ramzi Dagher, MD, Head of Regulatory Oncology
Albert Kraus, PhD, Global Regulatory Portfolio Lead, Women's' and Hematological Cancers
Michelle Yu Kite, MS, RAC, US Regulatory Lead
Maria Koehler, MD, PhD, Vice President, Strategic and Scientific Assessment Lead
Sophia Randolph, MD, PhD, Global Clinical Lead
Kourosh Parivar, MPharm, Vice President, Clinical Pharmacology
Diane Wang, PhD, Senior Director, Clinical Pharmacology Lead
Jenny Zheng, PhD, Director, Pharmacometrics
John Groskoph, MS, Senior Director, Global CMC
Susan C. Berlam, MS, RPh, Senior Director, Global CMC
Enayet Talukder, PhD, Head of Statistics Lead
Leena Das-Young, PharmD, Vice President, Late Phase Strategy, Development, Submission, and Lifecycle Management Group
Sindy Kim, A5481003 Clinical Lead
Daniel Arenson, PhD, Research Fellow, Pharmaceutical Sciences Team Lead
Xin Huang, PhD, Statistical Lead

1.0 BACKGROUND

Pfizer submitted a Type B, Pre NDA CMC meeting request to the FDA on February 10, 2014, requesting a meeting to discuss the findings from clinical pharmacology and biopharmaceutical Phase 1 studies of palbociclib in healthy volunteers investigating bioequivalence/ bioavailability (Studies 1020 and 1036), food effect (Study 1021), DDI with a PPI, rabeprazole (Study 1018) and proposal on the use of palbociclib free base capsule formulation for clinical and commercial purposes. A meeting requested granted letter was mailed on March 4, 2014 to Pfizer. Pfizer sent meeting briefing packages on April 10, 2014. After reviewing the Agency's preliminary responses, the sponsor stated that no further discussion was needed for questions. The sponsor wanted to proceed as planned with the meeting to present slides that includes a summary of the censoring information and the information request sent by OND PM , Amy Tilley on May 5, 2014 , see Attachments and Handouts section.

2.0 DISCUSSION

Question 1:

Does the Agency agree that the results of the relative bioavailability trial (Study 1036), which demonstrated bioequivalence between the palbociclib isethionate capsule formulation given under fasting conditions and the palbociclib free base commercial capsule formulation given with food, support the commercialization of the palbociclib free base capsule formulation taken with food?

FDA response to Question 1:

The bridging data submitted appear adequate to support your proposal. However, the final determination will be an NDA review issue.

Meeting Discussion:

No further discussion required.

Question 2:

The results of Study 1018 showed Proton Pump Inhibitor (PPI) reduced palbociclib Cmax and AUCinf by 62% and 80%, respectively, under fasting conditions. Based on with food, the result of this study will be used to support the product labeling. The top line report (TLR) of this study will be available by the end of July 2014 and final Clinical Study Report (CSR) is anticipated in early third quarter of 2014 (3Q2014).

Does the Agency agree that Study 1038 results may be submitted during the NDA review?

FDA response to Question 2:

Yes, the Agency agrees that results from Study 1038 may be submitted during the NDA review.

Meeting Discussion:

No further discussion required.

Additional Comments:

Pfizer presented slides regarding EU interactions on the potential palbociclib application, commercial product launch readiness, the status of Paloma-2, and KM PFS curves for investigator, BICR for combined and separate cohorts as well as the censoring information. A follow-up meeting on May 16, 2014 is scheduled to discuss this information.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no specific issues requiring further discussion at this time.

4.0 ACTION ITEMS

There are no specific due dates or time lines for submission of information or other action items.

5.0 ATTACHMENTS AND HANDOUTS

Handout provided by Pfizer on May 5, 2014, see attached.

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/s/

ALI H AL HAKIM
06/05/2014



****Revised Meeting Minutes to update PREA Requirements****

IND 069324

MEETING MINUTES

Pfizer Inc.
Attention: Michelle Yu Kite
Senior Manager, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Ms. Kite:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Palbociclib PD-0332991.

We also refer to the meeting between representatives of your firm and the FDA on May 16, 2014. The purpose of the meeting was to discuss the censoring information for A5481003.

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 Amy Tilley, Regulatory Project Manager at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Patricia Cortazar, 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
Sponsor Slides



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: FDA Requested Non-PDUFA Meeting
Meeting Category: Guidance

Meeting Date and Time: May 16, 2014
Meeting Location: WO22 Rm 1309

Application Number: IND 069324
Product Name: Palbociclib PD-0332991
Indication: In combination with letrozole for the treatment of postmenopausal women with ER-positive/HER2-negative (b) (4) advanced or metastatic breast cancer who have not received previous systemic treatment for their advanced disease.
Sponsor/Applicant Name: Pfizer Inc.

Meeting Chair: Patricia Cortazar, M.D., Clinical Team Leader
Meeting Recorder: Amy Tilley, Regulatory Project Manager

FDA ATTENDEES

Richard Pazdur, M.D., Director, OHOP
Amna Ibrahim, M.D., Acting Division Director, DOP1
Geoffrey Kim, M.D., Acting Deputy Director, DOP1
Patricia Cortazar, M.D., Clinical Team Leader
Laleh Amiri Kordestani, M.D., Clinical Reviewer
Julia Beaver, M.D., Clinical Reviewer
Thomas Gwise, Ph.D., Deputy Director BDV
Lijun Zhang, Ph.D., Biostatistics Reviewer
Amy Tilley, Regulatory Project Manager

SPONSOR ATTENDEES

Mace L. Rothenberg, M.D., Senior Vice President, Clinical Development and Medical Affairs
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Erling Donnelly, Ph.D., Palbociclib Submissions Strategy Team Leader
Ramzi Dagher, M.D., Head of Regulatory Strategy Oncology
Albert L. Kraus, Ph.D., Global Regulatory Portfolio Lead, Women's and Hematological Cancers
Michelle Yu Kite, MS, RAC, US Regulatory Lead
Sophia Randolph, M.D., Ph.D., Global Clinical Lead
Sindy Kim, A5481003 Clinical Lead
Enayet Talukder, Ph.D., Head of Oncology Statistics

Xin Huang, Ph.D., Statistical Lead

1.0 BACKGROUND

Pfizer is planning to submit an NDA to support Accelerated Approval of PD-0332991 (palbociclib) for the proposed indication of: "PD-0332991 in combination with letrozole for the treatment of postmenopausal women with estrogen receptor-positive (ER [+]) and human epidermal growth factor receptor 2 (HER2) negative ^{(b) (4)} advanced or metastatic breast cancer", based on the results of their Phase 1/2 study A5481003, entitled "Phase 1/2, Open-label, Randomized Study of the Safety, Efficacy, and Pharmacokinetics of Letrozole Plus PD-0332991 (oral CDK 4/6 Inhibitor) and Letrozole Single Agent for the First-Line Treatment of ER(+)/HER2-Negative Advanced Breast Cancer in Postmenopausal Women". A confirmatory Phase 3 trial A5481008 is currently enrolling.

During the pre-NDA meeting held on February 28th 2014, Pfizer presented the topline results of study A5481003. FDA is concerned with the high rate and imbalanced censoring rates in the study and requested that Pfizer provide a summary of: (1) Reasons for censoring in investigator assessed progression-free survival (PFS) events;(2). Reasons for censoring in Blinded Independent Central Review (BICR) assessed PFS events; and (3). Reasons for censoring, detailed by patient.

In addition to the CMC issues discussed at a meeting held on May 6, 2014, Pfizer presented the censoring information previously requested by FDA. In anticipation of the upcoming Clinical Type B meeting on 16 May 2014, FDA asked Pfizer to submit:(1) the number of discordance/concordance between blinded independent central review (BICR) and investigator (INV) PFS assessment by treatment arm for phase 2 combined, phase 2 part 1, and phase 2 part 2, separately;(2) the calculated early discrepancy rate (EDR) and late discrepancy rate (LDR) for each treatment arm in phase 2 combined population, phase 2 part 1, and phase 2 part 2, separately and (3) a sensitivity analysis as described in the table below:

	Palbociclib + Letrozole	Letrozole
BICR = INV = PFS event or BICR = INV = censoring	Use BICR data	Use BICR data
BICR = censoring and INV = event BICR = event and INV = censoring	Use INV event Use BICR event	Use BICR censoring Use INV censoring

2. DISCUSSION

FDA Comments to the sponsor's response to Information Requests dated April 8, 2014 and May 12, 2014:

We are concerned with the interpretability of the study results, including the significance of the statistical test(s), as well as estimation of treatment effect(s).

The concerns stem from the imbalance in the event disagreement rates between the 2 treatment arms for each cohort (Ph2P1 cohort: 29.4% vs. 50%; Ph2P2 cohort: 36.0% vs.

24.5%). The early discordance rate (EDR) and late discordance rate (LDR) also indicate that there may be an investigator assessment bias for PFS evaluation in this open-label study, particularly in the Ph2P1 cohort. In the Ph2P1 cohort, compared with the central review, investigator called more disease progression in the letrozole alone arm and less in the palbociclib and letrozole combination arm, which are indicative of bias in the investigator result in favor of the palbociclib and letrozole combination arm. This finding leaves the interpretability of the applicant's statistical inference obtained using the investigator assessments in question. Because the bias is differential across the treatment arms and unknown in origin, it is difficult or impossible to account for it through analytical methods. Removing or imputing subject data based on BICR-Investigator disagreement cannot correct the bias because the disease progression, as assessed, is likely correlated to some unidentified patient characteristics and any attempt at adjustment would likely be biased, as well.

Per the BICR assessment, the upper 95% CI of PFS is 1.02 in the combined population. With around 60% censoring per the BICR assessment and small number of PFS events, a null hypothesis of no treatment effect cannot be ruled out using type I error rate of 0.025, one-sided.

Given the existence of investigator bias and issues associated with BICR assessments, including high censoring rate, missing follow-up data for patients determined as progression by INV and lack of statistical significance, it would be difficult to have an accurate and reliable estimate of the magnitude of PFS improvement.

Meeting Discussion:

The Agency continued to express concerns regarding the censoring and the bias on the investigator arm. It appears from the data that the drug has some activity. However, it is difficult to characterize precisely the magnitude of this benefit. The Agency stated that if the NDA is submitted, it will need to be discussed at ODAC. An important ODAC discussion will be the benefit risk assessment of the phase 2 study results and what magnitude of PFS improvement will constitute a positive phase 3 confirmatory study.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. 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>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor Slides

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/s/

PATRICIA CORTAZAR
06/04/2014

From: Tilley, Amy
To: "[Yu-Kite, Michelle](#)"
Bcc: [Wittorf, Robert](#); [Ramanadham, Mahesh](#); [Cortazar, Patricia](#); [Amiri Kordestani, Laleh \(FDA\)](#)
Subject: IND 69324 (NDA 207103) Palbociclib - Manufacturing Facility Clarification
Date: Tuesday, June 03, 2014 2:10:00 PM

Michelle,

We acknowledge your submission dated 22-May-2014 in which lists the CMC manufacturing facilities. In addition to what has been provided, we request additional information as follows to assist in our facility evaluation:

1. Please list manufacturing facilities that were used to manufacture drug substance or drug product, or generate data in support of the application and list facilities that are intended for commercial manufacturing of the drug product. If the sites are the same for both, please indicate this.
2. Please list the sites in which stability testing of both the Drug Substance and Drug product will be performed. Please include Name, Address, Establishment Number, and Contact Information.
3. Please provide additional clarification about the operations at the Pfizer Pharmaceuticals, LLC (FEI: 2323619) and Pharmacia and Upjohn Company (FEI 1810189). Please be specific around the operations secondary packaging and labeling.

Kindly let me know once this information has been officially submitted.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
06/03/2014

From: Tilley, Amy
To: "[Yu-Kite, Michelle](#)"
Bcc: [Wittorf, Robert](#); [Ramanadham, Mahesh](#)
Subject: NDA 207103 Ibrance - Manufacturing Facilities Information Request
Date: Monday, June 02, 2014 5:07:00 PM
Importance: High

Michelle,

To facilitate our inspectional process for the upcoming NDA for palbociclib, we request that you provide, all manufacturing facilities responsible for the commercial process associated with your anticipated 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.

In addition to commercial manufacturing facilities, please include, all manufacturing facilities in which batches were made to support the application (if they differ from facilities intended for commercial manufacturing). 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.

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
06/02/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Bcc: [Iacono-Connor, Lauren](#); [Kacuba, Alice](#); [Cortazar, Patricia](#); [Amiri Kordestani, Laleh \(FDA\)](#)
Subject: Addtl Information re OSI Request for IND 69324 Palbociclib-NDA 207103 Ibrance
Date: Wednesday, May 28, 2014 12:33:00 PM
Attachments: [IND 69324 NDA 207103 - OSI Request Pre-Appl.doc](#)
Importance: High

Michelle,

I just heard back from the OSI Clinical Inspection folks and no, the PDF you submitted on May 22, 2014, is not sufficient to fulfill the OSI Request.

Pfizer must address all of the OSI requests in the attached document at the time of the NDA submission or before. Once you have reviewed the entire OSI request in the document then you will understand that what you have already submitted only addresses a very small part of the OSI request.

Should you have any further questions please contact me.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Thursday, May 22, 2014 5:37 PM
To: Tilley, Amy
Cc: Kacuba, Alice
Subject: RE: IND 69324 Palbociclib - Meeting Minutes from 5-16-14

Hi Amy,

I want to thank you for responding so quickly with all the submissions, meetings and activities that are involved with palbociclib.

Just a heads up on a submission from today with the contact information for the manufacturing sites and clinical sites that may be helpful for your inspection scheduling especially those ex-US. These same lists will be provided again in the initial NDA 207103.

Thanks,

Michelle

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Thursday, May 22, 2014 12:39 PM
To: Yu-Kite, Michelle
Subject: RE: IND 69324 Palbociclib - Meeting Minutes from 5-16-14

I will check and get back to but may not be till next week.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Thursday, May 22, 2014 3:32 PM
To: Tilley, Amy
Subject: RE: IND 69324 Palbociclib - Meeting Minutes from 5-16-14

Hi Amy,

Thank you. If possible, can we request a date between Friday, July 18 through July 31?

Thanks,

Michelle

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Thursday, May 22, 2014 11:33 AM
To: Yu-Kite, Michelle
Subject: RE: IND 69324 Palbociclib - Meeting Minutes from 5-16-14

Michelle,

As discussed during today's tcon, please send me Pfizer's proposed dates for the Application Orientation meeting regarding the upcoming NDA submission of Palbociclib.

Thanks.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Wednesday, May 21, 2014 3:09 PM
To: Tilley, Amy
Subject: RE: IND 69324 Palbociclib - Meeting Minutes from 5-16-14

Hi Amy,

During our call or email tomorrow, is it possible to also discuss the possibility of scheduling the orientation (NDA Overview) meeting with FDA in anticipation of the 30 June 2014 NDA submission, given FDA's busy schedules?

Thanks,

Michelle

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Wednesday, May 21, 2014 7:12 AM

To: Yu-Kite, Michelle
Subject: RE: IND 69324 Palbociclib - Meeting Minutes from 5-16-14

I need to check with my Chief. We may have a brief tcon with you tomorrow to discuss.

I will get back to you once I have confirmed with my Chief.

Amy

From: Yu-Kite, Michelle [<mailto:michelle.y.kite@pfizer.com>]
Sent: Tuesday, May 20, 2014 8:11 PM
To: Tilley, Amy
Subject: RE: IND 69324 Palbociclib - Meeting Minutes from 5-16-14

Hi Amy,

Based on the enclosed meeting minutes on page 4 (copied below), it appears that our pediatric waiver has been granted. Should I provide a copy of the PSP submission (and request for waiver) dated 24 April 2014 in the NDA under 1.9 Pediatric Information and also reference the waiver in these meeting minutes dated 19 May 2014?

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.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

Thanks,

Michelle

From: Tilley, Amy [<mailto:Amy.Tilley@fda.hhs.gov>]
Sent: Monday, May 19, 2014 1:37 PM
To: Yu-Kite, Michelle
Subject: IND 69324 Palbociclib - Meeting Minutes from 5-16-14

Michelle,

Below are the Meeting Minutes from our May 16th meeting.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,

CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

OSI:

OSI requests that the items in Attachment 1 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. 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 the submission in the format described, the Applicant can describe the location or provide a link to the requested information. Site-specific individual data listings for the pivotal study may be submitted prior to the submission of the NDA, but no later than the final component, of the NDA, for all clinical study sites that enrolled subjects in the pivotal study. Provision of complete information as requested in Parts I and II will facilitate, and more importantly accelerate, development of clinical investigator and sponsor/monitor/CRO inspection assignments and the preparation of the inspection-supporting background packages. In order for the application to be considered complete at submission, it should contain elements that fully address Part I (General Study Related Information and Comprehensive Clinical Investigator Information) and Part II (Subject Level Data Listings by Site) of the OSI Pre-NDA Request (See Attachment 1).

Attachment 2 provides instructions for where all OSI requested items should be placed within an eCTD submission.

Office of Scientific Investigations Attachment 1

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission describe the location or provide a link to the requested information).

1. Please include the following information in a tabular format in the 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.

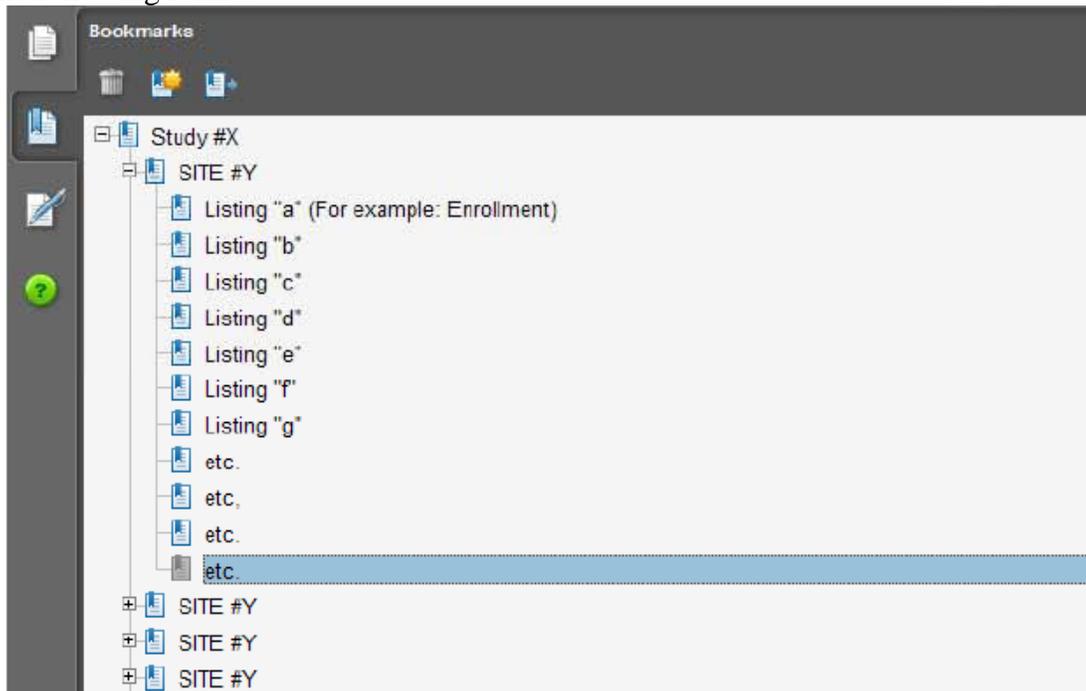
2. Please include the following information in a tabular format, *by site*, in the NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each 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.

Office of Scientific Investigations Attachment 2

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.”

OSI 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 Request document for a full description of requested data files

OSI Pre-NDA Request
IND 69324 palbociclib

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

AMY R TILLEY
05/28/2014

From: Tilley, Amy
To: ["Yu-Kite, Michelle"](#)
Bcc: [Iacono-Connor, Lauren](#); [Cortazar, Patricia](#); [Amiri Kordestani, Laleh \(FDA\)](#)
Subject: OSI Request re IND 69324 Palbociclib-NDA 207103 Ibrance
Date: Tuesday, May 27, 2014 4:38:00 PM
Attachments: [IND 69324 NDA 207103 - OSI Request Pre-Appl.doc](#)

Michelle,

This email is a follow-up to our telephone conversation today regarding an OSI Request.

Please see the OSI document/request below.

Should you have any additional questions please contact me.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

OSI:

OSI requests that the items in Attachment 1 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. 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 the submission in the format described, the Applicant can describe the location or provide a link to the requested information. Site-specific individual data listings for the pivotal study may be submitted prior to the submission of the NDA, but no later than the final component, of the NDA, for all clinical study sites that enrolled subjects in the pivotal study. Provision of complete information as requested in Parts I and II will facilitate, and more importantly accelerate, development of clinical investigator and sponsor/monitor/CRO inspection assignments and the preparation of the inspection-supporting background packages. In order for the application to be considered complete at submission, it should contain elements that fully address Part I (General Study Related Information and Comprehensive Clinical Investigator Information) and Part II (Subject Level Data Listings by Site) of the OSI Pre-NDA Request (See Attachment 1).

Attachment 2 provides instructions for where all OSI requested items should be placed within an eCTD submission.

Office of Scientific Investigations Attachment 1

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission describe the location or provide a link to the requested information).

1. Please include the following information in a tabular format in the 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.

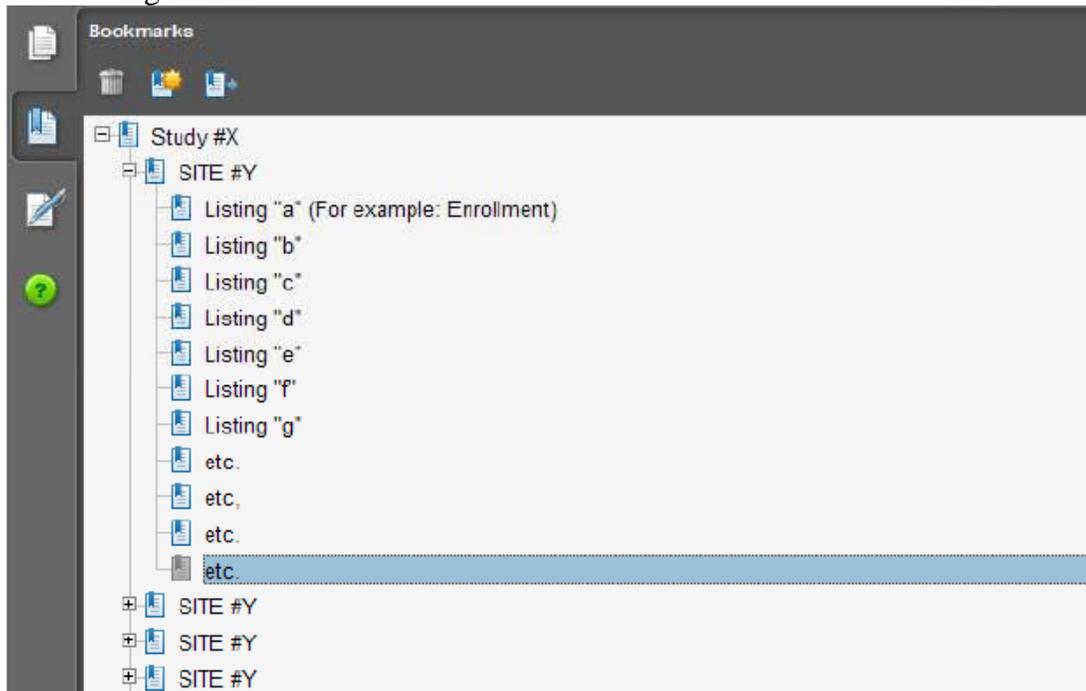
2. Please include the following information in a tabular format, *by site*, in the NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each 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.

Office of Scientific Investigations Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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OSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
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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 Request document for a full description of requested data files

OSI Pre-NDA Request
IND 69324 palbociclib

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

AMY R TILLEY
05/27/2014



IND 069324

MEETING MINUTES

Pfizer, Inc.
10646 Science Center Drive
San Diego, CA 92121

Attention: Michelle Yu-Kite, M.S., RAC
Senior Manager, Worldwide Regulatory Strategy

Dear Ms. Yu-Kite:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Palbociclib (PD-0332991).

We also refer to the meeting between representatives of your firm and the FDA on February 28, 2014. The purpose of the meeting was to discuss with FDA the Top Line Summary results from the final analysis from the phase 2 portion of the Phase 1/2 study A5481003 (Paloma-1) for the first-line treatment of ER+/HER2-negative advanced breast cancer.

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) 796-1441.

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

Patricia Cortazar, M.D.
Clinical Team Leader, Breast Oncology Group
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor Slides



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA - Discussion of Top Line Summary results

Meeting Date and Time: February 28, 2014, 10:00 a.m.
Meeting Location: White Oak Bldg. 22, Rm. 1315

Application Number: 069324

Product Name: palbociclib (PD-03329910)

Indication: Palbociclib in combination with letrozole is indicated for the treatment of postmenopausal women with estrogen receptor-positive (ER+) and human epidermal growth factor receptor 2 (HER2) negative advanced breast cancer who have not received any prior systemic anti-cancer treatment for their advanced disease.

Sponsor/Applicant Name: Pfizer Inc.

FDA ATTENDEES

Richard Pazdur, M.D., Director, OHOP
Richard Lostritto, Ph.D., Director, DNDQA, OPS
Amna Ibrahim, M.D., Deputy Division Director, DOP1
Patricia Cortazar, M.D., Clinical Team Leader, DOP1
Laleh Amiri-Kordestani, M.D., Clinical Reviewer, DOP1
Julia Beaver, Clinical Reviewer, DOP1
Amy McKee, M.D., Clinical Team Leader, DOP1
Tatiana Prowell, M.D., Clinical Reviewer, DOP1
Nancy Scher, M.D., Clinical Reviewer, DOP1
Suparna Wedam, M.D., Clinical Reviewer, DOP1
Al Ali Hakim, Ph.D., Branch Chief, DNDQAI, Branch II, ONDQA,
Haripada Sarker, Ph.D., CMC Lead, DNDQAI, Branch II, ONDQA,
Joyce Crich, Ph.D., CMC Reviewer, DNDQA, Branch II, ONDQA,
Robert Wittorf, Pharm.D., Compliance Officer, DGMPA, OMPQ, OC
Qi Liu, Ph.D., Clinical Pharmacology Team Leader, DCPV
Jeanne Fourie Zirkelbach, Ph.D., Clinical Pharmacology Reviewer, DCPV
Todd Palmby, Ph.D., Supervisory Pharmacologist/Toxicologist, DHOT
Wei Chen, Ph.D., Pharmacologist/Toxicologist, DHOT
Nam Atiqur Rahman, Ph.D., Director, DCPV

Minerva Hughes, Ph.D., Biopharmaceutics, ONDQA, OPS
Jingyu (Jerry) Yu, Ph.D., Pharmacometrics Reviewer, DPM
Liang Zhao, Ph.D., Pharmacometrics Team Leader, DPM
Rajeshwari Sridhara, Ph.D., Division Director, DBV
Somesh Chattopadhyay, Ph.D., Biometrics Reviewer, DBV
Frank Cross, Jr., M.A., MT (ASCP), Senior Regulatory Health Project Manager, DOP1

SPONSOR ATTENDEES

Mace L. Rothenberg, M.D., Senior Vice President, Clinical Development and Medical Affairs
Eric Kowack, M.S., MBA, Palbociclib Asset Team Leader
Maria Koehler, M.D., Ph.D., Vice President, Integrated Development Leader, Palbociclib
Sophia Randolph, M.D., Ph.D., Palbociclib Global Clinical Lead
Sindy Kim, Palbociclib Clinical Study Lead
David Readett, M.D., Palbociclib Safety Risk Lead
Albert L. Kraus, Ph.D., Global Regulatory Portfolio Lead, Women's Cancers
Ramzi Dagher, M.D., Head, Worldwide Regulatory – Oncology
Michelle Yu Kite, M.S., RAC, US Regulatory Lead
Xin Huang, Ph.D., Palbociclib Statistics Lead
Enayet Talukder, Ph.D., Head of Statistics, Oncology
Yuqiu (John) Jiang, Ph.D., Translation Oncology Lead
Diane Wang, Ph.D., Clinical Pharmacology Lead
Rebecca Hintze, Oncology Programming Lead
Kourosh Parivar, Ph.D., Vice President, Clinical Pharmacology Oncology
Susan C. Berlam, M.S., R.Ph; Senior Director, Global CMC
Daniel Arenson, Ph.D., Research Fellow; Pharmaceutical Sciences Team Lead

1.0 BACKGROUND

Pfizer requested a Type B Pre-NDA meeting to discuss a submission of an NDA to support approval of PD-0332991 (palbociclib), an oral CDK 4/6 inhibitor, in combination with letrozole for the treatment of postmenopausal women with estrogen receptor-positive (ER [+]) and human epidermal growth factor receptor 2 (HER2) negative (b) (4) advanced or metastatic breast cancer.

Pfizer submitted the top-line results of the study A5481003 (Paloma 1) entitled “*Phase 1/2, Open-label, Randomized Study of the Safety, Efficacy, and Pharmacokinetics of Letrozole Plus PD-0332991 (oral CDK 4/6 Inhibitor) and Letrozole Single Agent for the First-Line Treatment of ER(+)/HER2-Negative Advanced Breast Cancer in Postmenopausal Women*”. Pfizer also submitted a brief outline of an Expanded Access Program, documents to support the NDA format and content, a CRF sample and the mock define files.

2.0 DISCUSSION

FDA Introductory Comment:

Our preliminary assessment indicates that your formulation change may not be adequately supported. An NDA should be submitted after the formulation changes and bioequivalence issues have been resolved. You will also need to address the censoring imbalance in the investigator and BICR analyses. This application will likely require an ODAC meeting.

2.1. Summary of the Top-Line Results of Study A5481003

Question 1: Does the FDA agree that the final results from the Phase 1/2 Study A5481003 demonstrate a favorable benefit/risk profile for the combination of palbociclib plus letrozole when compared to letrozole alone for the treatment of patients with ER-positive, HER2-negative advanced breast cancer?

FDA Response: This is a review issue. At this time we cannot make a benefit:risk assessment.

Please address the imbalance in censoring on the two arms and provide detailed reasons for censoring observations in both investigator assessments and BICR analysis.

Meeting Discussion: The Sponsor agreed to submit the detailed patient level reasons for censoring in both treatment arms from the Phase 1/2 Study A5481003, prior to NDA submission.

Question 2: Based on the data presented, does the FDA support submission of an NDA under Accelerated Approval (Sub-Part H) regulations to seek approval for palbociclib in combination with letrozole for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer who have not received any systemic treatment for their advanced disease (results from the ongoing Phase 3 Study 1008 would serve as confirmation of benefit in this approach)?

FDA Response: In addition to the censoring issues in response to #1, please see the following issues regarding formulation changes and bioequivalence:

Drug administration conditions for the initial approval phase 2 trial (1003) are under the fasted condition (fasting 1 hour before and 2 hours after). We will need to evaluate drug administration conditions for the phase 2 trial (1003) and results from your proposed ER response analysis to assess whether the difference in exposure between your two formulations affects the efficacy and safety of your drug. For your upcoming Type C Meeting on May 6, 2014, we strongly recommend that you provide a complete

meeting briefing package with your pivotal BE trial (1020) and food effect trial (1021) results and your preliminary E/R analysis described below for review and discussion.

- **The E/R analysis should evaluate the relationship between AUC/Cmax and efficacy. The interpretation of the E/R analysis results will be a review issue.**
- **If such an E/R analysis is inconclusive, you should discuss with the FDA the feasibility of conducting another pivotal BE trial with both formulations administered under the fasted condition, as the results from your first pivotal BE trial (1020) may be due to a variety of reasons (e.g., under powered study, outlier response from one or more subjects, assay issues, etc.).**

The results from your ongoing trial 1036, comparing the to-be marketed formulation given with food to the Phase 2 formulation under fasted conditions will be a review issue. Please clarify the intent of trial 1036, given that the Phase 2 trial (1003) for the initial submission was done under a fasting condition.

Your phase 2 trial (1003) was conducted under fasted conditions. However, we note that your confirmatory phase 3 trial (1008), with the new free base to-be-marketed formulation, was conducted under fed conditions. Following review of the results for trial 1008, drug administration instructions with regard to food may need to be changed, and this will be a review issue.

Meeting Discussion: The Sponsor stated that the palbociclib formulation and the BE issues will be addressed prior to NDA submission.

FDA asked Pfizer to include the following information in the May 6, 2014 meeting briefing package:

- **results of studies 1020, 1036 and 1018, and food effect from study 1021**
- **preliminary exposure response analysis from study 1003, including all available datasets**
- **if higher drug exposures are observed for the free base formulation with food, include a discussion on the safety impact and a justification why the observed difference should not raise any safety concerns**
- **complete drug substance and drug product release test data for batches used in all studies, tabulated by study, along with a quantitative description of the formulation and manufacturing process differences, e.g., salt and/or excipients, among the batches used.**
- **Multipoint dissolution data for each batch, including a description of the method and any test method changes across studies.**

2.2 NDA Content and Format (provided as follow-up from 17 December 2013 Meeting per FDA request)

Question 3: Does the Agency agree with the proposed content of the NDA as presented in the proposed NDA Table of Contents (Appendix 1) or have any comments or suggestions?

FDA Response: Yes the proposed format and content appears to be adequate.

Question 4: Does the Agency agree with the Sponsor's request to provide a 60-day safety update during the review period instead of a 120-day safety update? The safety update will be provided 60 days after the NDA submission date.

FDA Response: Please provide your rationale for this request.

Question 5: Does the FDA consider the proposed type and format of datasets appropriate to support the proposed NDA? As agreed during the teleconference of 17 December 2013, a list of the derived datasets, including both the raw data collected and any derivations as a single dataset, and a mock define file of the efficacy datasets for Study 1003 are provided in Appendix 3. Additionally, the unique pages of a blank Case Report Form are provided in Appendix 2 of this briefing package, following a request by the Agency during the teleconference of 17 December 2013.

FDA Response: We recommend that you submit separate raw and derived datasets.

The CRF appears adequate. Please provide a CRF table of contents with hyperlinks.

Question 6: As agreed during the teleconference of 17 December 2013, follow-up comments regarding our proposal for case-control analysis may be provided during the meeting to discuss the top-line results. The sponsor will evaluate the potential confounding risk factors for PFS. If the confounding risk factors are balanced between the low and high dose/exposure groups, the sponsor will not apply case- control analysis to the exposure/response analysis. If the confounding risk factors are found to be imbalanced between the low and high dose/exposure groups, the sponsor will conduct the analysis as requested by the agency.

Does the FDA agree with the proposal that

(b) (4)

FDA Response: No.

(b) (4)

Meeting Discussion: Refer to discussion under Question 2 above.

2.3 Expanded Access Program

Question 7: Does the FDA agree with the proposed patient population and overall design of the EAP entitled, “An Expanded Access Study of Palbociclib in Combination with Letrozole as Treatment of Hormone Receptor Positive, HER2-Negative Postmenopausal Women with Advanced Breast Cancer for Whom Letrozole Therapy is Deemed Appropriate” (design outline in Appendix 4)?

FDA Response:

We have been receiving several SPI requests for patients with liposarcoma. Therefore, we suggest that you expand the population to include patients with refractory tumors for whom there is no available therapies that will confer clinical benefit.

Consider opening the EAP earlier than the proposed plan to include patients who are not eligible to other Palbociclib trials.

Meeting Discussion: The Sponsor will revisit its EAP and consider including other tumor types.

Additional Comment:

Please note that the formulation of the product used in the pivotal clinical efficacy and safety trials should preferably be the same as the intended commercial product, and the utility of your proposed E/R strategy to bridge the phase 2 and commercial formulations will be a review issue. Therefore, we would like to remind you that a fully supported demonstration of *in vivo* bioequivalence provides the best assurance of overall product quality for major formulation changes during development.

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>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor Slides.

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

/s/

PATRICIA CORTAZAR
03/31/2014



IND 69324

MEETING MINUTES

Pfizer Inc.
Attention: Michelle Kite, M.S., RAC
Senior Manager, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Ms. Kite:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Palbociclib (PD-0332991).

We also refer to the teleconference between representatives of your firm and the FDA on January 23, 2014. The purpose of the meeting was to obtain the Agency's advice and agreement on CMC strategies that the applicant intends to pursue during commercial development and in preparation of the initial NDA.

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 Teicher Agosto, Regulatory Project Manager at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre- NDA

Meeting Date and Time: January 23, 2014, 2:00- 3:00 PM EST
Meeting Location: TCON

Application Number: 69324
Product Name: Palbociclib
Indication: Treatment of postmenopausal women with metastatic breast cancer
Sponsor/Applicant Name: Pfizer

Meeting Chair: Ali Al Hakim, Branch Chief
Meeting Recorder: Teicher Agosto, Regulatory Project Manager

FDA ATTENDEES

Ali Al Hakim, PhD, Branch Chief, ONDQA
Haripada Sarker, CMC Lead, ONDQA
Joyce Crich PhD, CMC Reviewer, ONDQA
Minerva Hughes, PhD, Biopharmaceutics Reviewer, ONDQA
Robert Wittorf, Pharm D, Compliance Officer, OMPQ
Wei Chen, Pharmacology/Toxicology Reviewer, OHOP/DHOT
Jewell Martin, MA, MBA, PMP, Regulatory Project Manager, ONDQA
Teicher Agosto, PharmD, Regulatory Project Manager, ONDQA

SPONSOR ATTENDEES

Mary T. am Ende, Research Fellow, Drug Product Design
Daniel R. Arenson, Research Fellow, Pharmaceutical Sciences Team Leader
Susan C. Berlam, Senior Director, Global CMC
Susan M. Decoteau, Associate Director, Global CMC
Nathan D. Ide, Senior Principal Scientist, Chemical R&D
Kyle R. Leeman, Senior Principal Scientist, Analytical R&D
Cynthia A. Oksanen, Senior Director, Drug Product Design
Brian Weekley, Associate Research Fellow, Analytical R&D
Michelle Yu-Kite, Senior Manager, Regulatory Strategy
Ciaran Byrne, API New Products Lead, Pfizer Global Supply, Ringaskiddy, Ireland
Andreas Muehlenfeld, Director, Product and Process Development, Pfizer Global Supply, Freiburg, Germany
Nick Thomson, Director, Chemical R&D

1.0 BACKGROUND

Pfizer submitted a Type B, CMC meeting request to the FDA on October 23, 2013, requesting a meeting to obtain the Agency's advice and agreement on CMC strategies that the applicant intends to pursue during commercial development and in preparation of the initial NDA. A meeting requested granted letter was mailed on November 18, 2013 to Pfizer. Pfizer sent meeting briefing packages on December 23, 2013. Meeting Preliminary comments were sent to Pfizer on January 17, 2014. The sponsor requested to change the meeting format from a face to face meeting to a teleconference on January 21, 2014. After reviewing the Agency's preliminary responses, the sponsor stated that Questions 1, 3 and 6, needed no further discussion and requested further discussion on Questions 2, 4, 5, 7, 8, 9 and 10. Additionally, the sponsor sent additional information to be discussed during the meeting on January 23, 2014, see Attachments and Handouts section.

2.0 DISCUSSION

Question 1: The Applicant will have limited drug substance and drug product registration stability data available at the time of an accelerated submission in June 2014. The applicant will provide stability data through 9 months for drug substance and through 9 months for drug product at the time of submission. Stability data from the 12-month timepoint for drug substance and for drug product will be available for FDA review within 8 weeks of submitting the NDA. The Applicant anticipates proposing a 24-month (b) (4) commercial expiry (DP), per ICH Q1E.

- a) Does the Agency agree that the slight delay in submitting the 12 month data is acceptable and will not extend the PDUFA goal date?
- b) Assuming the 12 month data is submitted within 8 weeks of initial NDA submission, will the Agency commit to reviewing the 12 month stability data and considering the data as part of the drug product shelf life designation?

FDA Response Question 1:

As discussed at the EOP2, submit the additional stability data within 30-day period from the initial NDA submission. If 12 months of stability data is not available within the 30 days we will establish a shelf life based on the available stability data, considering the fast track nature of the break through therapy.

Meeting Discussion:

No further discussion required.

Question 2: Given the successful inspection history at the proposed commercial drug substance and drug product manufacturing facilities, the Applicant proposes waiving the traditional pre approval inspections for these three facilities. If it is the Agency's preference, Pfizer would welcome post-operational visits in lieu of the traditional preapproval inspections. Does the Agency agree with this proposal?

FDA response to Question 2:

It is the Agency's expectation that all firms submitted in the application are ready for inspection at the time of submission. On-site inspections in support of filed applications may occur at any time during the review cycle. The decision to perform a pre-approval inspection will take into account many factors including, but not limited to, the acceptability and timeliness of FDA's inspection history at the facility, the manufacturing complexity of the proposed operation, and the relatedness of the proposed process to the site's current operations. The decision will be made during the application review.

In order to facilitate our evaluation of manufacturing facilities and the determination of the need for pre-approval inspections, please explicitly clarify or confirm the duties of each proposed facility for commercial operations in support of the NDA.

Meeting Discussion:

The sponsor will provide the additional information requested in the NDA. The information will be reviewed accordingly.

Question 3: The Applicant would like to discuss with the Agency the most appropriate format for future interactions regarding CMC development topics that may arise prior to the anticipated NDA submission date. The applicant seeks additional guidance on how to engage in informal teleconferences and e-mail communication on this program. Given the Breakthrough Therapy designation, Pfizer requests to reduce the procedural timelines to request meetings and provide briefing packages for formal agency meetings from 4 weeks to not less than 2 weeks. Does the Agency agree with this proposal?

FDA Response Question 3:

We cannot commit to a specific time line as it depends on time and resources of the review staff. We do acknowledge that this is break through therapy and we take that into consideration as needed.

Meeting Discussion:

No further discussion required.

Question 4: Due to the anticipated commercial needs of the palbociclib capsules, the Applicant proposes conducting the drug product process validation for the two lower strength capsules (100 mg and 75 mg) using both printed capsule shells and non-printed capsule shells to allow use of these supplies in clinical studies. The applicant plans to place the printed and non-printed capsules on stability to satisfy the post approval stability commitment for the (b) (4) commercial batches. Does the Agency agree with this proposal?

FDA response to Question 4:

For post approval proposal, the above approach appears reasonable. However, please confirm the registrations batches are equivalent to the marketed drug product batches.

Regarding commercial process validation, the proposed process performance qualification (PPQ) plan to support commercial operations appears reasonable assuming that any effect that the capsule shell has on the commercial process is accounted for in the PPQ protocol and supporting studies. Additionally, data from stability studies in support of PPQ batches provide representative data in determining the success of PPQ activities. Changes to the process due to increased product and process knowledge should be accounted for and previous work used to support the PPQ should be justified. Please note that FDA does not approve process validation approaches, protocols, or number of specific batches used in process validation studies. The adequacy of the actual protocols, acceptance criteria and study outcomes will be evaluated during an inspection.

It is the company's responsibility to conduct all studies necessary to ensure that the commercial manufacturing process is capable of consistently delivering quality product. FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not stipulate the order of multiple sites' process validation activities. Prior to marketed product distribution it is necessary for firms to demonstrate that the intended manufacturing process will reliably reproduce the intended product for each individual site. Process performance qualification studies are evaluated during on-site inspections.

Please find more information in the Guidance for Industry, Process Validation: General Principles and Practices (January 2011).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

Meeting Discussion:

The sponsor clarified that the registration batches are equivalent to the marketed product, [REDACTED] (b) (4). Additionally, stability data will be collected for both printed and non-printed capsules.

Question 5: In order to ensure launch supplies are available at the time of approval, the Applicant plans to use the Pre-Launch Activities Importation Request (PLAIR) to import supplies prior to NDA approval. The Applicant requests specific guidance on how to apply for early importation when the NDA approval is expected to be in advance of the PDUFA date.

FDA response to Question 5:

A PLAIR only applies to unapproved finished dosage form drug products based on anticipated approval of a pending original application. The PLAIR is submitted within 60 days of expecting approval. For further information regarding a PLAIR submission, the following link includes the PLAIR process which may be provided to the firm.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM362177.pdf>

If the firm has other inquiries non-PLAIR related, it may be addressed to the following email address: CDERImportsExports@fda.hhs.gov. For PLAIR related, it may be sent to CDER-OC-PLAIR@fda.hhs.gov mailbox.

Meeting Discussion:

The sponsor acknowledged the information provided and plans to follow the FDA's recommended guidelines.

Question 6: Pfizer is providing the proposed dissolution method for palbociclib to the agency for comment. Does the agency agree with dissolution method and development rationale?

FDA response to Question 6:

Your proposed rationale for the dissolution method development appears reasonable; however, a final decision on the acceptability of the proposed dissolution method and acceptance criterion will be made during the NDA review when the complete data are available. Please ensure that your dissolution method development report clearly outline the sample size, testing conditions and raw data for each variable tested. In addition, details on the manufacturing process

variations for all (b) (4) formulations used to demonstrate the method's discriminating ability should be provided.

Any statistical assessments performed to support your proposed dissolution acceptance criterion should appropriately stratify the data, as pooling across different processes or studies (e.g., including accelerated stability data) may not be scientifically appropriate. The statistical analysis report and input data sets should also be available for FDA review upon request. Please consider the following points for setting the acceptance criterion of your proposed drug product.

1. For an immediate release product, the selection of the specification time point should be where $Q = \frac{(b)}{(4)}$ % dissolution occurs and based on the mean data for 12 samples or stage 2 testing.
2. The dissolution profile data from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value).

Meeting Discussion:

No further discussion required.

Question 7: A discussion of the drug product manufacturing learnings and process improvements is provided in the briefing document. Pfizer has made modifications to the (b) (4) post registration stability to optimize the process as described in this briefing document. Does the FDA agree that these changes can be implemented for the commercial process without the need for additional stability studies prior to commercialization?

In addition to the above questions, the Applicant is providing additional information on the CMC development program for the Agency's awareness and comment, as applicable.

FDA response to Question 7:

We recommend that you provided supportive stability data for manufacturer modification described above.

The FDA acknowledges the process improvements reflective in the improved (b) (4) for the 125mg strength capsules. Although the modification to the (b) (4) shows improved control of dissolution across the (b) (4), there is no dissolution data provided for the (b) (4). Also, based on information presented, it is unclear if (b) (4)

(b) (4) are being placed on stability. The agency requests that the sponsor submit the following:

1. (b) (4) batches at commercial scale (refer to page 27 and 28 of briefing package).
2. Provide clarification as to whether stability studies for commercialization will include (b) (4).

Upon receipt of this information, an evaluation will be conducted to determine the need for additional stability studies prior to commercialization.

Meeting Discussion:

The Sponsor clarified their stability data collection plans and noted that the registration stability batches were manufactured without the (b) (4). The Sponsor asked if additional information is needed prior to NDA submission, and FDA stated that no additional information is required prior to the NDA. The sponsor will provide any additional information in the NDA, and the information will be reviewed accordingly.

Question 8: In the written feedback from the End of Phase 2 CMC briefing document, the Agency requested additional information on the regulatory starting material designation. A summary of the RSM designation and justification have been provided in this package. The NDA will detail the overall control strategy for palbociclib drug substance and control of the drug substance starting materials.

FDA response to Question 8:

1. We have serious concerns for designation of (b) (4) as a regulatory starting material for the following reasons:

a. The provided information for the (b) (4) (b) (4) (b) (4) Additionally, the proposed specification may not be valid for future changes in vendors, raw materials, intermediates, synthetic routes, etc. for (b) (4).

b. The proposed specification for (b) (4) does not seem to include all possible known impurities from different possible routes from the very beginning of the synthesis, including, but not limited to, potential regio-isomers, and carryover impurities through the synthesis from raw materials, reagents, and unreacted intermediates.

c. The proposed test method may not be adequate for all potential impurities as mentioned in b. Additional test methods may need to be developed if any of the potential impurities can't be identified by the proposed test method.

d. The proposed acceptance criteria for impurities in (b) (4) may need to be adjusted based on b. and c.

We recommend you to reconsider your proposed regulatory starting material (e.g. (b) (4)) and its specifications. Alternatively, provide adequate rationale/justification to support your current proposal and to address these points listed above.

2. Based on the provided information in the meeting package, we view (b) (4) as an intermediate, and recommend you to consider (b) (4) as a starting material, considering the (b) (4) and the control of all possible potential impurities (associated with different routes and vendors in the future). Refer to comments above for (b) (4).

Meeting Discussion:

FDA reiterated their original response to the applicant regarding the starting materials designation. The sponsor will provide additional information in the NDA. The information will be reviewed accordingly.

Question 9: The Applicant has provided the draft drug substance and drug product release specifications for the Agency's review and comment in [Appendix 2](#) and [Appendix 4](#).

FDA response to Question 9:

In general, as the development proceeds, the proposed acceptance criteria for drug substance and drug product specifications need to be adjusted, supported and justified by your batch data, manufacturing experience/capability, and a complete scientific rationale.

We have the following specific concerns:

Drug substance

1. List of organic impurity levels

Please note: besides individual specified, individual unspecified and total impurities, individual specified identified and individual specified unidentified impurities need to be listed. Refer to ICH Q3A. Alternatively, provide justifications for not listing these impurities.

Provide a justification in your NDA submission for the proposed drug substance acceptance criteria of (b) (4) % and (b) (4) % for (b) (4) and (b) (4) organic impurities, respectively. We cannot comment on the acceptability of these drug substance impurity specifications prior to our review of data from nonclinical toxicology studies and clinical trials and CMC information including batch analyses for batches used in these studies.

Drug product

1. List of degradation products

Please note: besides any unspecified and total degradation products, individual specified identified degradation product and individual specified unidentified degradation product need to be listed. Refer to ICH Q3B. Alternatively, provide justifications for not listing these degradation products.

2. Omitting (b) (4) test

3. The dissolution acceptance criterion (refer to question 6)

Meeting Discussion:

The applicant will provide additional information and justification for their specifications in the NDA.

Question 10: Based on available stability data and product knowledge, we anticipate proposing a lean post-approval stability proposal in the NDA with supporting justification. The draft post-approval stability proposals for drug substance and drug product are presented in [Appendix 5](#) and [Appendix 6](#).

FDA response to Question 10:

Please include the following

- 1. Tests for *Appearance, Assay, Impurities*, and (b) (4) in your proposed post-approval stability protocol for drug substance in the retest period confirmation testing and annual testing.**
- 2. Tests for *Microbial Limits* and (b) (4) in your proposed post-approval stability protocol for drug product in the retest period confirmation testing and annual testing. Alternately, provide justifications for omitting these tests in the protocol. See comments below from microbiology.**
- 3. Test intervals at 3 months, 6, months, 9 months, and 18 months in the proposed stability protocol for both drug substance (at 25°C/60 %RH) and drug product (at 30°C/75% RH) in the retest period confirmation testing.**

Refer to ICH Q1A (R2) Section 2.1.8 for guidance on post approval stability studies

Microbiology comment:

You propose waiving microbial limits release testing for your drug product. This proposal may be acceptable provided adequate (b) (4) controls are established and documented. More information on your process is needed. Address the following points.

- 1. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.**
- 2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.**
- 3. Describe activities taken when microbiological acceptance criteria are not met at control points.**

In addition to these points, address the following:

- 1. Provide the results of microbial limits testing performed on exhibit or stability batches of the drug product.**
- 2. You should minimally perform microbial limits testing at the initial stability testing time point.**

Meeting Discussion:

The applicant will provide additional information and justification for their stability program in the NDA.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no specific issues requiring further discussion at this time.

4.0 ACTION ITEMS

There are no specific due dates or time lines for submission of information or other action items.

5.0 ATTACHMENTS AND HANDOUTS

Handout provided by Pfizer on January 23, 2014, see attached.

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

/s/

HARIPADA SARKER

02/11/2014

Sign-off on behalf of Ali Al Hakim



IND 069324

MEETING MINUTES

Pfizer, Inc.
10646 Science Center Drive
San Diego, CA 92121

Attention: Michelle Yu-Kite, M.S., RAC
Senior Manager, Worldwide Regulatory Strategy

Dear Ms. Yu-Kite:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Palbociclib (PD-0332991).

We also refer to the teleconference between representatives of your firm and the FDA on December 17, 2013. The purpose of the meeting was to reach agreement on the content and format of the NDA to support the proposed indication: “Palbociclib in combination with letrozole is indicated for the treatment of postmenopausal women with estrogen receptor-positive (ER [+])/human epidermal growth factor receptor 2 (HER2)-negative ^{(b) (4)} advanced or metastatic breast cancer who have not received previous systemic treatment for their advanced disease.”

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 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

Patricia Cortazar, M.D.
Clinical Team Leader, Breast Oncology Group
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 (Format and Content)

Meeting Date and Time: December 17, 3:00 p.m.
Meeting Location: White Oak Bldg. 22, Rm. 5201

Application Number: IND 069324
Product Name: Palbociclib (PD-0332991)
Indication: Palbociclib in combination with letrozole is indicated for the treatment of postmenopausal women with estrogen receptor-positive (ER [+])/human epidermal growth factor receptor 2 (HER2)-negative ^{(b) (4)} advanced or metastatic breast cancer who have not received previous systemic treatment for their advanced disease

Sponsor/Applicant Name: Pfizer, Inc.

Meeting Chair: Patricia Cortazar, M.D., 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
Laleh Amiri-Kordestani, M.D., Clinical Reviewer, DOP1
Patricia Cortazar, M.D., Clinical Team Leader, DOP1
Amy McKee, M.D., Clinical Team Leader, DOP1
Wei Chen, Ph.D., Pharmacologist/Toxicologist, DHOT
Todd Palmby, Ph.D., Supervisory Pharmacologist/Toxicologist, DHOT
Sarah J. Schrieber, Pharm.D., Clinical Pharmacology Reviewer, DCPV
Somesh Chattopadhyay, Ph.D., Biometrics Reviewer, DBV
Jibril Abdus-Samad, Senior Regulatory Review Officer, Division of Medication Error Prevention and Analysis, OSE
Frances Fahnbulleh, R.Ph., Pharm.D., Safety RPM, OSE
Cynthia LaCivita, Pharm.D., Drug Risk Management Analyst Team Leader, Division of Risk Management, OSE
Frank Cross, Jr., M.A., MT (ASCP), Senior Regulatory Health Project Manager, DOP1

SPONSOR ATTENDEES

Eric Kowack, M.S., MBA, Asset Team Leader, Pfizer, Inc.
Heather Neumann, DVM, PM, Submission Team Lead, Pfizer, Inc.
Maria Koehler, M.D., Ph.D., Integrated Development Leader for Palbociclib, Pfizer, Inc.
Sophia Randolph, M.D., Ph.D, Global Clinical Lead, Pfizer, Inc.
Sindy Kim, A5481003 Clinical Lead, Pfizer, Inc.
Yuqiu (John) Jiang, Ph.D., Translation Oncology Lead, Pfizer, Inc.
Walter Greg Roberts, Ph.D., Safety Risk Lead, Pfizer, Inc.
Xin Huang, Ph.D., Statistical Lead, Pfizer, Inc.
Diane Wang, Ph.D., Clinical Pharmacology Lead, Pfizer, Inc.
Ramzi Dagher, M.D., Head, Worldwide Regulatory - Oncology, Pfizer, Inc.
Albert Kraus, Ph.D., Global Regulatory Portfolio Lead, Women's and Hematological Cancers
Patrizia Salmoiraghi, Global Regulatory Lead, Pfizer, Inc.
Michelle Yu Kite, M.S., RAC, US Regulatory Lead, Pfizer, Inc.
Rebecca Hintze, Oncology Programming Lead, Pfizer, Inc.
Helen Yang, Oncology Programming, Pfizer, Inc.
Lisa Dunne, Submissions Manager, Pfizer, Inc.
Natasha Bartash-Price, Development Operations Asset Lead, Pfizer, Inc.
Aida Sacaan, Ph.D., Nonclinical Drug Safety Research and Development Lead, Pfizer, Inc.

1.0 BACKGROUND

Palbociclib (PD-0332991, Investigational New Drug Application (IND) 069324, is a Cyclin-Dependent Kinase [CDK] 4/6 Inhibitor. Palbociclib is in phase 2 and 3 trials in ER-positive breast cancer. The Sponsor requested a Type B pre- New Drug Application (NDA) meeting to discuss a NDA submission based on the anticipated results of the study A5481003 (Paloma 1). The results of this study are expected in February 2014. A5481003 (Paloma 1) is, Phase 1/2, open label, randomized study of safety, efficacy and pharmacokinetics of letrozole plus palbociclib and letrozole single agent for the first line treatment of ER positive, HER2 negative advanced breast cancer in postmenopausal women. The study is ongoing but recruitment is complete. Under the assumption that this study meets its primary endpoint (investigator assessed PFS) and blinded independent central review (BICR) confirms the results, with an acceptable benefit-risk, it will be submitted as the pivotal study to support a NDA.

The purpose of this Type B Pre-NDA meeting is to reach agreement on the content and format of the NDA to support the proposed indication: "Palbociclib in combination with letrozole is indicated for the treatment of postmenopausal women with estrogen receptor-positive (ER [+])/human epidermal growth factor receptor 2 (HER2)-negative (b) (4) advanced (b) (4) metastatic breast cancer who have not received previous systemic treatment for their advanced disease." The Sponsor would like to seek our feedback on the overall approach to the NDA filing and on the content and format of Modules 1, 2, 4, and 5 of the application. Pfizer plans to schedule a second pre-NDA meeting after the results of the pivotal study are available.

2. DISCUSSION

2.1. General

Question 1: Does the Agency agree with the proposed content of the NDA as presented in the background package?

FDA Response: The proposed information provided in the package is insufficient for us to respond.

Pfizer Response: Please note that the top-line results for the pivotal study will be provided in February 2014. We also acknowledge and will provide the requested information detailed in response to Question 5 and 7. Are there any further information that we can provide to FDA to ensure the proposed content of the NDA is appropriate?

Discussion: FDA clarified that additional details on the content of Module 5 as well as the information referenced in the Table of Contents, should be submitted in the February Briefing Package.

Question 2: Does the Agency agree with the Sponsor's plans to modeling the Guidance for Industry entitled, "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document" dated April 2009, Section V.D – Example 4, for the Summary of Clinical Efficacy and the Summary of Clinical Safety to meet the requirements of the Integrated Summary of Efficacy and the Integrated Summary of Safety, respectively?

FDA Response: The ISE and ISS can be split across Module 2 and Module 5, with the narrative portion located in section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in section 5.3.5.3. If the ISE or ISS is split across modules in this way, it is critical to include a clear explanation of where the parts are located with hyperlinks. This explanation should be placed both in Module 2 (section 2.7.3 or 2.7.4) and in Module 5 (section 5.3.5.3). We remind you that the ISE/ISS should have sufficient detail to support an NME.

2.2. DATA POOLING

Question 3:

(b) (4)

FDA Response: No. We recommend that you pool the safety data only from studies with similar patient populations, similar disease status and baseline risk factors. In addition, do not pool safety data from monotherapy and combined therapy studies.

Pfizer Response: Thank you and we amend our pooling strategy based on your feedback. This includes providing separate safety data for the two Phase 1 Studies A5481001 and A5481002. And for the IIRs we will add an additional group per your guidance to separate the monotherapy and non-chemotherapy combinations.

Also, just for confirmation, for the Phase 1/2 A5481003, we will provide the safety data as both pooled and separate for the Phase 2 Part 1 and Phase 2 Part 2.

Discussion: FDA stated that the Sponsor's proposal is acceptable.

2.3. SAFETY UPDATE

Question 4: Does the Agency agree with the Sponsor's request to provide a 60-day safety update during the review period instead of a 120-day safety update. The safety update will be provided 60-days following the NDA submission date.

FDA Response: The timing of the submission of the safety update will be determined at the pre-submission meeting.

Pfizer Response: For clarity, our next meeting to discuss the top-line results has been requested in late Feb which is 4 months from our targeted NDA submission date. To anticipate the activities to support the submission of the safety update, would this next meeting be an appropriate time to ask this question again?

Discussion: FDA will answer this question during the meeting to discuss the top-line results.

Question 5: Does the Agency agree with the criteria for providing the patient narratives and Case Report Forms (CRF; treatment-related serious adverse events, discontinuations due to adverse events, and deaths) in the NDA, as described in Section 10.5?

FDA Response: No. You should provide the following:

- patient narratives for all patients who experience any serious adverse event, regardless of causality.
- all the CRFs from the pivotal trial.

We recommend that you provide us with a blank CRF with the briefing package for the next meeting.

Pfizer Response: Thank you for your feedback, we will provide the requested narratives and CRFs in the NDA submission.

For clarification, regarding the blank CRF, would FDA prefer the full or unique pages? The full set includes duplicate pages such as each potential cycle of treatment. The blank CRF will not include annotations, however, the blank CRF that we provide in the NDA will include annotations.

Rather than providing in the next briefing document (next BD would be 14 February 2014), we propose to provide the blank CRF the week of 20 January 2013 as a follow up to this meeting under an information amendment to the IND.

Discussion: FDA stated that the Sponsor's proposal is acceptable. Since the blank CRFs and the mock define files are large, these could be provided electronically.

2.4. RADIOGRAPHIC IMAGES

Question 6: Does the Agency agree with Pfizer's proposal provide radiographic images (PDF) from the independent radiologic review upon request during the NDA review process?

FDA Response: Yes.

2.6 PROGRAMMING

Question 7: The Sponsor proposes non-CDISC format of SAS Datasets for Clinical Study Report (CSR) and pooled safety data, including .xpt files, define.pdf, and annotated CRFs (where available), as well as Text (.txt), and documentation (*.pdf files) for pharmacokinetic modeling and simulation output. Does the Agency agree with the types and format of datasets to be included in the NDA submission?

FDA Response: For the next pre-NDA meeting package, please provide:

- A list of the raw and derived datasets you are planning to submit in the NDA.
- A mock define file to show variables to be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons for censoring, dates of PFS event or censoring and variables for subgroups analyses, etc. Variables for sensitivity analyses should be included as well.

At the time of the NDA submission, provide the SAS programs used for analyses. In addition, provide a derived response dataset that has one record of response (CR, PR, SD, PD or NA) per visit per patient.

We also refer you to the following pharmacometric data and models submission guidelines at <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm>.

Pfizer Response: *Pfizer's standard practice is to submit the derived datasets which include both the raw collected data as well as any derivations as a single dataset. A list of these datasets and a mock define file of the efficacy datasets for Study A5481003 will be provided to FDA the week of the 20 January 2013 as a follow up to this meeting under an information amendment to the IND. Pfizer will also submit the SAS programs used for efficacy analyses for Study A5481003 as well as the additional derived response dataset requested with the NDA submission. Does FDA agree with this approach?*

Discussion: FDA stated that the proposal for combining the raw and derived data sets may be acceptable. However, FDA would like to review the mock define file to further advise the Sponsor. Also, this information should be submitted with the February Meeting Briefing Package.

2.7 CLINICAL PHARMACOLOGY

Question 8: Does the Agency agree with the proposal for the presentation of clinical pharmacology data, as described in the background package?

FDA Response: Yes, we agree with your proposal.

Question 9: The population pharmacokinetic and exposure/electrocardiogram analysis report will be included in the Summary of Clinical Pharmacology, however, the population pharmacokinetic/pharmacodynamic assessments for neutropenia and thrombocytopenia, and exposure/response analysis for progression-free survival (PFS) will be excluded from the Summary of Clinical Pharmacology and the Clinical Overview but will be included as stand-alone documents. Does the Agency agree with this proposal as described in Section 10.8?

FDA Response: We agree with your proposal to submit a stand-alone exposure-response (ER) analysis report for safety and efficacy.

For the ER analysis for PFS, both univariate and multivariate analysis adjusting for baseline risk factors should be conducted. In addition, case-control analysis should be conducted to support the proposed dosing regimen (Jun Yang et. Al., The combination of exposure-response and case-control analysis in regulatory decision making, Journal of Clinical Pharmacology, 53 (2) 160-168 (2013)).

Pfizer Response: *The sponsor appreciates the Agency's request of conducting case-control analysis in combination with the exposure/response analysis to account for potential confounding effect resulted from the imbalance in confounding risk factors of PFS between the low and high dose/exposure groups. The sponsor will carefully evaluate the potential confounding risk factors for PFS. If the confounding risk factors are balanced between the low and high dose/exposure groups, the sponsor will not apply case-control analysis to the exposure/response analysis. If the confounding risk factors*

are found to be imbalanced between the low and high dose/exposure groups, the sponsor will conduct the analysis as requested by the agency. However, in the case that case-control analysis is conducted, this part of the analysis will not be included in the initial NDA submission, but will be submitted within 30 days of the initial submission. Does the agency agree with the proposal and in the event the case-control analysis is submitted, it will not affect the PDUFA review clock or FDA's ability to determine the filability of the application?

FDA Response: We are unable to discuss Question 9 during this meeting, and will follow-up with more written responses if needed.

We generally agree with your proposal. While it appears unlikely, at this time, that a less than 30 day delay of the submission of the report will impact fileability of the application, we are unable to provide a definitive response. We strongly recommend that you submit a complete application with the initial submission.

Discussion: Additional followup around this topic may be provided during the meeting to discuss the top line results.

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>.

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/

PATRICIA CORTAZAR
12/23/2013



IND 069324

MEETING MINUTES

Pfizer, Inc.
10646 Science Center Drive
San Diego, CA 92121

Attention: Michelle Yu-Kite, M.S., RAC
Senior Manager, Worldwide Regulatory Strategy

Dear Ms. Yu-Kite:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Palbociclib (PD-0332991).

We also refer to the meeting between representatives of your firm and the FDA on November 14, 2013. The purpose of the meeting was to present a comprehensive overview of the palbociclib development program.

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

If you have any questions, call 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

Patricia Cortazar, M.D.
Clinical Team Leader, Breast Oncology Group
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Meeting Minutes
Sponsor Slides



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Breakthrough Meeting follow-up

Meeting Date and Time: November 14, 2013, 11:00 a.m.
Meeting Location: White Oak Bldg. 22, Rm. 1315

Application Number: IND 069324
Product Name: palbociclib (PD-0332991)
Indication: In combination with letrozole for the treatment of postmenopausal women with ER+ and HER2- advanced breast cancer

Sponsor/Applicant Name: Pfizer, Inc.

Meeting Chair: Patricia Cortazar, M.D., Clinical Team Leader, DOP1
Meeting Recorder: Amy Tilley, Regulatory Project Manager, DOP1

FDA ATTENDEES

Anthony J. Murgo, M.D., M.S., FACP, Acting Director, DOP1, Associate Office Director for Regulatory Science, OHOP
Amna Ibrahim, M.D., Deputy Division Director, DOP1
Laleh Amiri-Kordestani, M.D., Clinical Reviewer, DOP1
Julia Beaver, Clinical Reviewer, DOP1
Patricia Cortazar, M.D., Clinical Team Leader, DOP1
Amy McKee, M.D., Clinical Team Leader, DOP1
Tatiana Prowell, M.D., Clinical Reviewer, DOP1
Nancy Scher, M.D., Clinical Reviewer, DOP1
Wei Chen, Ph.D., Pharmacologist/Toxicologist, DHOT
Todd Palmby, Ph.D., Supervisory Pharmacologist/Toxicologist, DHOT
Qi Liu, Ph.D., Clinical Pharmacology Team Leader, DCPV
Somesh Chattopadhyay, Ph.D., Biometrics Reviewer, DBV
Shenghui Tang, Ph.D., Biometrics Team Leader, DBV
Jibril Abdus-Samad, Senior Regulatory Review Officer, Division of Medication Error Prevention and Analysis, OSE
Shawnetta Jackson, MS, OSE Public Health Analyst
Amy Tilley, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Mace L. Rothenberg, M.D., Senior Vice President, Clinical Development and Medical Affairs, Pfizer, Inc.
Eric Kowack, M.S., MBA, Asset Team Leader, Pfizer, Inc.

Maria Koehler, M.D., Ph.D., Integrated Development Leader for Palbociclib, Pfizer, Inc.
Sophia Randolph, M.D., Ph.D, Global Clinical Lead, Pfizer, Inc.
Ramzi Dagher, M.D., Head, Worldwide Regulatory - Oncology, Pfizer, Inc.
Michelle Yu Kite, M.S., RAC, US Regulatory Lead, Pfizer, Inc.
Xin Huang, Ph.D., Statistical Lead, Pfizer, Inc.
Diane Wang, Ph.D., Clinical Pharmacology Lead, Pfizer, Inc.
Walter Greg Roberts, Ph.D., Safety Risk Lead, Pfizer, Inc.
Aida Sacaan, Ph.D., Nonclinical Drug Safety Research and Development Lead, Pfizer, Inc.
Daniel R. Arenson, Ph.D., Pharmaceutical Sciences Team Lead, Pfizer, Inc.
Susan C. Berlam, R.Ph., MS, Global Regulatory CMC, Pfizer, Inc.
Yuqiu (John) Jiang, Ph.D., Translation Oncology Lead, Pfizer, Inc.

1.0 BACKGROUND

Pfizer has requested this meeting to provide an overview of the palbociclib breast cancer program and seeks agency's advice to further accelerate their program. Palbociclib (PD-0332991, IND #69,324) is an oral cyclin-dependent kinase (CDK) 4 and 6 inhibitor. Based on the preliminary results of a Phase 1/2 data of study A5481003, Breakthrough Therapy designation was granted to palbociclib on April 09, 2013. Pfizer is planning to submit the final results of this phase 2 study to support the accelerated approval of palbociclib in combination with letrozole. The confirmatory Phase 3 (A5481008) study of palbociclib in combination with letrozole in women with ER+/HER2 negative advanced breast cancer (i.e., similar to the A5481003 Phase 2 study population) has started in March 2013. Additionally, two other phase 3 trials are planned. A5481023 trial is in patients with recurrent or metastatic disease and PENELOPE is a trial in adjuvant setting for early breast cancer patients with high risk of recurrence.

2.1. Clinical/Biostatistics

Question 1: During the End-of-Phase 2 meeting on 05 September 2012, FDA suggested inclusion of an early efficacy analysis for Phase 3 trial A5481008. Reference is made to the final protocol for the Phase 3 (A5481008) study submitted on 27 November 2012. The interim analysis would be conducted when $\frac{(b)}{(4)}$ % of intended final analysis PFS events have occurred.

Does FDA want to be informed of the results of top line interim Phase 3 A5481008 results (prior to availability of complete datasets and study report) if available during the A5481003 Phase 2 data based NDA review? Could this additional information impact the initial review and/or label?

FDA Response to Clinical/Biostatistics Question 1: Yes, we would like to see the top line results from the Phase 3 (A5481008) study as this may impact the review of the NDA. As you state, you should reach $\frac{(b)}{(4)}$ % of the PFS events as planned for the interim PFS analysis.

Meeting Discussion: The Sponsor clarified that the interim analysis would probably not be available at the time of the NDA submission and review cycle. Additional data from the phase 3 trial will not be required before the results of the interim analysis are available.

Question 2: Reference is made to the revised Statistical Analysis Plan (SAP) and independent review committee charter for the Phase 3 (A5481023) study submitted on 06 September 2013. Similar to the interim analysis for efficacy proposed for the Phase 3 A5481008 and PENELOPE studies we plan to include an efficacy evaluation at the already incorporated interim analysis currently supporting futility, safety, and sample size adjustment analyses for the A5481023 study. This interim analysis would be conducted when $\frac{(b)}{(4)}$ % proportion of primary endpoint events have occurred.

Question 2(a): Does FDA agree, that should the primary endpoint of progression-free survival (PFS) based on investigator assessment be met for the A5481023 study at the time of interim analysis (and supported by an agreed blinded independent radiology assessment approach), with an acceptable safety profile, it could serve as an adequate experience in relapsed advanced breast cancer to support a future NDA or sNDA?

FDA Response to Clinical/Biostatistics Question 2(a): This will be a review issue. Please note that an interim PFS analysis may not provide an accurate or reproducible estimate of the treatment effect size due to inadequate follow-up, missing assessments, disagreements between radiological reviewers and/or disagreements between investigator and independent assessments. As documented in literature, interim results overestimate the treatment effect.

Meeting Discussion: None

Question 2(b): Positive interim analysis results from A5481023 study in recurrent metastatic breast cancer could become available during the review of the initial NDA examining palbociclib in newly diagnosed metastatic breast cancer based on A5481003 study. What would be the mechanism for this Breakthrough Therapy-designated product, to expedite the submission of the additional Phase 3 study data (A5481023) also in HR (+)/HER2-negative metastatic breast cancer but in a later line of therapy and in combination with fulvestrant? Could this new information impact the initial review/and or label?

FDA Response to Clinical/Biostatistics Question 2(b): This will be a review issue. The new information may impact the initial review. We would like to clarify that the breakthrough designation is for first-line metastatic breast cancer indication.

Meeting Discussion: None.

Question 3: Does FDA have suggestions on any areas that the sponsor should adjust further within the Breakthrough Therapy program that may accelerate the development and registration of palbociclib in breast cancer?

FDA Response to Clinical/Biostatistics Question 3: Not at this time. As previously discussed, prior to submission of your NDA, we would like to have a meeting with you to discuss updated topline results from Study A5481003 and whether this new data continues to support the present results.

Meeting Discussion: The Sponsor stated that the top line results will be available to the FDA by mid February 2014. The Sponsor will request a meeting with the FDA as soon as possible.

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

Sponsor Slides.

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/s/

PATRICIA CORTAZAR
12/09/2013



IND 069324

MEETING MINUTES

Pfizer, Inc.
10646 Science Center Drive
San Diego, CA 92121

Attention: Michelle Y. Kite, M.S., RAC
Senior Manager, Worldwide Regulatory Strategy

Dear Ms. Kite:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PD-0332991.

We also refer to the meeting between representatives of your firm and the FDA on May 17, 2013. The purpose of the meeting was to reach agreement on the statistical analysis plan, safety information and central review of radiology data for the Phase 2 study and to discuss presentation and content for a proposed NDA submission (Pre-NDA).

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

If you have any questions, call Christy Cottrell, Regulatory Project Manager at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

Patricia Cortazar, M.D.
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA (Clinical & Statistics only)

Meeting Date and Time: May 17, 2013 at 11:00 am
Meeting Location: WO22, Room 1311

Application Number: IND 069324
Product Name: PD-0332991
Indication: In combination with letrozole for the treatment of postmenopausal women with ER-positive/HER2-negative (b) (4) advanced (b) (4) metastatic breast cancer who have not received previous systemic treatment for their advanced disease

Sponsor/Applicant Name: Pfizer, Inc.

Meeting Chair: Patricia Cortazar, M.D.
Meeting Recorder: Christy Cottrell

FDA ATTENDEES

Richard Pazdur, M.D., Director, OHOP
Robert Justice, M.D., M.S., Director, DOP1 (internal pre-meeting only)
Amna Ibrahim, M.D., Deputy Director, DOP1
Patricia Cortazar, M.D., Clinical Team Leader, DOP1
Laleh Amiri-Kordestani, M.D., Clinical Reviewer, DOP1
Rajeshwari Sridhara, Ph.D., Director, DB5 (internal pre-meeting only)
Shenghui Tang, Ph.D., Biometrics Team Leader, DB5
Somesh Chattopadhyay, Ph.D., Biometrics Reviewer, DB5
Cynthia LaCivita, Lead Pharmacist, OSE
Thomas Gwise, Ph.D., Deputy Director, DB5
Christy Cottrell, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Mace L. Rothenberg, M.D., Sr. Vice President, Clinical Development & Medical Affairs
Eric Kowack, M.S., M.B.A., PD-0332991 Asset Team Leader
Maria Koehler, M.D., Ph.D., Vice President, Strategic and Scientific Assessment
Sophia Randolph, M.D., Ph.D., PD-0332991 Global Clinical Lead
Sindy Kim, PD-0332991 Clinical Study Lead
Walter Greg Roberts, Ph.D, PD-0332991 Safety Risk Lead
Albert Kraus, Ph.D., Global Regulatory Portfolio Lead, Women's & Hematological Cancers
Ramzi Dagher, M.D., Head, Worldwide Regulatory – Oncology
Michelle Yu Kite, M.S., RAC, US Regulatory Lead
Xin Huang, Ph.D., Statistics Lead

BACKGROUND

Pfizer requested a Type B Pre-NDA meeting to discuss a future submission of an NDA in 2014 to support Accelerated Approval of PD-0332991 (palbociclib) for the proposed indication of:

“PD-0332991 in combination with letrozole for the treatment of postmenopausal women with estrogen receptor-positive (ER [+]) and human epidermal growth factor receptor 2 (HER2) negative ^{(b) (4)} advanced or metastatic breast cancer”. The proposed NDA submission is based on the results of their Phase 1/2 study A5481003, entitled “*Phase 1/2, Open-label, Randomized Study of the Safety, Efficacy, and Pharmacokinetics of Letrozole Plus PD-0332991 (oral CDK 4/6 Inhibitor) and Letrozole Single Agent for the First-Line Treatment of ER(+)/HER2-Negative Advanced Breast Cancer in Postmenopausal Women*”. A confirmatory Phase 3 trial is currently enrolling and is expected to be near completion of enrollment at the time of NDA submission.

The Phase 2 portion of Study A5481003 is divided into two cohorts. Cohort 1 is designed to assess the efficacy and safety of the combination of letrozole plus PD-0332991 compared to single agent letrozole in an unselected ER(+)/HER2-negative advanced breast cancer population, and Cohort 2 is designed to evaluate tumor response in prospectively selected biomarker-positive (cyclin D1 [CCND1] amplification and/or p16 loss) patients. This study has a primary endpoint of progression-free survival (PFS) by investigator assessment. Two interim analyses of the Phase 2 data have been conducted with data cut-offs in January and July 2012, with the most recent analysis including a total of 165 patients randomized.

This meeting was requested to reach agreement on the statistical analysis plan, safety information, and central review of radiology data of the Phase 2 study in support of the proposed NDA submission. In addition, the applicant wanted to discuss early efficacy analysis in the Phase 3 confirmatory trial, as well as presentation and content for a near term proposed NDA for Accelerated Approval.

Draft responses were sent to the applicant on May 14, 2013.

DISCUSSION

1. Improvements in PFS (by investigator assessment and supported by BICR) for the final analyses from the 2 independently randomized cohorts from Study A5481003 demonstrate a clinical benefit over current standard of care therapy for patients with ER (+)/HER2-negative metastatic breast cancer. Additionally, a global randomized Phase 3 trial is currently enrolling to confirm the clinical benefit demonstrated in Study A5481003.

Does the Agency agree that statistically significant and clinically meaningful improvement in PFS in the randomized Phase 2 study cohorts in Study A5481003 and in the context of an acceptable safety profile, would be adequate to support submission of an NDA for consideration of accelerated approval under Subpart H in this indication?

FDA RESPONSE: We are willing to accept the NDA submission based on the top line results from Study A5481003 as they appear to be promising, pending review of your complete NDA submission. Prior to submission, we would like to have a meeting with you to discuss updated topline results and whether this new data package continues to support the present results. We note that there have been multiple looks at this data which may make interpretation from a statistical point of view difficult. Please provide your plans for a robust statistical analysis plan of this data, particularly, the

interpretation of your p-value in light of the multiple analyses and ad hoc changes.

If you believe that a delay in the final analysis will deprive breast cancer patients from a therapy that will provide substantial clinical benefit, then we encourage you to open an expanded access program.

***MEETING DISCUSSION:** The applicant proposed a gatekeeping strategy to maintain statistical rigor. The proposal includes a plan to analyze the study as a whole and if positive, then move to individual cohort analyses. As the final analysis has not yet taken place, the applicant considers this to be a pre-specified analysis. The Division recommended to conduct the analysis as two separate studies since duplication of results in the second study could be a strength of this application package. The Division cautioned the applicant that interpretation of p-values will be difficult since there have already been multiple looks at the data making the analysis not entirely pre-specified. In general, the Division noted that a gatekeeping approach is acceptable, but ultimately will be a review issue.*

The applicant deferred detailed discussion of expanded access until the next Pre-NDA meeting (as requested in FDA's response to Question 1).

2. The A5481003 study aims to detect a hazard ratio (HR) = 0.67 with 80% power and 1-sided significance level of 0.10. Based on the event rate evaluation and the observed effect size from the 2 interim analyses, PFS events are being observed at a slower pace than originally hypothesized and the determination of 114 events for the final analysis may be overestimated. In addition, despite the available patients who remain follow up, 114 PFS events may not be accumulated in a practical timeframe. However, delaying the final analysis for 114 events to occur may seriously compromise the potential substantial clinical benefit that PD-0332991 plus letrozole treatment could provide for breast cancer patients. Therefore, the Sponsor proposes that the final analysis of the primary endpoint PFS will be performed when approximately 90 events have occurred. With 90 events there will be more than 97% power to detect a HR of 0.50 at 1-sided 10% level or a 72% power to detect a HR of 0.67. It is estimated that approximately 50 PFS events would be observed in Cohort 2 (N = 99) at the final analysis. This would assure maturity of both Cohort 1 and Cohort 2 data and allow a reasonable estimate of median PFS in separate analyses for both cohorts. At final analysis all additional analyses as per amended SAP will be performed and included in the Clinical Study Report (CSR). The protocol will also be amended to update the change from 114 events to approximately 90 events for the final analysis. This final analysis is anticipated 2H2013.

Does the FDA agree with the proposed SAP amendment (see Appendix 7 and Section 9.2.7 in this briefing document) including the proposed plan for the updated final analysis?

FDA RESPONSE: No. We do not agree to decrease the number of PFS events to 90. This proposal is based on the observed data and is not pre-planned. Please also let us know when you expect to have the pre-specified 114 events for the PFS data to mature.

***MEETING DISCUSSION:** The Division proposed to revisit this discussion at the next*

Pre-NDA meeting when additional data is available (end of 2013). The applicant noted that they accept the risk and will continue to plan for an analysis when approximately 90-95 events have occurred. Whether the FDA will support filing of an application based on this data will be discussed at the next Pre-NDA meeting (as requested in FDA's response to Question 1).

3. In response to the FDA request to conduct separate analyses of the 2 patient cohorts of the Phase 1/2 (A5481003) study, the Sponsor proposes to amend the SAP prior to an upcoming final analysis. Details are provided in Appendix 7 and can be summarized as follows: In addition to final analysis of the primary PFS endpoint for all randomized patients in Cohort 1 (N = 66) and Cohort 2 (N = 99) based on the investigator assessment, analyses for the 2 cohorts separately are added with a formal hypothesis testing procedure. Therefore, individual inference of all randomized patients (Cohort 1 and Cohort 2 combined), Cohort 1 and Cohort 2 separately can be made by controlling the type 1 error rate. The significance level for the final PFS analysis will be adjusted for 2 previous interim analyses. At the final analysis of the primary endpoint PFS, a gate-keeping procedure will be used for hypotheses testing in a hierarchical approach to control the family-wise error rate. The testing begins with all randomized Intent-to-Treat subjects (N = 165). If the null hypothesis can be rejected, then the Holm's step down procedure will be used to test the hypotheses for Cohort 1 and Cohort 2 as 2 individual study cohorts.

Does FDA agree with the proposed SAP amendment including the plan to analyze the 2 randomized Phase 2 trial cohorts separately?

FDA RESPONSE: Your statistical plan is data-driven and not pre-specified.

MEETING DISCUSSION: See discussion for Question 1.

4. During the End of Phase 2 meeting on 05 September 2012, the FDA recommended that the Sponsor conduct a BICR of the scans for the Phase 2 study (A5481003) as soon as possible. Pfizer has initiated an analysis of the BICR of radiographic data from the previously reported interim efficacy data (data cut of July 2012). As described in the BICR Charter, discordances in date of progression between the 2 radiologists are adjudicated by a third radiologist. Complete BICR data for Study A5481003 will be included in the NDA and the analysis performed based on the BICR assessed PFS data is considered a secondary analysis with an appropriate set of sensitivity analyses to support the primary analysis of investigator assessment.

a) Does the Agency agree with the plan and methodology for a BICR for all randomized patients in Phase 2 portion of Study A5481003 as defined in the BICR Charter (Appendix 6)?

FDA RESPONSE: This is acceptable. BICR assessments should be done on 100% of the patients.

MEETING DISCUSSION: None.

b) Does the Agency agree with the analysis of BICR as a secondary analysis as defined in the proposed SAP, including planned sensitivity analyses (defined in Section 8.1.4 of proposed SAP amendment (Appendix 7))?

FDA RESPONSE: Given the size of the study and the unplanned analysis, the BICR analysis should be the primary analysis.

MEETING DISCUSSION: *The applicant expressed concern about changing to BICR analysis as the primary analysis at this time since there would be many differences if the study were prospectively designed with BICR as the primary analysis (e.g., sample size would be much larger, more censoring, etc). The applicant noted that they do not anticipate discrepancy between BICR and investigator assessed PFS. The Division stated that if the applicant keeps PFS by investigator assessment as the primary analysis, they will need to provide a convincing argument that minimal bias is present.*

5. By the time of the NDA submission, clinical experience will consist of data for approximately 550 subjects and will include safety data for more than 300 patients or subjects who will have received PD-0332991 in Pfizer sponsored trials. Of these, 74 subjects were treated in Study A5481001, 17 subjects in Study A5481002, 95 subjects in Study A5481003 (in combination with letrozole), 51 subjects in Study A5481004 (in combination with bortezomib/dexamethasone) and ~50 subjects in clinical pharmacology studies. In addition, 12 subjects treated with single agent PD-0332991 are enrolled in the ongoing A5481010 Japan only study with an anticipated total accrual of 18 subjects. Of the ~550 subjects, an estimated 250 to 300 subjects will have received PD-0332991 plus letrozole on the current Phase 3 breast cancer trial. Supplemental safety information (i.e., serious adverse events) will also be provided from approximately 600 subjects enrolled in other ongoing Pfizer sponsored trials (~ 400 subjects) and IIR trials (~200 subjects).

Does the FDA agree that the estimated subject experience is sufficient to adequately characterize the PD-0332991 safety profile to support an NDA submission and adequate benefit/risk determination in the proposed indication?

FDA RESPONSE: Yes.

MEETING DISCUSSION: None

6. Does FDA agree to a waiver for pediatric assessment regarding PD-0332991 for the Breast Cancer indications?

FDA RESPONSE: It is likely that a waiver for pediatric assessment will be granted for this breast cancer indication; however, final determination is made by the Pediatric Review Committee (PeRC) after reviewing your Pediatric Study Plan (PSP). You are required to submit your PSP no later than 210 days prior to submission of the marketing application. Additional information about required content for Pediatric Study Plans is available at the following link:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentReso>

[urces/UCM338453.pdf](#)

MEETING DISCUSSION: *None*

7. Will the Breakthrough Therapy designation allow for a rolling submission or will a separate request for Fast-Track designation be needed?

FDA RESPONSE: All benefits of Fast Track designation are available to those who have received Breakthrough Therapy designation. You do not need to submit a separate request for Fast Track designation. You should, however, submit a request for Rolling Review that describes your proposed submission timeline. If your timeline is acceptable, you will receive a letter granting Rolling Review.

MEETING DISCUSSION: *None*

ADDITIONAL COMMENT

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

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, you should 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.

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

Note that we are deferring discussion on contents of a complete application until the next Pre-NDA meeting (as requested in our response to Question 1).

MEETING DISCUSSION: *None*

ISSUES REQUIRING FURTHER DISCUSSION

To be discussed at a future Pre-NDA meeting:

- Contents of a complete application
- Adequacy of 90-95 PFS events to support filing of an application
- Expanded access

ACTION ITEMS

Action Item/Description	Owner	Due Date
Finalize meeting minutes	FDA –Christy Cottrell	June 16, 2013

ATTACHMENTS AND HANDOUTS

Slide shown at meeting is attached.

Christy Cottrell
Regulatory Project Manager
Minutes Recorder

Concurrence: _____
Patricia Cortazar, M.D.
Clinical Team Leader
Meeting Chair

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/s/

CHRISTY L COTTRELL
05/23/2013

PATRICIA CORTAZAR
05/23/2013

From: Cottrell, Christy L.
Sent: Tuesday, May 14, 2013 7:42 PM
To: 'Yu-Kite, Michelle'
Subject: RE: IND 069324 for PD-0332991: Pre-Phase 3 meeting confirmation

Importance: High

Attachments: 5-17-13 PreNDA clin pharm only meeting questions.doc; 5-17-13 PreNDA clinical and stats only meeting questions.doc
[Michelle-](#)

I'm so sorry. I (b) (6) am just now getting back to checking emails. Here are our responses for both the clinical and clin pharm meetings. Hopefully your team can still make a last minute decision about whether to travel or not.

Christy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Tuesday, May 14, 2013 4:35 PM
To: Cottrell, Christy L.
Subject: RE: IND 069324 for PD-0332991: Pre-Phase 3 meeting confirmation

Hi Christy,

Sorry to bother you. I was hoping to meet with my Clin Pharm team tonight before we get on our flights tomorrow morning in the event that we accept the comments and cancel the meeting.

I hate to rush you, but do you know if you will send them before 5pm today?

I appreciate it.

Thanks,

Michelle

From: Cottrell, Christy L. [mailto:Christy.Cottrell@fda.hhs.gov]
Sent: Tuesday, May 14, 2013 7:11 AM
To: Yu-Kite, Michelle
Subject: RE: IND 069324 for PD-0332991: Pre-Phase 3 meeting confirmation

We wanted to send the clin pharm and clinical comments together (as they will probably reference one another). Will send both this afternoon.

Christy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Monday, May 13, 2013 10:44 PM
To: Cottrell, Christy L.
Subject: RE: IND 069324 for PD-0332991: Pre-Phase 3 meeting confirmation

Hi Christy,

Sorry to bother you. I just wondered if the draft responses for the Clin Pharm meeting will be available before Tuesday evening?

Thanks,

Michelle

From: Cottrell, Christy L. [mailto:Christy.Cottrell@fda.hhs.gov]
Sent: Tuesday, April 30, 2013 1:36 PM
To: Yu-Kite, Michelle
Subject: RE: IND 069324 for PD-0332991: Pre-Phase 3 meeting confirmation

Our internal meeting for the clinical meeting is on May 14th and the internal meeting for the clin pharm meeting is on May 10th. We should be able to send you draft responses ahead of time for both of them.

Christy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Tuesday, April 30, 2013 4:02 PM
To: Cottrell, Christy L.
Subject: RE: IND 069324 for PD-0332991: Pre-Phase 3 meeting confirmation

Thanks Christy! I really appreciate all your efforts.

For the two upcoming meetings on May 17th, I was wondering if you know when the internal meetings are scheduled and perhaps if/when we might get written feedback. Sorry to be a pain!

Michelle

From: Cottrell, Christy L. [mailto:Christy.Cottrell@fda.hhs.gov]
Sent: Tuesday, April 30, 2013 12:59 PM
To: Yu-Kite, Michelle
Subject: IND 069324 for PD-0332991: Pre-Phase 3 meeting confirmation

Michelle-

Attached is a letter confirming the July 11, 2013, Pre-Phase 3 meeting for PD-0332991. I'll be working on scheduling the new meeting this week.

Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

 301.796.4256 (phone) • 301.796.9845 (fax) |  christy.cottrell@fda.hhs.gov



consider the environment before printing this e-mail

1. Does the Agency agree that the proposed clinical pharmacology overall plan is adequate to support an NDA submission?

FDA RESPONSE: Your clinical pharmacology overall plan appears generally acceptable. The final determination of its adequacy to support an NDA submission will be an NDA review issue.

2. Does the Agency agree that the biopharmaceutics and clinical pharmacology studies described in Section 9.4.1 and Section 9.4.2 are adequate to support an NDA under an accelerated approval (Subpart H) scheme?

FDA RESPONSE: Your proposed studies appear adequate to support an NDA under an accelerated approval (Subpart H) scheme. However, the final determination will be an NDA review issue.

3. The sponsor proposed 6 biopharmaceutics and clinical pharmacology studies listed in Section 9.4.2 as post-approval commitments. Study designs and status of each will be included in the NDA. Does the Agency agree with the Sponsor proposal to provide study reports for the identified specific biopharmaceutics and clinical pharmacology studies listed in Section 9.4.2 as post-approval commitments?

FDA RESPONSE: Your proposal may be acceptable. However, the determination of requirements and/or commitments for post-marketing studies will be made during the NDA review period.

4. Does the Agency agree that the QTc evaluation using data from studies A5481001, A5481002, and A5481003 is adequate to support an accelerated approval of PD-0332991 in the NDA submission (under Subpart H scheme) and that the QTc evaluation from the A5481008 electrocardiogram (ECG) sub-study could be provided as a Postmarketing commitment as indicated in Section 9.4.3?

FDA RESPONSE: Please note that on September 10, 2012 we agreed to your plan to submit ECG data from Studies A5481001, A5481003 and A5481004 to support the NDA. We also agreed with the collection of ECGs from Study A5481008. The determination of requirements for post-marketing studies will be made during the NDA review period.

5. The Sponsor plans to conduct exposure/response analysis using data obtained from studies A5491001, A5481002, and A5481003 for safety endpoints, and data obtained from A5481003 for efficacy endpoints to support accelerated approval of PD-0332991. Exposure/response analysis using data from A5481008 will be provided as a post-marketing commitment. Does the Agency agree with this plan?

FDA RESPONSE: See response to 3 above.

1. Improvements in PFS (by investigator assessment and supported by BICR) for the final analyses from the 2 independently randomized cohorts from Study A5481003 demonstrate a clinical benefit over current standard of care therapy for patients with ER (+)/HER2-negative metastatic breast cancer. Additionally, a global randomized Phase 3 trial is currently enrolling to confirm the clinical benefit demonstrated in Study A5481003.

Does the Agency agree that statistically significant and clinically meaningful improvement in PFS in the randomized Phase 2 study cohorts in Study A5481003 and in the context of an acceptable safety profile, would be adequate to support submission of an NDA for consideration of accelerated approval under Subpart H in this indication?

FDA RESPONSE: We are willing to accept the NDA submission based on the top line results from Study A5481003 as they appear to be promising, pending review of your complete NDA submission. Prior to submission, we would like to have a meeting with you to discuss updated topline results and whether this new data package continues to support the present results. We note that there have been multiple looks at this data which may make interpretation from a statistical point of view difficult. Please provide your plans for a robust statistical analysis plan of this data, particularly, the interpretation of your p-value in light of the multiple analyses and ad hoc changes.

If you believe that a delay in the final analysis will deprive breast cancer patients from a therapy that will provide substantial clinical benefit, then we encourage you to open an expanded access program.

2. The A5481003 study aims to detect a hazard ratio (HR) = 0.67 with 80% power and 1-sided significance level of 0.10. Based on the event rate evaluation and the observed effect size from the 2 interim analyses, PFS events are being observed at a slower pace than originally hypothesized and the determination of 114 events for the final analysis may be overestimated. In addition, despite the available patients who remain follow up, 114 PFS events may not be accumulated in a practical timeframe. However, delaying the final analysis for 114 events to occur may seriously compromise the potential substantial clinical benefit that PD-0332991 plus letrozole treatment could provide for breast cancer patients. Therefore, the Sponsor proposes that the final analysis of the primary endpoint PFS will be performed when approximately 90 events have occurred. With 90 events there will be more than 97% power to detect a HR of 0.50 at 1-sided 10% level or a 72% power to detect a HR of 0.67. It is estimated that approximately 50 PFS events would be observed in Cohort 2 (N = 99) at the final analysis. This would assure maturity of both Cohort 1 and Cohort 2 data and allow a reasonable estimate of median PFS in separate analyses for both cohorts. At final analysis all additional analyses as per amended SAP will be performed and included in the

Clinical Study Report (CSR). The protocol will also be amended to update the change from 114 events to approximately 90 events for the final analysis. This final analysis is anticipated 2H2013.

Does the FDA agree with the proposed SAP amendment (see Appendix 7 and Section 9.2.7 in this briefing document) including the proposed plan for the updated final analysis?

FDA RESPONSE: No. We do not agree to decrease the number of PFS events to 90. This proposal is based on the observed data and is not pre-planned. Please also let us know when you expect to have the pre-specified 114 events for the PFS data to mature.

3. In response to the FDA request to conduct separate analyses of the 2 patient cohorts of the Phase 1/2 (A5481003) study, the Sponsor proposes to amend the SAP prior to an upcoming final analysis. Details are provided in Appendix 7 and can be summarized as follows: In addition to final analysis of the primary PFS endpoint for all randomized patients in Cohort 1 (N = 66) and Cohort 2 (N = 99) based on the investigator assessment, analyses for the 2 cohorts separately are added with a formal hypothesis testing procedure. Therefore, individual inference of all randomized patients (Cohort 1 and Cohort 2 combined), Cohort 1 and Cohort 2 separately can be made by controlling the type 1 error rate. The significance level for the final PFS analysis will be adjusted for 2 previous interim analyses. At the final analysis of the primary endpoint PFS, a gate-keeping procedure will be used for hypotheses testing in a hierarchical approach to control the family-wise error rate. The testing begins with all randomized Intent-to-Treat subjects (N = 165). If the null hypothesis can be rejected, then the Holm's step down procedure will be used to test the hypotheses for Cohort 1 and Cohort 2 as 2 individual study cohorts.

Does FDA agree with the proposed SAP amendment including the plan to analyze the 2 randomized Phase 2 trial cohorts separately?

FDA RESPONSE: Your statistical plan is data-driven and not pre-specified.

4. During the End of Phase 2 meeting on 05 September 2012, the FDA recommended that the Sponsor conduct a BICR of the scans for the Phase 2 study (A5481003) as soon as possible. Pfizer has initiated an analysis of the BICR of radiographic data from the previously reported interim efficacy data (data cut of July 2012). As described in the BICR Charter, discordances in date of progression between the 2 radiologists are adjudicated by a third radiologist. Complete BICR data for Study A5481003 will be included in the NDA and the analysis performed based on the BICR assessed PFS data is considered a secondary analysis with an appropriate set of sensitivity analyses to support the primary analysis of investigator assessment.

a) Does the Agency agree with the plan and methodology for a BICR for all randomized patients in Phase 2 portion of Study A5481003 as defined in the BICR Charter (Appendix 6)?

FDA RESPONSE: This is acceptable. BICR assessments should be done on 100% of the patients.

b) Does the Agency agree with the analysis of BICR as a secondary analysis as defined in the proposed SAP, including planned sensitivity analyses (defined in Section 8.1.4 of proposed SAP amendment (Appendix 7)?

FDA RESPONSE: Given the size of the study and the unplanned analysis, the BICR analysis should be the primary analysis.

5. By the time of the NDA submission, clinical experience will consist of data for approximately 550 subjects and will include safety data for more than 300 patients or subjects who will have received PD-0332991 in Pfizer sponsored trials. Of these, 74 subjects were treated in Study A5481001, 17 subjects in Study A5481002, 95 subjects in Study A5481003 (in combination with letrozole), 51 subjects in Study A5481004 (in combination with bortezomib/dexamethasone) and ~50 subjects in clinical pharmacology studies. In addition, 12 subjects treated with single agent PD-0332991 are enrolled in the ongoing A5481010 Japan only study with an anticipated total accrual of 18 subjects. Of the ~550 subjects, an estimated 250 to 300 subjects will have received PD-0332991 plus letrozole on the current Phase 3 breast cancer trial. Supplemental safety information (i.e., serious adverse events) will also be provided from approximately 600 subjects enrolled in other ongoing Pfizer sponsored trials (~ 400 subjects) and IIR trials (~200 subjects).

Does the FDA agree that the estimated subject experience is sufficient to adequately characterize the PD-0332991 safety profile to support an NDA submission and adequate benefit/risk determination in the proposed indication?

FDA RESPONSE: Yes.

6. Does FDA agree to a waiver for pediatric assessment regarding PD-0332991 for the Breast Cancer indications?

FDA RESPONSE: It is likely that a waiver for pediatric assessment will be granted for this breast cancer indication; however, final determination is made by the Pediatric Review Committee (PeRC) after reviewing your Pediatric Study Plan (PSP). You are required to submit your PSP no later than 210 days prior to submission of the marketing application. Additional information about required content for Pediatric Study Plans is available at the following link:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf>

7. Will the Breakthrough Therapy designation allow for a rolling submission or will a separate request for Fast-Track designation be needed?

FDA RESPONSE: All benefits of Fast Track designation are available to those who have received Breakthrough Therapy designation. You do not need to submit a separate request for Fast Track designation. You should, however, submit a request for Rolling Review that describes your proposed submission timeline. If your timeline is acceptable, you will receive a letter granting Rolling Review.

ADDITIONAL COMMENT

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

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, you should 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.

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

Note that we are deferring discussion on contents of a complete application until the next Pre-NDA meeting (as requested in our response to Question 1).

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

/s/

CHRISTY L COTTRELL
05/20/2013



IND 69324

MEETING PRELIMINARY COMMENTS

Pfizer Inc.
Attention: Michelle Y. Kite, M.S., RAC
Senior Manager, Worldwide Regulatory Strategy
10646 Science Center Drive
San Diego, CA 92121

Dear Ms. Kite:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Palbociclib (PD-0332991) oral immediate release capsule.

We also refer to your February 12, 2013, correspondence, received DATE, requesting a meeting to discuss agency's advice and agreement on CMC strategies that the applicant intends to pursue during commercial development and in preparation of the NDA.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call RPM Rogelio Ruvalcaba, at (301) 796-1876.

Sincerely,

{See appended electronic signature page}

Ali Al-Hakim, PhD
CMC Branch Chief
Division I
Office of Drug New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: April 23, 2013, 2:00 – 3:00 PM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: IND 69324
Product Name: Palbociclib (PD-0332991)
Indication: In combination with letrozole, treatment of postmenopausal women with estrogen receptor-positive (ER+) and human epidermal growth factor receptor 2 (HER@) negative advanced breast cancer.
Sponsor/Applicant Name: Pfizer Inc.

FDA ATTENDEES (tentative)

Ali Al-Hakim PhD, CMC Branch Chief
Haripada Sarker, PhD, CMC Lead
Xiao Chen, PhD, CMC Reviewer
Wei Chen, PhD, Pharm/Tox Reviewer
Todd Palmby, PhD, Pharm/Tox Team Lead
Juandria Williams, PhD, OC/OMPQ/NDMAB
Mahesh Ramanadham, PharmD, MBA, Team Leader (acting), OC/OMPQ/NDMAB
Rogelio Ruvalcaba, MS, Regulatory Project Manager

SPONSOR ATTENDEES

Daniel R. Arenson, Fellow, Pharmaceutical Sciences Team Leader
Susan C. Berlam, Senior Director, Global CMC
Jennifer L. Brown, Senior Regulatory Manager, Global CMC
Rachael Buckley, Quality Operations Director, Cork, Ireland, Pfizer Global Supply
John G. Groskoph, Senior Director, Global CMC
Nathan D. Ide, Senior Principal Scientist, Chemical R&D
Alber Kraus, Senior Director, Regulatory Strategy
Kyle R. Leeman, Senior Principal Scientist, Analytical R&D



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for April 23, 2013, 2:00 – 3:00 PM (EST), FDA White Oak between Pfizer Inc. and the Division I Office New Drug Quality Assessment. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

Purpose of this meeting is to discuss CMC and GMP topics described in the briefing package, to support the successful review and approval of this potential breakthrough therapy. In light of the accelerated nature of this program and the limited development knowledge at this time, the applicant anticipates that additional engagements with the Agency on CMC and GMP topics, including specifications, pre-approval inspections, process validation, etc., may be warranted.

The isethionate salt of palbociclib drug substance (PD-0332991-0054) was prepared and used for toxicology and clinical studies through Phase 2. The PD-0332991 freebase (PD-0332991-00) has been elected for the Phase 3 clinical studies and proposed commercial use.

The PD-0332991 proposed commercial manufacturing process is a (b) (4) synthesis as shown in briefing package. The proposed drug substance starting materials are (b) (4)

(b) (4)

2. DISCUSSION

Question 1: Due to the anticipated early filing date and accelerated approval process for PD-0332991, the applicant will have limited drug substance and drug product registration stability data available at the time of submission. The applicant will provide stability data through 6 months for drug substance and through 6 months for drug product at the time of submission, in addition to supportive stability data. Stability data from additional time points for drug substance and drug product will be submitted during the review period. (b) (4)

a) Does the Agency agree that submission of additional drug substance and drug product stability data during the NDA review is acceptable and will not extend the regulatory review period?

FDA Response to Question 1- a): Submission of updated drug substance and drug product stability data during the NDA review is acceptable if the information is provided within 30-day period from the initial NDA submission and this may not lead to the extension of the regulatory review period.

b) Does the Agency agree with the submission of a comparability protocol, as part of the NDA, to extend the commercial expiry based on additional registration stability data generated after approval?

FDA Response to Question 1- b): Based on the limited CMC information regarding the comparability protocol submitted in the meeting package, the Agency cannot comment on the acceptability of the (b) (4) approach. Please note that the expiration dating period is determined based on the stability data submitted in the NDA. Please refer to the ICH Q1E guidance document regarding evaluation of stability data and determination of expiration dating period for the drug product.

Question 2: 2. PD-0332991 is being developed to treat advanced breast cancer in patients with serious and life threatening malignancies. Does the Agency concur that ICH S9 is applicable to PD-0332991, and that 1) control of mutagenic impurities to limits based on increased lifetime risk of cancer is not appropriate, and 2) exceeding the established limits for impurities as described in ICH Q3A/B may be appropriate, if justified?

FDA Response to Question 2: Yes, your proposed approach appears to be acceptable.

Question 3: 3. Does the Agency agree that alternative approaches to validation, such as those outlined in the briefing document, would be acceptable for palbociclib, and does the Agency have any comments on the proposed approaches?

FDA Response to Question 3: Your proposal to concurrently release three drug substance validation lots and three drug product (75 and 100 mg) lots may be considered acceptable under a

breakthrough therapy designation provided they conform to applicable quality standards as defined in the process performance qualification (PPQ) protocol. You indicate in your proposal that process knowledge may be gained such that lots may be released prior to completion of PPQ. You should justify the release of each validation lot such that the outcome reflects an appropriate level of assurance. That is, the circumstances and rationale for concurrent release should be fully described in the PPQ protocol. We would expect that if any newly identified and included CPPs and CMAs adversely impact the acceptability of previously distributed lots, you re-assess the acceptability of those previously manufactured, and potentially distributed, lots. And while we would not expect a full PPQ study to be executed prior to distribution for concurrent release, the released lot must comply with all CGMPs, regulatory approval requirements, and the PPQ lot release criteria. A lot release prior to completion of PPQ should be based on meeting confidence levels appropriate for each quality attribute of the drug.

We encourage you to review the "Guidance for Industry: Process Validation: General Principles and Practices" (January 2011) for more information.

Additional FDA Comments:

CMC:

1. Since the meeting package does not contain sufficient CMC information for the drug substance and the drug product, it is recommended that you have a CMC specific pre-NDA meeting with the Agency to discuss relevant CMC information for this drug.
2. Per ICH Q1A guidelines, a minimum of 3 batches/lots of 12-month primary stability data for both drug substance and drug product should be submitted in the initial NDA submission.
3. If the drug products stability program consists of (b) (4) designs, it is recommended that you discuss the stability protocol with the Agency in a CMC specific pre NDA meeting. Please refer to ICH (b) (4) Guidelines for the (b) (4) designs for the drug product stability testing.
4. (b) (4) and (b) (4) may not be considered as appropriate starting materials for the manufacture of PD-0332991 drug substance since no sufficient justification has been provided in the meeting package. It is recommended that you discuss the designation of the starting materials for the manufacture of PD-0332991 drug substance in a CMC specific pre-NDA meeting with adequate rationale/justification.

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/s/

ALI H AL HAKIM
04/19/2013



IND 069324

MEETING MINUTES

Pfizer, Inc.
10646 Science Center Drive
San Diego, CA 92121

Attention: Michelle Yu-Kite, MS, RAC
Senior Manager, Worldwide Regulatory Strategy

Dear Ms. Yu-Kite:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PD-0332991.

We also refer to the meeting between representatives of your firm and the FDA on September 5, 2012. The purpose of the meeting was to discuss the proposed breast cancer development plan and reach concurrence on a pivotal Phase 3 study to support approval.

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

If you have any questions, call me at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

Patricia Cortazar, M.D.
Team Lead (Breast/Gyn 1)
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: September 5, 2012
Meeting Location: WO22 Room 1309

Application Number: IND 069324
Product Name: PD-0332991
Indication: In combination with Letrozole for the treatment of postmenopausal women with estrogen receptor-positive (ER+) and human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer

Sponsor/Applicant Name: Pfizer, Inc.

Meeting Chair: Patricia Cortazar, M.D.
Meeting Recorder: Christy Cottrell

FDA ATTENDEES

Robert Justice, M.D., M.S., Director, DOP1
Amna Ibrahim, M.D., Deputy Director, DOP1
Patricia Cortazar, M.D., Clinical Team Leader, DOP1
Laleh Amiri-Kordestani, M.D., Clinical Reviewer, DOP1
Shenghui Tang, Ph.D., Biometrics Team Leader
Somesh Chattopadhyay, Ph.D., Biometrics Reviewer
Jeanne Fourie-Zirkelbach, Ph.D., Acting Clinical Pharmacology Team Leader
Sarah Schrieber, Pharm.D., Clinical Pharmacology Reviewer
Anthony Murgo, M.D., Associate Director, OHOP
Gideon Blumenthal, M.D., Clinical Reviewer, DOP1
Richard Pazdur, M.D., Director, OHOP
Nitin Mehrotra, Ph.D., Clinical Pharmacology Reviewer
Gwynn Ison, M.D., Clinical Reviewer, DOP1 (*internal meeting only*)
Christy Cottrell, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Eric Kowack, M.S., MBA, PD-0332991 Asset Team Leader
Maria Koehler, M.D., Ph.D., Strategic and Scientific Assessment Lead
Albert Kraus, Ph.D., Regulatory Tumor Strategy Lead
Sophia Randolph, M.D., Oncology Clinical Development
Michelle Yu, M.S., RAC, Worldwide Regulatory Strategy Oncology
Diane Wang, Ph.D., Clinical Pharmacology
Xin Huang, Ph.D., Biostatistics
David A. Roth, M.D., Head, Oncology Early Development
Aida Sacaan, Ph.D., Drug Safety Research and Development

Yuqiu (John) Jiang, Ph.D., Translational Oncology
Mace L. Rothenberg, M.D., Senior Vice President, Clinical Development and Medical Affairs
Ramzi Dagher, M.D., Head, Worldwide Regulatory Strategy Oncology

BACKGROUND

The proposed Phase 3 Study (A5481008) is a randomized, multicenter, (b) (4), double-blind study comparing the efficacy and safety of PD-0332991 in combination with letrozole versus placebo in combination with letrozole in postmenopausal women with ER (+)/HER2 negative advanced breast cancer. The primary endpoint proposed is PFS. PFS is defined as the time from date of randomization to the first radiographically and/or clinically documented progression of disease (PD) per RECIST v.1.1 criteria or death due to any cause in the absence of documented PD. Secondary objectives include comparison of additional measures of clinical activity between treatment arms by assessing OS, 1-year, 2-years, and 3-years survival probabilities, objective response (OR), duration of response (DR), and disease control (DC) (CR+PR+SD \geq 24 weeks), comparison of the safety, and patient reported health related quality of life between treatment arms.

Draft responses were sent to the applicant on August 30, 2012.

DISCUSSION

1. In the proposed pivotal randomized, double-blind, placebo-controlled study (A5481008), postmenopausal women with ER (+)/HER2 negative advanced breast cancer who have not received any prior systemic anti-cancer treatment for advanced disease will be randomized in a 2:1 ratio, to either PD-0332991 plus Letrozole or placebo plus Letrozole without opportunity for crossover. As described in Section 10.1.1, Letrozole provides benefit and is commonly used in this patient population. Does the Agency concur that Letrozole plus placebo is an appropriate comparator in the target Phase 3 patient population?

FDA RESPONSE: Not as defined. You will need to define a population that would be suitable to treat with hormonal therapy alone. We question whether this will be a blinded trial given the toxicities of PD-0332991.

MEETING DISCUSSION: The sponsor will propose a more clearly defined patient population that is appropriate for Letrozole treatment.

2. As described in Section 10.1.2, the addition of a CDK4/6 inhibitor may improve efficacy in patients eligible for Letrozole treatment, i.e., post-menopausal women with ER (+)/HER2 negative advanced breast cancer. The proposed pivotal Phase 3 study (A5481008) will include patients who meet the inclusion and exclusion criteria described in the protocol (see Appendix 3, Section 4.0 of Protocol A5481008 for inclusion/exclusion criteria). Does the Agency agree that the overall inclusion/exclusion criteria and confirmation for eligibility including ER and HER2 status in the proposed Phase 3 study are appropriate?

FDA RESPONSE: See response to question 1.

Patients with HER2/CEP17 ratio of 2-2.2 should be excluded from the study as they may benefit from HER2 targeted therapies. Follow ASCO/CAP guidelines for HER2 testing.

MEETING DISCUSSION: None

3. A statistically-significant and clinically-meaningful improvement in PFS or time to progression has been the basis for approval of several drugs for treatment of breast cancer, including everolimus, pertuzumab, Lapatinib, Letrozole, and anastrozole. Given the magnitude of PFS improvement seen in Phase 2 Part 1 of the randomized Phase 1/2 study (and expected to be shown at study completion), it is expected that the improvement of PFS in the planned pivotal randomized Phase 3 study (A5481008) will be confirmed in this PFS benefit. The Sponsor considers that an improvement in median PFS of significant magnitude (e.g., 50% improvement) represents a clinically meaningful outcome for the patient population to be enrolled in the proposed Phase 3 study, with no coexisting detriment in overall survival.
 - a. Does FDA agree that PFS is an appropriate primary endpoint?

FDA RESPONSE: Yes, PFS is an appropriate endpoint.

MEETING DISCUSSION: None

- b. Does FDA agree that superiority in PFS of sufficient magnitude in the PD-0332991 plus Letrozole arm of the proposed pivotal randomized Phase 3 trial together with the large magnitude PFS of this combination observed in the current randomized Phase 2 trial and early directional improvement in OS or no detriment in OS may form the basis of an NDA demonstrating clinical benefit in the target patient population?

FDA RESPONSE: In general, 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. The toxicity of your drug may require that you show a bigger benefit than would need to be shown by a relatively non-toxic agent such as hormonal therapy. 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.

MEETING DISCUSSION: None

4. By the time of the submission of the NDA, the safety database will include 802 subjects who have received PD-0332991. This includes approximately 444 patients with ER (+)/HER2 negative advanced breast cancer who will have received the combination of PD-0332991 and Letrozole. Does the Agency agree that the estimated patient experience is sufficient to adequately characterize the PD-0332991 safety profile to support an NDA for regular approval in the proposed indication?

FDA RESPONSE: Yes.

MEETING DISCUSSION: None

5. With the positive randomized Phase 2 data (n=165) and the planned pivotal Phase 3 study (A5481008; n=(b) (4)), the Sponsor considers that a significant magnitude improvement in median PFS from these two randomized trials and no decrement in OS represents a clinically meaningful outcome for the patient population to be enrolled in the proposed Phase 3 study and should qualify for regular approval.
- a. Does FDA agree with the design elements of disease assessment and PFS determination in the Phase 3 protocol including timing of assessments and proposed investigator progression assessment (i.e., (b) (4)), as described in this briefing document Section 11.2 and draft Protocol A5481008 in Section 7.1 and 7.5?

FDA RESPONSE: No. (b) (4)
Alternative strategies to examine bias will need to be proposed and discussed with the Agency in a separate meeting.

MEETING DISCUSSION: The sponsor will submit a proposal for minimizing bias in the proposed Phase 3 study (e.g., centralized review). A primary endpoint of PFS with investigator assessment may be acceptable provided that an acceptable plan for minimizing bias is submitted.

- b. Does FDA agree with the proposed statistical analysis plan as defined in this briefing document Section 11.3.2 and draft Phase 3 Protocol A5481008 in Section 9?

FDA RESPONSE: The plan is acceptable in general. However, we have the following comment.

- **Your proposed stratification at randomization is acceptable. However, at the time of analysis, interpretation of study results may be problematic if you do not have a sufficient number of patients for each combination of stratification factors. We recommend that you reduce the number of stratification factors or use un-stratified log-rank test for the primary analysis.**

MEETING DISCUSSION: None

6. The Sponsor plans to conduct the following Clinical Pharmacology studies to support the NDA submission:
- A mass balance study to evaluate the disposition of PD-0332991 and its routes of elimination in humans.
 - The activity of at least one of the metabolites has been evaluated and found to be similar to that of the parent compound. Depending on its abundance, the Sponsor will consider characterizing the pharmacokinetics of this metabolite. Activity of other circulating metabolite(s) will be evaluated after the completion of the ADME study in humans. Monitoring of metabolite in plasma will be considered in selected clinical studies if the metabolite contributes to $\geq 25\%$ of activity based on pharmacologic activity index.
 - Drug-drug interaction (DDI) studies including ketoconazole, midazolam, and rifampin studies.
 - Organ impairment studies including hepatic and renal impairment studies.
 - Absolute bioavailability study.
 - Formal food effect study using the final-market-image formulation.
 - A bioavailability study to compare the formulation to be used in the pivotal Phase 3 trial to that used in early clinical trials.
 - A bioequivalent study will be performed only if there are significant formulation changes between the formulation used in the pivotal Phase 3 trial and the marketed formulation.

Does the Agency concur with the clinical pharmacology plan?

FDA RESPONSE: Generally, yes. Please refer to the appropriate clinical pharmacology and biopharmaceutics guidances to industry found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> for more information.

MEETING DISCUSSION: None

7. Data from Studies A5481001, A5481003 and A5481004 will be used to assess QT/QTc interval prolongation to support the NDA submission. In addition, the Sponsor will also collect time-matched ECG and PK data in the proposed pivotal Phase 3 trial and the design details will be included in the protocol. Briefly, serial ECGs and PK matched ECGs will be collected in triplicates from ~60 patients (~40 of them will be from PD-0332991 treatment arm) for time-matched baseline measurements on Day 0, and on Day 14 of Cycle 1, respectively. Details regarding PK matched ECGs will be discussed in the protocol. Does the Agency concur with the proposed QT interval assessment plan?

FDA RESPONSE: Yes, your QT interval assessment plan is reasonable.

We recommend the following subjects be excluded from study A5481008:

- **Subjects with serum potassium, magnesium and calcium levels outside of the central laboratory's reference range.**
- **Subjects receiving medications (within the last 7 days prior to screening) that have the potential of prolonging the QT interval.**

We also recommend that if QTc increases to >500 ms or if a change from baseline of ≥ 60 ms is observed on study, dose should be reduced, electrolytes (K, Mg, and Ca) should be monitored, and any electrolyte abnormalities should be corrected prior to increasing dose (once QTc interval decreases to < 500 ms).

MEETING DISCUSSION: None

8. The Sponsor plans to perform population PK analysis to establish the population PK model for PD-0332991 and identify potential covariate effect(s) on PK parameters using PK data collected from Phase 1 and Phase 2 studies. The Sponsor plans to [REDACTED] (b) (4) [REDACTED]. The data will be used to explore the relationship between exposure and PD, efficacy and safety endpoints. Details regarding the PD, efficacy and safety endpoints will be discussed in the protocol. Does the Agency concur with the population PK and exposure/response analysis plan?

FDA RESPONSE: Generally, yes. We recommend you collect sparse PK samples for all patients in the PD-0332991 treatment arm in the efficacy trial. We can provide more specific recommendations once you submit your detailed analysis plans.

Please refer to the clinical pharmacology population PK & exposure-response guidances to industry found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm> for more information.

We encourage you to refer to the following pharmacometric data and models submission guidelines

(<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm>):

- **All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**
- **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).**
- **A model development decision tree and/or table which gives an overview of modeling steps.**
- **For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of**

subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

MEETING DISCUSSION: The sponsor agreed to collect trough concentrations in all patients in the Phase 3 trial.

9. A series of non-clinical safety studies (safety pharmacology and toxicology) with PD-0332991 have either been completed (Table 1) or are planned (Table 3) to support the proposed advanced breast cancer indication.
- a. Does the Agency concur that the non-clinical safety package will be adequate following completion of the rat and dog 3-month toxicity studies to support initiation of the planned Phase 3 clinical trial?

FDA RESPONSE: Yes.

MEETING DISCUSSION: The responses to Question 9 were deferred during the September 5, 2012 meeting and were not discussed. Written responses are being provided in these minutes as follow-up.

- b. Does the Agency concur that the proposed non-clinical safety package is adequate to support the proposed indication for registration?

FDA RESPONSE: Yes, your proposed nonclinical package appears appropriate to support an NDA for patients with advanced cancer. However, the adequacy of the nonclinical studies will be determined after review of the study results.

MEETING DISCUSSION: The responses to Question 9 were deferred during the September 5, 2012 meeting and were not discussed. Written responses are being provided in these minutes as follow-up.

ADDITIONAL COMMENT:

We suggest that you briefly present the slides you recently submitted to Dr. Pazdur at the September 5th meeting. Your presentation should include the pre-specified statistical analysis plan for these studies.

MEETING DISCUSSION: None

ADDITIONAL MEETING DISCUSSION: A proposal for the FDA to consider a Subpart H approval based on the randomized Phase 2 trials will need to be discussed in a separate meeting. FDA asked the sponsor to submit the pre-specified SAP and any amendments to the SAP for the Phase 2 trial. Details on safety information should also be provided. FDA

recommends that there be a central review of the Phase 2 PFS data as soon as possible. FDA considers the Phase 2 trial as two individual studies. FDA suggests incorporating an early efficacy analysis (if expecting a large effect) or size the trial for the larger effect for Phase 3 trial.

ISSUES REQUIRING FURTHER DISCUSSION

See additional meeting discussion.

ACTION ITEMS

None

ATTACHMENTS AND HANDOUTS

See attachment for slides shown at meeting.

Christy Cottrell
Regulatory Project Manager
Minutes Recorder

Concurrence: _____
Patricia Cortazar, M.D.
Team Lead (Breast/Gyn 1)
Meeting Chair

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

/s/

CHRISTY L COTTRELL
10/02/2012

PATRICIA CORTAZAR
10/02/2012