

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207103Orig1s000**

**OTHER REVIEW(S)**

## 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.

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NDA # 207103  
Product Name: Ibrance (palbociclib)

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PMR 2860-1  
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 trial completion.

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PMR Schedule Milestones:

Trial Completion:	<u>12/2016</u>
Final PFS Report Submission:	<u>06/2017</u>
Final OS Report Submission:	<u>11/2020</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?

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**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.*

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## 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.

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NDA # 207103  
Product Name: Ibrance (palbociclib)

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PMR 2860-2 Description: 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.

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PMR Schedule Milestones:

Trial Completion:	<u>06/2017</u>
Final Report Submission:	<u>12/2017</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

Insufficient clinical and pharmacokinetic data are available to determine if a starting dose adjustment is needed for patients with pre-existing moderate or severe hepatic impairment. Ongoing trial A5481013 addresses this question.

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."

A change in palbociclib exposure is expected in patients with pre-existing hepatic impairment, vs. patients with normal hepatic function. Ongoing trial A5481013 will determine the appropriate dose for patients with moderate or severe hepatic impairment.

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 A5481013 was designed to assess the pharmacokinetics of palbociclib in subjects with pre-existing moderate or severe hepatic impairment vs. those with normal hepatic function. The final protocol was reviewed and found acceptable by FDA.

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.*
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**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.

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NDA # 207103  
Product Name: Ibrance (palbociclib)

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PMC 2860-3  
Description: 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.

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PMC Schedule Milestones:

Trial Completion:	<u>04/2015</u>
Final Report Submission:	<u>10/2015</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

A clinical drug interaction trial showed that palbociclib exposure was significantly decreased when it was coadministered with a strong CYP3A inducer. The effect of a moderate CYP3A inducer on the pharmacokinetics of palbociclib in vivo is not known.

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."

Palbociclib is metabolized by CYP3A. A clinical drug interaction trial will determine the magnitude of palbociclib exposure change and an appropriate dose of palbociclib when a moderate CYP3A inducer is coadministered.

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 A5481039 was designed to assess the effect of modafinil (moderate CYP3A inducer) on the pharmacokinetics of palbociclib. The final protocol was reviewed and found acceptable by FDA.
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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  
Pharmacokinetic trial with palbociclib in healthy volunteers
- 

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?
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## PMR/PMC Development Template

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NDA # 207103  
Product Name: Ibrance (palbociclib)

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PMC 2860-4  
Description: 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.

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PMC Schedule Milestones:

Trial Completion:	<u>12/2016</u>
Final Report Submission:	<u>06/2017</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 to further define the prognostic/predictive significance of the genetic alteration to the safety and efficacy of palbociclib
- 

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?

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**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.*

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/s/  
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AMY R TILLEY  
02/02/2015

KATHERINE M FEDENKO  
02/03/2015

**MEMORANDUM**  
**FOOD AND DRUG ADMINISTRATION**  
**Center for Drug Evaluation and Research**  
**Office of Prescription Drug Promotion (OPDP)**

\*\*\*\*Pre-decisional Agency Information\*\*\*\*

Memorandum

**Date:** January 27, 2015

**To:** Amy Tilley, RPM  
Division of Oncology Products 1 (DOP1)  
Office of Hematology Oncology Products (OHOP)

**From:** Marybeth Toscano, PharmD, RAC, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

Jessica Cleck-Derenick, PhD, Team Leader  
OPDP

**Subject:** Addendum to OPDP comments on draft product labeling for  
Ibrance (Palbociclib) NDA 207103

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In response to your consult request dated September 24, 2014, OPDP has reviewed the proposed product labeling (PI) for Ibrance. OPDP provided initial comments in DARRTS based on the proposed draft of the PI as of January 14, 2015.

This addendum is for OPDP's provided final comments (see attached PI) during the January 27, 2015 meeting.

If you have any questions, please contact Marybeth Toscano at 6-2617 or at [Marybeth.Toscano@fda.hhs.gov](mailto:Marybeth.Toscano@fda.hhs.gov).

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/s/  
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MARYBETH TOSCANO  
01/27/2015

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: January 26, 2015

To: Amna Ibrahim, MD  
Director  
**Division of Oncology Products 1(DOP1)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

From: Morgan Walker, PharmD, MBA  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Jessica Cleck Derenick, PhD  
Team Leader, Team 3  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): IBRANCE (palbociclib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 207103

Applicant: Pfizer, Inc.

## 1 INTRODUCTION

On , June 30, 2014, Pfizer, Inc. submitted for the Agency's review an original New Drug Application (NDA) 207103 for IBRANCE (palbociclib) capsules for the proposed indication for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP1) on September 24, 2014 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for IBRANCE (palbociclib) capsules.

## 2 MATERIAL REVIEWED

- Draft IBRANCE (palbociclib) PPI received on June 30, 2014, and received by DMPP and OPDP on January 22, 2015.
- Draft IBRANCE (palbociclib) Prescribing Information (PI) received on June 30, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 22, 2015.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the PPI is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/  
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MORGAN A WALKER  
01/26/2015

JESSICA N CLECK-DERENICK  
01/26/2015

SHARON R MILLS  
01/26/2015

LASHAWN M GRIFFITHS  
01/26/2015

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

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DATE: January 21, 2015

TO: Amna Ibrahim, MD  
Director, Division of Oncology Products 1 (DOP1)  
Office of Hematology and Oncology Products  
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D., Pharmacologist  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance

THROUGH: Sam H. Haidar, Ph.D., R.Ph.,  
Acting Director  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR covering NDA 207103, Palbociclib,  
sponsored by Pfizer, Inc.

At the request of the Office of Hematology and Oncology Products, Division of Oncology Products 1, the Division of Generic Drug Bioequivalence Evaluation (DGDBE, formerly the Division of Bioequivalence and GLP Compliance, OSI), Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the clinical portion of the following bioequivalence study, conducted by Pfizer's New Haven Clinical Research Unit (NHCRU), New Haven, CT.

Please note that DBGLPC/OSI issued a Decline to Inspect memo on December 8, 2014 for the bioanalytical portion of this study, done at [REDACTED] (b)(4). This decision was based on recent inspection history of the firm. This memo was uploaded into DARRTS.

**Study Number:** A5481036  
**Study Title:** "A Phase I, open-label 6-sequence 3-period crossover study of Palbociclib (PD-0332991) in Healthy Volunteers to Estimate Relative Bioavailability of Palbociclib Formulations"

The inspection of the clinical portion of this study was conducted by Michelle M. Noe (ORA Investigator, NWE-DO) at NHCRU

in New Haven, CT from January 8 to January 14, 2015. This was the first clinical bioequivalence inspection at this facility.

The audit assessed adequacy of the facilities, equipment, personnel, methods, and procedures. The audit also assessed the informed consent process and documents, electronic and paper study records for enrolled subjects, test article accountability records including collection of reserve samples, correspondence between the Institutional Research Board (IRB) and the clinical unit, and adverse event reporting. Ms. Noe observed no objectionable conditions, no under-reporting of adverse events, and no discrepancies between the data listings submitted to the agency and source data. She verified the randomization scheme. Following completion of the inspection of NHCRU, she did not issue Form FDA-483.

**Conclusion:**

Following a thorough review of the inspectional outcomes for the clinical portions of study A5481036, we recommend that the data for this study be accepted for further agency review.

Kara A. Scheibner, Ph.D.  
Division of Generic Drug Bioequivalence Evaluation, OSIS

**Final Classification:**

**NAI - New Haven Clinical Research Unit, New Haven, CT  
FEI# 3006521170**

DARRTS CC:  
OSIS/Taylor/Dejernett/Nkah/Fenty-Stewart/Johnson  
OSIS/DGDBE/Haidar/Skelly/Choi/Scheibner  
OSIS/DNDBE/Bonapace/Dasgupta/Cho  
CDER/OND/OHOP/DOPl/Tilley/Ibrahim  
ORA/NWE-DO/Michelle Noe  
Draft: KAS 1/20/2015  
Edits: MFS 1/20/2015; SHH 1/21/2015  
OSI: File#: BE 6758  
ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical  
Sites/New Haven Clinical Research Unit, New Haven, CT  
FACTS: 11473478

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/s/  
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MICHAEL F SKELLY  
01/21/2015

SAM H HAIDAR  
01/21/2015



**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

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Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**Division of Pediatric and Maternal Health Review**

**Date:** January 21, 2015

**From:** Carrie Ceresa, Pharm D, MPH  
Clinical Analyst, Maternal Health Team  
Pediatric and Maternal Health Staff

**Through:** Tamara Johnson, M.D., M.S.  
Acting Team Leader, Maternal Health Team  
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Acting Division Director,  
Division of Pediatric and Maternal Health

**To:** The Division of Oncology Products 1 (DOP1)

**Drug:** IBRANCE (palbociclib) capsules

**NDA:** 207103

**Subject:** Maternal Health Labeling Recommendations

**Applicant** Pfizer

**Materials Reviewed:**

- August 13, 2014, NME NDA– Original Priority submission from Pfizer

**Consult Question:** DOP1 requests assistance to apply the new Pregnancy and Lactation Labeling Rule requirements to the IBRANCE labeling.

## INTRODUCTION

On August 13, 2014, Pfizer submitted NDA 207103 for IBRANCE (palbociclib) oral capsules to be used in combination with letrozole, for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease.

DOP1 consulted DPMH to review and update the Pregnancy, Lactation, and Females and Males of Reproductive Potential information in the IBRANCE labeling.

This review provides recommended revisions and structuring of existing information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

## BACKGROUND

### Product Background

Palbociclib is a small molecule inhibitor of cyclin dependent kinases 4 and 6.<sup>1</sup> Preclinical *in vitro* studies showed growth-inhibitory activity in estrogen receptor-positive breast cancer cells and synergy with anti-estrogens.<sup>1</sup> Palbociclib is to be used in combination with letrozole in postmenopausal women as first-line treatment in patients with advanced, estrogen receptor-positive, HER2-negative breast cancer. The NDA submission is primarily based on Study 1003, a Phase 2 randomized study with palbociclib plus letrozole versus letrozole alone. The clinical development program for palbociclib also includes study 1010 which evaluates the combination of palbociclib plus letrozole in a similar population of Japanese patients with advanced breast cancer; Study 1008<sup>2</sup> which is a Phase 3 study of palbociclib in combination with letrozole as first line treatment of advanced breast cancer; and Study 1023<sup>3</sup> an additional Phase 3 study of palbociclib in combination with fulvestrant with or without gonadotropin-releasing hormone agonist in women with recurrent hormone receptor-positive, HER2-negative refractory metastatic breast cancer. The FDA designated palbociclib as Breakthrough Therapy on April 9, 2013<sup>4</sup>, based on preliminary review of the data and also because breast cancer meets the criteria for a serious or life-threatening disease. The designation of Breakthrough Therapy automatically qualified palbociclib for Fast Track designation. Palbociclib was also granted priority review status.

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<sup>1</sup> Finn, R., Crown, J., Lang, I., Boer, K., Bondarenko, K., Kulyk, S., et al. (2015). The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncology*, 16, 25-35.

<sup>2</sup> Study 1008, “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”. Pfizer August 13, 2014, submission. Clinical Overview.

<sup>3</sup> Study 1023, “Multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial of fulvestrant (Faslodex®) with or without PD-0332991 (palbociclib) ± goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy”. Pfizer, August 13, 2014, submission. Clinical Overview.

<sup>4</sup> April 9, 2014. DARRTS. Letter to the sponsor. IND 69324. Grant – Breakthrough Therapy Designation.

## **Pregnancy and Lactation Labeling Rule (PLLR)**

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”<sup>5</sup> also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule<sup>6</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

The PLLR will officially take effect on June 30, 2015. In the meantime, conversion to the PLLR format is voluntary. The recommendations in this review are consistent with the PLLR format.

## **DISCUSSION**

### **Review of Data**

#### **Pregnancy**

A search of published literature was performed and no data were found reporting the use of IBRANCE (palbociclib) in pregnant women. DPMH notes that the proposed indication limits the use of palbociclib to post-menopausal women; therefore, pregnancy is highly unlikely in the target patient population. In addition, IBRANCE is to be used only in combination with letrozole which is contraindicated in women who are or may become pregnant.

In animal reproduction studies, palbociclib was teratogenic and fetotoxic at greater than or equal to 3 times the human exposure based on AUC at the recommended human dose.

#### **Lactation**

The Drugs and Lactation Database (LactMed)<sup>7</sup> was searched for available lactation data with the use of palbociclib, and no information was located. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

There are no animal data on the use of palbociclib and breast milk. DPMH notes that the proposed indication includes the use of IBRANCE to be used only in combination with letrozole which is (b) (4). DPMH recommends discontinuing breast feeding while using IBRANCE.

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<sup>5</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

<sup>6</sup> *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

<sup>7</sup> United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed)*. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

## **Females and Males of Reproductive Potential**

### *Infertility*

There are no human data available regarding the effects of palbociclib on fertility. In repeat-dose toxicity studies in rats and dogs, testicular degeneration was observed.

### *Contraception*

The sponsor has recommended that females use contraception during treatment with palbociclib and for (b) (4) days after the last dose. DOP1 recommends using contraception in females for six half-lives after the last dose. The half-life for IBRANCE is approximately 29 ( $\pm$ 5) hours. For products with short half-lives such as IBRANCE, DOP1 recommends contraception use for two weeks after last dose. DPMH agrees with recommending contraception use for two weeks after the last dose.

## **CONCLUSION**

The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling were structured to be consistent with the PLLR.

DPMH discussed our labeling recommendations with DOP1 at a meeting on January 14, 2015. DPMH team recommendations are below and reflect the discussions with DOP2 at that meeting. DPMH refers to the NDA action for final labeling. The sponsors draft labeling recommendation can be found in Appendix A.

## **DPMH LABELING RECOMMENDATIONS**

### **HIGHLIGHTS**

#### **----- WARNINGS AND PRECAUTIONS -----**

- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.4, 8.1, 8.3)

## **5 WARNINGS AND PRECAUTIONS**

### **5.4 Embryo-Fetal Toxicity**

Based on mechanism of action, IBRANCE can cause fetal harm. Furthermore, IBRANCE caused embryo-fetal toxicities in animals at maternal exposures that were greater than or equal to 3 times the human clinical exposure based on area under the curve (AUC). Advise females of reproductive potential to use effective contraception during therapy with IBRANCE and for at least two weeks after the last dose [see *Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)*].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### **Risk Summary**

Based on mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. Furthermore, in animal studies, palbociclib was teratogenic and fetotoxic at maternal exposures that were greater than or equal to (b) (4) times the human clinical exposure based on AUC at the recommended human dose. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a

fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

## Data

### *Animal Data*

In a fertility and early embryonic development study in female rats, palbociclib was administered orally for 15 days before mating through to day 7 of pregnancy, which did not cause embryo toxicity at doses up to 300 mg/kg/day with maternal systemic exposures approximately 4 times the human exposure (AUC) at the recommended dose.

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses up to 300 mg/kg/day and 20 mg/kg/day palbociclib, respectively, during the period of organogenesis. The maternally toxic dose of 300 mg/kg/day in rats caused reduced fetal body weights and a skeletal variation (increased incidence of a rib present at the seventh cervical vertebra). The maternally toxic dose of 20 mg/kg/day in rabbits caused an increased incidence of small phalanges on the <sup>(b) (4)</sup>. At these doses in rats and rabbits, the maternal systemic exposures were approximately <sup>(b) (4)</sup> and 9 times the human exposure (AUC) at the recommended dose.

<sup>(b) (4)</sup> CDK4/6 knockout mice die in late stages of fetal development (gestation day 14.5 until birth) due to severe anemia.

## **8.2 Lactation**

### Risk Summary

There are no data on the presence of palbociclib in human milk, the effects of IBRANCE on the breastfed infant, or the effects of IBRANCE on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IBRANCE, advise a nursing woman to discontinue breastfeeding during treatment with IBRANCE.

## **8.3 Females and Males of Reproductive Potential**

### Contraception

#### *Females*

Advise females of reproductive potential to use effective contraception during treatment with IBRANCE and for at least two weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with IBRANCE [see *Use in Specific Populations (8.1)*]

### Infertility

#### *Males*

Based on findings in animals, male fertility may be compromised by treatment with IBRANCE [see *Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)*].

## 17 PATIENT COUNSELING INFORMATION

- Advise females of reproductive potential to use effective contraception during IBRANCE therapy and for at least two weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with IBRANCE [see *Warnings and Precautions (5.4) and Use in Specific Populations (8.1 and 8.3)*].

## APPENDIX A - Pfizer Labeling Recommendations

### 5. WARNINGS AND PRECAUTIONS

(b) (4)

#### 5.5. Embryo-Fetal Toxicity

(b) (4)  
based on the mechanism of action, IBRANCE can cause fetal harm. IBRANCE caused embryo-fetal toxicities in (b) (4) at maternal exposures that were  $\geq$  (b) (4) times the human clinical exposure based on area under the curve (AUC) Females of (b) (4) potential (b) (4) should use (b) (4) contraceptive methods during therapy and for at least (b) (4) after (b) (4) [see *Use in Specific Populations (8.1)*].

## 8. USE IN SPECIFIC POPULATIONS

### 8.1. Pregnancy

(b) (4)  
Based on its mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman. In animal studies, palbociclib was teratogenic and fetotoxic at maternal (b) (4)  $\geq$  (b) (4) times the human clinical exposure based on AUC at the recommended human dose. (b) (4)

(b) (4)

## 17. PATIENT COUNSELING INFORMATION

(b) (4) potential to use (b) (4) during therapy  
and for at least (b) (4) after (b) (4). Advise (u) (4) to (u) (4) their (b) (4) if they (b) (4)  
their partners are pregnant or think they may be pregnant. (b) (4)  
(b) (4) [see *Use in Specific Populations* (8.1 and 8.3)].

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/s/  
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CARRIE M CERESA  
01/21/2015

TAMARA N JOHNSON  
01/21/2015

LYNNE P YAO  
01/21/2015

**MEMORANDUM**  
**FOOD AND DRUG ADMINISTRATION**  
**Center for Drug Evaluation and Research**  
**Office of Prescription Drug Promotion (OPDP)**

\*\*\*\*Pre-decisional Agency Information\*\*\*\*

Memorandum

**Date:** January 14, 2015

**To:** Amy Tilley, RPM  
Division of Oncology Products 1 (DOP1)  
Office of Hematology Oncology Products (OHOP)

**From:** Marybeth Toscano, PharmD, RAC, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** OPDP comments on draft product labeling for Ibrance (Palbociclib)  
NDA 207103

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In response to your consult request dated September 24, 2014, OPDP has reviewed the proposed product labeling (PI) for Ibrance. OPDP's comments are based on the proposed draft of the PI as of January 14, 2015, available at the following link:

<\\cdsnas\transfer\DDOP RPM\Amy Tilley\NDA 207103>

**OPDP will provide final comments at the January 29, 2015 labeling meeting.**

<b>Section</b>	<b>Statement from draft</b>	<b>Comment</b>
<b>1 INDICATIONS AND USAGE</b>	IBRANCE is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received previous systemic treatment for their advanced	Is use of the term "first-line" appropriate since these patients have not received previous systemic treatment for metastatic disease?

	disease.	
<b>14 CLINICAL STUDIES</b>	Overall response rate assessed by the investigator was higher in the IBRANCE plus letrozole compared to the letrozole alone arm (55.4% versus 39.4%).	Please report the number of complete and partial responses.

If you have any questions, please contact Marybeth Toscano at 6-2617 or at [Marybeth.Toscano@fda.hhs.gov](mailto:Marybeth.Toscano@fda.hhs.gov).

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MARYBETH TOSCANO  
01/14/2015

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## **LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** January 12, 2015  
**Requesting Office or Division:** Division of Oncology Products 1 (DOP1)  
**Application Type and Number:** NDA 207103  
**Product Name and Strength:** Ibrance (Palbociclib) Capsules,  
75 mg, 100 mg, and 125 mg  
**Product Type:** Single Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Pfizer Inc.  
**Submission Date:** June 30, 2014 and December 24, 2014  
**OSE RCM #:** 2014-1280  
**DMEPA Primary Reviewer:** Davis Mathew, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

---

## 1 REASON FOR REVIEW

As part of the New Drug Application 207103 for the new molecular entity Palbociclib, this review evaluates the proposed container labels, carton labeling and Prescribing Information (PI) for Ibrance (Palbociclib) capsules for areas of vulnerability that could lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B – N/A
Previous DMEPA Reviews	C – N/A
Human Factors Study	D – N/A
ISMP Newsletters	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review noted the use of dangerous symbols in the PI, and the ambiguous statement “For Oncology Use Only” on the container label and carton labeling. Additionally, we noted that per section 7.1 of PI that coadministration of Ibrance with strong inhibitors of CYP3A4 may increase palbociclib exposure and thus should be avoided. Therefore, section 17 of PI should include a statement informing patients not to take palbociclib with grapefruit or grapefruit juice. However, we defer to clinical pharmacology or the clinical team on this matter.

## 4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote safe use of the product.

#### **4.1 COMMENTS TO THE DIVISION**

##### **A. Prescribing Information**

1. We note section 2 consists of symbols  $\leq$ ,  $<$ ,  $>$ ,  $/$ , throughout the PI to represent “less than or equal to,” “less than,” “greater than,” or “per” respectively. These error prone symbols can be misinterpreted as the opposite of the intended symbol.<sup>1</sup> We suggest spelling out these symbols to prevent any misinterpretation.
2. We note per section 7.1 that coadministration of Ibrance with strong inhibitors of CYP3A4 may increase palbociclib exposure and thus should be avoided. Therefore, we note that section 17 should include a statement informing patients not to take palbociclib with grapefruit or grapefruit juice. However, we defer to clinical pharmacology or the clinical team on whether this increase in plasma concentration of Ibrance is clinically significant.

#### **4.2 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR**

##### **A. Carton and Container labeling**

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.

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<sup>1</sup> Institute for Safe Medication Practices (ISMP). ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP:2010

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ibrance that Pfizer, Inc. submitted on December 24, 2014.

<b>Table 2. Relevant Product Information for Ibrance</b>	
<b>Active Ingredient</b>	Palbociclib
<b>Indication</b>	Ibrance is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER) – Positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease.
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	Capsules
<b>Strength</b>	75 mg, 100 mg, and 125 mg
<b>Dose and Frequency</b>	The recommended dose is 125 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.
<b>How Supplied</b>	Bottles of 21 capsules each comprising of 125 mg, 100 mg and 75 mg capsules.
<b>Storage</b>	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).
<b>Container Closure</b>	High density polyethylene (HDPE) (b) (4)

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with postmarket medication error data, we reviewed the following Ibrance labels and labeling submitted by Pfizer Inc. on June 30, 2014 and December 24, 2014.

- Container label submitted on June 30, 2014
- Carton labeling submitted on June 30, 2014
- Professional Sample Container Labeling submitted on June 30, 2014
- Full Prescribing Information submitted on December 24, 2014

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

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<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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DAVIS MATHEW  
01/12/2015

CHI-MING TU  
01/12/2015

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY**

DATE: December 12, 2014

TO: Amy Tilley, Regulatory Health Project Manager  
Julia Beaver, M.D., Medical Reviewer (Efficacy)  
Laleh Amiri-Kordestani, M.D., Medical Reviewer (Safety)  
Division of Oncology Products 1

FROM: Lauren Iacono-Connors, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207103

APPLICANT: Pfizer, Inc.

DRUG: Ibrance (palbociclib, PD 0332991)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION(S): For the treatment of advanced breast cancer.

CONSULTATION REQUEST DATE:		August 11, 2014
INSPECTION SUMMARY GOAL DATE:	Original:	February 2015
	Updated:	December 2014
DIVISION ACTION GOAL DATE:	Original:	April 13, 2014
	Updated:	Mid-January 2015
PDUFA DATE:		April 13, 2015

## I. BACKGROUND:

Pfizer, Inc., [Pfizer] seeks approval to market Ibrance (palbociclib; PD-0332991) for the treatment of advanced breast cancer. Palbociclib received Breakthrough Therapy designation from the FDA in April 2013, for the first-line systemic treatment of women with advanced or metastatic ER+, HER2-breast cancer. This designation was based on interim data from the PALOMA-1 trial.

Palbociclib, is an investigational oral targeted agent that selectively inhibits cyclin-dependent kinases (CDKs) 4 and 6 to regain cell cycle control and block tumor cell proliferation. Loss of cell cycle control is a hallmark of cancer, and CDK 4/6 are overactivated in numerous cancers, leading to loss of proliferative control. CDK 4/6 are key regulators of the cell cycle that trigger cellular progression from growth phase (G1) into phases associated with DNA replication (S). The key study supporting this application is Study A5481003 (PALOMA [Palbociclib Ongoing trials in the Management of Breast Cancer] -1 study). This was an open-label, randomized, Phase 1/2 clinical study aimed to assess the efficacy, safety and PK of palbociclib in combination with letrozole and of letrozole alone for the first-line treatment of ER-positive, HER2-negative advanced breast cancer in postmenopausal women. The study had a Phase 1 portion to assess the safety and tolerability of the combination and to exclude a drug-drug interaction (DDI) within the combination. Additionally, the study had a randomized Phase 2 portion in two parts to assess the efficacy and safety of palbociclib in combination with letrozole and of letrozole alone in the first-line treatment of ER-positive, HER2-negative postmenopausal patients with advanced breast cancer (Phase 2, Part 1 [Ph2P1]) and in a prospectively defined population of ER-positive, HER2-negative postmenopausal patients with tumors also demonstrating CCND1 gene amplification and/or loss of CDKN2A (Phase 2, Part 2 [Ph2P2]). Both Ph2P1 and Ph2P2 consisted of a screening period of up to 28 days, a treatment period that continued until discontinuation criteria were met, and a follow-up visit completed approximately 28 days after the last dose of study treatment.

It was planned that 12-30 patients would be enrolled in Phase 1 of Study A5481003. A total of 12 patients were enrolled and treated. It was planned that 60 patients would be enrolled in Phase 2 Part I of Study A5481003. A total of 66 patients were randomized and 62 were treated. It was planned that 150 patients would be enrolled in Phase 2 Part 2 of Study A5481003. A total of 99 patients were randomized and 98 were treated.

Following Protocol Amendment 5 (20 June 2012), accrual to Ph2P2 was terminated and the protocol amended to determine the clinical benefit of the combination in patients randomized

in both Ph2P1 and Ph2P2. Briefly, an interim analysis of Ph2P1 data was performed and supported that clinical activity of PD 0332991 in combination with letrozole for the first-line treatment of ER+/HER2 negative advanced breast cancer in postmenopausal women is independent of patients' biomarker (CCND1/p16) status. In addition, the analysis suggested that the combination of PD 0332991 plus letrozole may demonstrate substantially better efficacy than previously hypothesized. The protocol was amended to determine the clinical benefit of the combination in patients randomized in both Part 1 and Part 2 and for additional interim analyses.

The Phase 1 study was conducted at three centers in one country (United States). The Phase 2 study was conducted at 50 centers in 12 countries (Canada [2 sites], France [2 sites], Germany [8 sites], Hungary [7 sites], Ireland [4 sites], Italy [1 site], Russia [4 sites], South Africa [1 site], South Korea [2 sites], Spain [5 sites], Ukraine [4 sites], and the United States [10 sites]).

This study was conducted under IND 069324.

Four clinical sites were chosen for inspection: Site 1033 (Dr. John Paul Crown, Dublin, Ireland), Site 1011 (Dr. Istvan Lang, Budapest, Hungary), Site 1008 (Dr. Katalin Boer, Budapest, Hungary) and Site 1001 (Dr. Richard Finn, Los Angeles, California) based on enrollment of large numbers of study subjects. The study sponsor, Pfizer, Inc., and CRO (b) (4), who performed the function of the Blinded Independent Central Review (BICR)/Central Imaging Vendor, were also inspected.

## II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
<b>CI#1: Dr. Richard Samuel Finn</b> UCLA School of Medicine Division of Hematology/Oncology 10945 Le Conte Avenue, Suite 3360 Los Angeles, CA 90095	Protocol: A5481003  Site Number: 1001  Number of Subjects: 20	September 2, 2014 – November 18, 2014  34 Days on site.	Pending  Interim classification: OAI
<b>CI#2: Prof. John Paul Crown</b> Medical Oncology Research Department 2nd Floor, Clinical Research Center (CRC) Elm Park, Dublin, 4 Ireland	Protocol: A5481003  Site Number: 1033  Number of Subjects: 13	October 20-23, 2014	Pending  Interim classification: NAI

<b>Name of CI or Sponsor/CRO, Location</b>	<b>Protocol #, Site #, and # of Subjects</b>	<b>Inspection Date</b>	<b>Final Classification</b>
<b>CI#3: Dr. Istvan Lang</b> Orszagos Onkologiai Intezet, Kemoterapia B Rath Gyorgy u. 7-9. Budapest 1122 Hungary	Protocol: A5481003 Site Number: 1011 Number of Subjects: 9	November 3-7, 2014	Pending Interim classification: NAI
<b>CI#4: Dr. Katalin Boer</b> Szent Margit Korhaz Onkologia Becsí Ut 132 Budapest, 1032 Hungary	Protocol: A5481003 Site Number: 1008 Number of Subjects: 8	October 26-30, 2014	Pending Interim classification: NAI
<b>Sponsor: Pfizer, Inc.</b> 445 Eastern Point Rd, Groton Connecticut 06340	Protocol: A5481003 Site Numbers: 1001, 1033, 1011, and 1008, plus 2 additional randomly selected sites.	December 1-5, 2014	Pending Interim classification: NAI
<b>CRO:</b> (b) (4)	Protocol: A5481003 Site Numbers: 1001, 1033, 1011, 1008, 1054, and 1102.	(b) (4)	Pending Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

**1. CI#1: Dr. Richard Samuel Finn (Site 1001)**

- a. What was inspected:** The site screened 28 subjects, and 20 subjects were enrolled. At the time of the inspection 13 subjects had completed the study. The study records of 20 enrolled subjects were audited as well as informed consent documents for all 28 screened subjects. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. Areas covered during the inspection include principal investigator oversight, conduct of the study, study recruitment, informed consent, Form FDA 1572/investigator agreements, financial disclosure compliance, subject screening and enrollment, clinical monitoring, source documents, drug accountability, review of the eCRF, safety and primary efficacy endpoint

data, IRB correspondence and approval, and correspondence between the sponsor and site.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be inadequate. The inspection revealed numerous protocol deviations and GCP compliance deficiencies. The primary efficacy endpoints were verified. However, there was evidence of underreporting of adverse events. The firm had transcription errors where AEs were inadvertently not transcribed onto the eCRF, and in some cases AEs were transcribed onto the eCRF after the data cut-off date.

A Form FDA 483 was issued citing 5 inspectional observations for failure to follow the investigational plan, failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation (AEs and concomitant medications), subjects not signing the most current informed consent document or being properly re-consented when informed consents were updated, inaccurate investigational drug disposition records and Form FDA 1572s not being updated in a timely fashion to reflect changes in study staff and clinical laboratory facilities. Protocol deviations and GCP compliance deficiencies are summarized here and detailed in the following sections.

**In summary, protocol deviations included the following:**

1. One subject took 200 mg of investigational product from April 2-12, 2010 instead of 125 mg due to the pharmacist mislabeling one of the bottles.
2. One subject was enrolled despite not having documentation that Inclusion Criterion 5 (measurable disease according to RECIST) was met, and then was incorrectly stratified at randomization. This subject withdrew from the study prior to taking any study medication.
3. Two subjects were incorrectly stratified at randomization.
4. Six subjects did not have all required lab safety assessments performed.
5. One SAE was reported within 2 days instead of within 24 hours per the protocol.
6. Three subjects had pharmacokinetic (PK) samples that were collected out of window.

**In summary, other GCP compliance deficiencies included:**

1. Discrepancies between source documents and the eCRF pertaining to AEs, concomitant medications, and doses taken.
2. Two subjects did not sign informed consent forms (ICF) with the most recent ICF. Also, three subjects were not re-consented with an ICF dated 7/23/2009 which included changes in procedures pertaining to fasting and IP dosing. These subjects were verbally informed of this change in procedure and the IP bottles from the pharmacist also specified the proper dosing instructions.

3. The total number of days the investigational product was taken during cycles 11-18 for one subject could not be verified. The investigational product Accountability records showed that the subject returned 5 of the 25 capsules indicating 20 doses taken, while the eCRF showed that the subject took 21 doses.
4. The 1572's were not updated in a timely manner to reflect changes for two sub-investigators and five laboratories. Also, two laboratories were utilized but were not included on the Form FDA 1572. All labs were accredited.

In addition, there were five discussion items not included on the Form FDA-483 addressed during the close-out of the inspection regarding the following: 1) ensuring that the delegation log is accurate; 2) ensuring that the Form FDA 1572's contain accurate information; 3) maintaining documentation showing that all study staff have received study specific training; 4) completing financial disclosure forms in a timely manner and; 5) ensuring that laboratory reports are signed and dated when they are reviewed, and to document if abnormal values are clinically significant (CS) or not clinically significant (NCS).

**Form FDA 483 Inspectional Observations:**



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

- c. Assessment of data integrity:** The reliability of data for Dr. Finn's site, associated with Study A5481003 submitted to the Agency in support of NDA 207103, could not be verified based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

**2. CI#2: Prof. John Paul Crown (Site 1033)**

- a. What was inspected:** The site screened 27 subjects, and 13 subjects were enrolled. At the time of this inspection seven subjects had completed the study and one was still on treatment. Study records of 13 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 207103, focusing on protocol compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Records and procedures were clear, and generally well organized. The primary efficacy endpoints, as determined by the investigator, were verified. The source records audited at this site also supported the Blinded Independent Central Review (BICR) Vendor-reported

tumor assessments. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles, and drug accountability found no major discrepancies. A Form FDA 483 Inspectional Observations was not issued.

- c. **Assessment of data integrity:** The data for Dr. Crowns' site, associated with Study A5481003 submitted to the Agency in support of NDA 207103, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

### 3. CI#3: Dr. Istvan Lang (Site 1011)

- a. **What was inspected:** The site screened 23 subjects and 9 subjects were enrolled. At the time of this inspection, one subject was still on treatment, five subjects were in follow up, and three had died. Study records of 23 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 207103, focusing on protocol compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.

- b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The primary efficacy endpoints, as determined by the investigator, were verified. The source records audited at this site also supported the Blinded Independent Central Review (BICR) Vendor-reported tumor assessments. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no major discrepancies. A Form FDA 483 was not issued.

- c. **Assessment of data integrity:** The data for Dr. Langs' site, associated with Study A5481003 submitted to the Agency in support of NDA 207103, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

#### 4. Dr. Katalin Boer (Site 1008)

- a. **What was inspected:** The site screened 14 subjects, and 8 subjects were enrolled. At the time of this inspection one subject was in follow up, one was lost to follow up, and six had died. Study records of 14 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 207103, focusing on protocol compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.
- b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The primary efficacy endpoints, as determined by the investigator, were verified. The source records audited at this site also supported the Blinded Independent Central Review (BICR) Vendor-reported tumor assessments. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles, and drug accountability found no major discrepancies. A Form FDA 483 was not issued.
- c. **Assessment of data integrity:** The data for Dr. Boer's site, associated with Study A5481003 submitted to the Agency in support of NDA 207103, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

#### 5. Sponsor: Pfizer, Inc.

- a. **What was inspected:** The sponsor was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection focused on study Sites 1001, 1033, 1011, 1008, and 2 additional randomly selected sites. The inspection included but was not limited to assessment of adverse events/serious adverse events reporting, efficacy endpoint data, Principal Investigator site qualification (financial disclosure, IRB, and curriculum vitae), study specific training for investigators and monitors, Form FDA 1572 and investigator agreements, and monitoring reports.
- b. **General observations/commentary:** Records and procedures were clear, and generally well organized. The sponsor maintained adequate oversight over the study. Monitoring appeared to be adequate; AEs were verifiable. There was no evidence of under-reporting AEs/SAEs by the sponsor. The primary efficacy

endpoint data were verifiable; specifically, subject eCRFs were compared with datalistings submitted to the application. No discrepancies were noted. Compliance with the study protocol, the sponsor's own SOPs and relevant regulatory requirements appeared to be adequate. No study sites were closed due to non-compliance. Monitoring reports showed the monitors informed the study sites of any issues and provided re-training where necessary. The majority of issues noted within the inspectional observations at Site 1001 (Dr. Finn) were detected by the monitors and the majority of the issues noted were included in the CSR. There was no evidence of any major recurring issues within monitoring reports for the study sites reviewed. No Form FDA 483 was issued.

- c. Assessment of data integrity:** With the exception of Dr. Finn's Site (1001), the data from this sponsor submitted to the Agency associated with Study A3481003 in support of NDA 207103 appear reliable based on available information.

**6. CRO:** (b) (4) (BICR)

- a. What was inspected:** The CRO was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection focused primarily on assessing the integrity of the tumor response and disease progression source records for data generated by the Blinded Independent Central Review (BICR) Vendor, for the clinical study, A3481003, and comparing those source data to the data listings submitted to the application. The inspection also included a review of the firm's organization and personnel, staff and contract staff qualification and training, correspondence, quality assurance, data collection and handling, computer system validation, standard operating procedures review and adherence, and BICR Charter adherence.
- b. General observations/commentary:** Records and procedures were adequate, and generally well organized. The primary efficacy endpoint support data, tumor response, generated by the BICR Contractor and submitted to NDA 207103 were verifiable for the 4 clinical sites referred to above, as well as 2 additional sites, 1054 and 1102. For all 6 sites, all subjects' image readings performed by the CRO radiologist were verified against the data listings submitted to the application. There were no discrepancies. Also, there was no evidence of BICR non-compliance with the Charter. No Form FDA 483 was issued.
- c. Assessment of data integrity:** The data from this contractor, (b) (4) who performed the function of the Blinded Independent Central Review (BICR)/Central Imaging Vendor, associated with Study A3481003 in support of NDA 207103, appear reliable and may be used in support of the respective indication.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for Site 1033 (Dr. John Paul Crown, Dublin, Ireland), Site 1011 (Dr. Istvan Lang, Budapest, Hungary), Site 1008 (Dr. Katalin Boer, Budapest, Hungary), Site 1001 (Dr. Richard Finn, Los Angeles, CA), the study sponsor, Pfizer, Inc., and CRO (b) (4), who performed the function of the Blinded Independent Central Review (BICR) Vendor, the Study A5481003 data submitted to the Agency in support of NDA 207103, with the exception of Site 1001 (Dr. Finn), appear reliable based on available information.

The preliminary classification for clinical investigators Dr. Crown, Dr. Lang and Dr. Boer, and for the study sponsor, Pfizer, and for the CRO Central Imaging Vendor, (b) (4) is No Action Indicated (NAI). The preliminary classification for clinical investigator Dr. Finn is Official Action Indicated (OAI).

Site 1001 (Dr. Richard Finn, Los Angeles, CA) had a number of protocol deviations, and GCP compliance violations. Due to the totality of these observations, OSI is recommending that the data generated at this site not be used. A preliminary assessment of impact on site data exclusion was conducted by the DOP1 clinical and statistical reviewers. It was confirmed that none of the Form FDA 483 inspectional observations put subjects at significant risk nor affected key study outcome measures. However, OSI still recommends Site 1001 data be excluded from all study analyses in support of the respective indication. Briefly, the totality of inspectional observations demonstrated poor ability of this site to adhere to the investigational plan. In addition, a BIMO inspection and the findings are not intended to be an all-inclusive accounting of GCP compliance and study conduct, but instead are intended to be representative of the same. Therefore, there may be additional GCP violations and protocol noncompliance that were not uncovered during the inspection. For these reasons OSI recommends excluding all Study A5481003 data generated by Site 1001.

The inspectional findings of the study sponsor found no significant issues, and confirmed that the inspectional observations and issues raised at Dr. Finn's site were not systemic across study clinical sites.

With the exception of Dr. Finn's site, associated with Study A5481003, the data submitted to the Agency in support of NDA 207103, appear reliable.

**Note:** The observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{ See appended electronic signature page }

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Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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Susan D. Thompson, M.D.  
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/s/  
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LAUREN C IACONO-CONNORS  
12/12/2014

SUSAN D THOMPSON  
12/12/2014

KASSA AYALEW  
12/12/2014

**MEMORANDUM**

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

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DATE: December 8, 2014

TO: Richard Pazdur, M.D.  
Director, Office of Hematology and Oncology Products  
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Recommendation to accept data for NDA 207-103,  
Palbociclib (PD-0332991) by Pfizer, Inc. without  
on-site inspection of the bioanalytical site

The Division of Bioequivalence and GLP Compliance (DBGLPC) recommends accepting bioanalytical data for NDA 207-103 study A5481036 without on-site inspection of the analytical site, (b) (4). This memo provides the rationale for this recommendation and why DBGLPC is declining to inspect (b) (4). Please note that an inspection of the requested clinical site (New Haven Clinical Research Unit, New Haven, CT) for study A5481036 has been requested to proceed via the New England District Office. A review memo for this inspection will be provided soon after completion of the inspection.

**Background**

The Division of Oncology Products 1 (DOP1) requested inspections of clinical and analytical sites for the following study.

A5481036: "A phase 1, Open-Label 6-Sequence 3-Period Crossover Study of Palbociclib (PD-0332991) in Healthy Volunteers to Estimate Relative Bioavailability of Palbociclib Formulations"

Bioanalytical portions of this study were conducted at the following site:

**Analytical Site:** [redacted] (b) (4)

OSI-DBGLPC has inspect [redacted] (b) (4) times in the last three years, covering [redacted] (b) (4) applications. [redacted] (b) (4) following is a list of applications with s [redacted] (b) (4) es audited during those inspections, the dates of bioanalyses for the audited studies, and the analytical methods for the subject sample analyses employed in these studies.

Application	Analytical Method	Bioanalysis Period
[redacted] (b) (4)	HPLC-MS/MS	[redacted] (b) (4)
[redacted] (b) (4)	HPLC-MS/MS	[redacted] (b) (4)
[redacted] (b) (4)	HPLC-MS/MS	[redacted] (b) (4)
[redacted] (b) (4)	HPLC-MS/MS	[redacted] (b) (4)
[redacted] (b) (4)	HPLC-MS/MS	[redacted] (b) (4)
[redacted] (b) (4)	HPLC-MS/MS	[redacted] (b) (4)
[redacted] (b) (4)	HPLC-MS/MS	[redacted] (b) (4)
[redacted] (b) (4)	HPLC- UV Abs	[redacted] (b) (4)
[redacted] (b) (4)	Radioimmunoassay	[redacted] (b) (4)

Each inspection included a thorough review of all records associated with the studies and method validations, correspondence with the sponsors and the clinical sites, records of subject sample receipt and storage, notebooks and electronic records, standard operating procedures (SOPs), as well as examination of facilities, and interviews and discussions with the firm's management and staff. No significant adverse observations were identified during these inspections and the inspectional outcomes from all inspections were classified as No Action Indicated (NAI).

The quantification of Palbociclib (PD-0332991) in human plasma from thirty-six healthy volunteers was conducted by HPLC-MS/MS detection during a period spanning (b) (4) (b) (4) the method (b) (4) y is representative of methodology employed in (b) (4) of the (b) (4) audited studies. The validation for this study (b) (4) s comple (b) (4) during two periods; initial validation was conducted from (b) (4), and additional validations were conducted from (b) (4) - (b) (4). The initial validations were conducted contemporaneously with previously audited studies. The study analyses were conducted at times between the last two inspections, which confirmed that proper facilities, procedures, and controls were in place at (b) (4). Thus, the inspectional outcomes from previous inspections, along with careful review of the method validation and bioanalytical study reports for the current study, provide reasonable assurance to DBGLPC that (b) (4) conducted study A5481036 without significant irregularities.

**Conclusion:**

Based on the satisfactory inspections in recent years, their final inspectional classifications, and the similarity of the methodologies and processes used to conduct the studies inspected compared with the current study requested, this reviewer concludes that bioanalytical data from study A5481036 are acceptable (b) (4) on-site inspection at (b) (4).

Kara A. Scheibner, Ph.D.  
BE Branch, DBGLPC, OSI

DARRTS cc:

OSI/Kassim/Taylor/Haidar/Bonapace/Skelly/Choi/Dasgupta/Dejernett  
/Nkah/Fenty-Stewart/Johnson  
CDER/OND/OHOP/DOPl/Pazdur/Tilley

Email cc:

ORA DO BIMO mailbox  
Draft: KAS 9/18/2014  
Edit: MFS 9/18/2014; SHH 12/3/2014; WHT 12/8/2014  
ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice (b) (4) ONS/BE Program  
/Analytical Sites/ (b) (4)

File: BE6758 (NDA 207-103)

**FACTS: 11473478**

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/s/  
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KARA A SCHEIBNER  
12/09/2014

SAM H HAIDAR  
12/09/2014

WILLIAM H TAYLOR  
12/09/2014

**Interdisciplinary Review Team for QT Studies Consultation:  
Thorough QT Study Review**

<b>IND or NDA</b>	207103
<b>Brand Name</b>	Ibrance®
<b>Generic Name</b>	Palbociclib (PD-0332991)
<b>Sponsor</b>	Pfizer, Inc,
<b>Indication</b>	Advanced Breast Cancer (ABC)
<b>Dosage Form</b>	Capusle
<b>Drug Class</b>	Reversible inhibitor of CDK 4 and 6
<b>Therapeutic Dosing Regimen</b>	3/1 Schedule: 125 mg PO QD x 21 days on, 7 days off
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	<u>Single Dose:</u> 225 mg PO <u>Multiple Dose:</u> 3/1 Schedule: 125 mg PO QD x 21 days on, 7 days off 2/1 Schedule: 200 mg PO QD x 14 days on, 7 days off
<b>Submission Number and Date</b>	001 / 6/30/2014
<b>Review Division</b>	DOP1

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

## 1 SUMMARY

### 1.1 OVERALL SUMMARY OF FINDINGS

This study pooled data from Studies 1001, 1002, and 1003. For Study 1003, no large change (i.e., > 20 ms) in the QTc interval was detected when administered of therapeutic dosing regimen of palbociclib. Using an estimated study specific correction (QTcS) interval, the largest upper bounds of the 2-sided 90% confidence interval (CI) for the mean changes from baseline for 125 mg QD for 2 weeks on/1 week off is 14.2 ms in Study 1003 on Cycle 1 Day 14. The sponsor did not have a positive control (moxifloxacin) arm.

All three studies are open-labels, 184 patients provided a total of 569 PK-ECG matched pairs for exploring RR-C and QTc-C relationships. Overall summary of study 1003 findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds of  $\Delta$ QTcS for Palbociclib (FDA Analysis – Study 1003, Cycle 1 Day 14)**

Treatment	Time (H)	Mean (ms)	Std Dev (ms)	90% CI (ms)
125 mg QD on the 2/1 schedule	96	5.2	17.4	(-3.9, 14.2)
125 mg QD on the 3/1 schedule	4	2.7	13.7	(-2.3, 7.8)

The median and mean  $C_{max,ss}$  in patients receiving a therapeutic regimen of 125 mg palbociclib QD for 3 weeks on/1 week off and in combination with 2.5 mg letrozole QD values were 107 and 112 ng/mL, respectively. Based on the population PK analysis, mild hepatic impairment has no impact on the exposure of palbociclib. Expected high clinical exposure scenarios may include concomitant use of strong CYP3A inhibitors and administration of palbociclib in patients with severe hepatic impairment. Clinical studies for such scenarios have not been conducted. Such supra-therapeutic exposure is expected to be avoided through recommended labeling.

## 2 PROPOSED LABEL

Following proposed labeling information is provided by the sponsor related to cardiac Electrophysiology:

### 12. CLINICAL PHARMACOLOGY

#### Cardiac Electrophysiology

(b) (4) 184  
 patients (b) (4)  
 At the mean observed maximal steady-state palbociclib concentration following a therapeutic schedule (e.g., 125 mg daily for 21 consecutive days followed by 7 days off to comprise a complete cycle of 28 days), (b) (4)

### QT-IRT RECOMMENDATIONS

*Our recommendations are suggestions only. We defer final labeling decisions to the review division.*

#### 12.2 Pharmacodynamics

##### Cardiac Electrophysiology

The effect of Ibrance® on the QTc interval was evaluated (b) (4) 184 patients. (b) (4)  
 However, at the therapeutic schedule (e.g., 125 mg daily for 21 consecutive days followed by 7 days off to comprise a complete cycle of 28 days), (b) (4)

### **3 BACKGROUND**

The Sponsor requested a Type B Meeting to reach agreement with FDA on the design of the registration trial to support approval of PD-0332991 (palbociclib) for the proposed indication of use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor- positive and human epidermal growth factor 2 negative advanced breast cancer.

#### **3.1 PRODUCT INFORMATION**

PD-0332991 is an oral reversible inhibitor of cyclin-dependent kinases 4 and 6. The proposed dose is 125 mg once daily for 21 continuous days followed by 7 days off treatment.

#### **3.2 MARKET APPROVAL STATUS**

Palbociclib is not approved for marketing in any country.

#### **3.3 PRECLINICAL INFORMATION**

Please refer to previous review (September 10, 2012)

The potential for QT prolongation and hemodynamic effects were identified from in vitro assays and/or in vivo cardiovascular dog studies. Palbociclib caused a small but statistically significant increase on APD90 at 10 uM (4475 ng/mL) in the dog Purkinje fiber assay, and had an IC50 of 3.2 uM (1432 ng/mL) in a hERG assay. The potential for QTc interval prolongation was identified from conscious telemetered dogs at unbound plasma concentrations  $\geq 67$  ng/mL, while QT interval prolongation was not noted in dogs given doses up to 2 mg/kg/day in the 3- or 15-week toxicity studies, with unbound Cmax values of up to 80 and 42 ng/mL, respectively. In addition to the potential for QT prolongation, hemodynamic effects were noted in conscious telemetered dogs, where decreases in HR (up to 8 bpm) that correlated with increases in RR interval (up to 73 msec) and modest increases in systolic blood pressure (up to 6 mmHg) were observed at unbound plasma concentrations  $\geq 140$  ng/mL. No cardiovascular effects are anticipated at plasma concentrations  $< 4$  times those associated with the unbound Cmax at the human clinical dose of 125 mg QD (17 ng/mL).

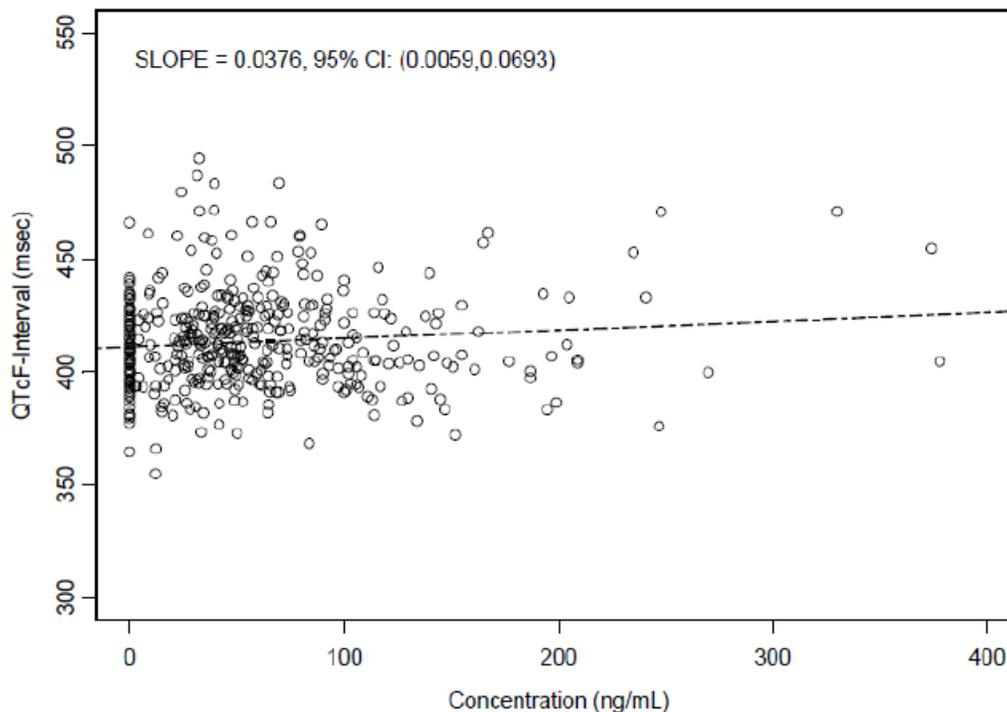
#### **3.4 PREVIOUS CLINICAL EXPERIENCE**

The safety of palbociclib was investigated in 18 clinical studies in which 659 subjects/patients received either palbociclib or a comparator and 126 patients were randomized to blinded therapy in dosing ranging from 25 to 225 mg on a 14/21 or 21/28 cycle.

The available safety data for studies A5481001, A5481002, A5481003, A5481004, A5481008 and A5481010 were reviewed and there were few cardiac safety events (per ICHE14 criteria) identified. There were three fatal cardiac arrests (in setting of: (1) progressive disease (2) prior CABG and angina (3) blinded case: thrombophlebitis with possible PE). There was one case of “grade one” syncope that spontaneously resolved. There were no adverse events of seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or QT prolongation (QTcS)  $> 500$  msec and/or postbaseline maximum mean QTcF.

A potential relationship between QTcF and palbociclib concentrations was noted from Study A5481001. The Sponsor reports that triplicate ECGs were collected from 73 patients at multiple time points with matched PK samples at the expected  $T_{max}$ . The relationship between plasma concentrations and QTcF is illustrated in Figure 1.

**Figure 1: QTcF Interval vs. PD-0332991 Plasma Concentration (Study A5481001)**



*Source: Meeting Background Materials, Figure 3, Page 42.*

### 3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of Palbociclib's clinical pharmacology.

## 4 SPONSOR'S SUBMISSION

### 4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 69,324. The sponsor submitted the study report PMAR- EQDD-A548b-DP4-287 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

### 4.2 TQT STUDY

#### 4.2.1 Title

Palbociclib QTc-Concentration Analysis in Cancer Patients

#### 4.2.2 Protocol Number

PMAR- EQDD-A548b-DP4-287

#### 4.2.3 Study Dates

Date Issued: April 24, 2014

#### 4.2.4 Objectives

- To characterize the effects of palbociclib exposure on the QT interval (QTc or heart rate-corrected QT) in cancer patients.
- To assess whether palbociclib exposure affects heart rate (via effect on RR).

#### 4.2.5 Study Description

##### 4.2.5.1 Design

Study 1001, the first-in-human study, provided ECG data at doses higher than the therapeutic dose, Study 1002 provided limited data (17 patients only), and Study 1003 provided ECG data using the target dose in the intended population. The studies and design characteristics utilized in the QTc-concentration (QTc-C) analysis are shown below (Table 2).

**Table 2: Palbociclib Studies Used for QT Assessment**

S	Design/Population	Dose/Regimen
A5481001	Phase 1, open-label, dose escalation in advanced cancer patients	Schedule I: 21 day on/7 day off Cycle 25, 50, 75, 100, 125, and 150 mg daily orally Schedule II: 14 day on/7 day off cycle 100, 125, 200, and 225 mg daily orally
A5481002	Phase 2, single arm, open-label in mantle cell lymphoma (MCL) patients	125 mg daily in a 21 day on/7 day off cycle
A5481003	Phase 1/2, open-label, multicenter, randomized study in postmenopausal women with ER+ HER2-negative advanced breast cancer (Phase 2 Part 1) and in biomarker-positive (CCND1/p16) patients (Phase 2 Part 2)	<u>Phase1</u> Cycle 1: 125 mg daily palbociclib orally 14 day on/7 day off Cycles 2+: 125 mg palbociclib 21 days on/7 days off plus 2.5 mg letrozole daily orally <u>Phase2</u> Arm A: 2.5 mg letrozole plus 125 mg palbociclib daily orally in 21 day on/7 day off cycle Arm B: 2.5 mg letrozole daily orally

Source: Protocols for Studies A5481001, A5481002, and A5481003.  
Study A5481001 CSR Section 9.1.1 Table 20/Figure 3.

##### 4.2.5.2 Controls

No placebo and positive (moxifloxacin) controls.

### 4.2.5.3 Blinding

Treatment conducted in open-labels.

## 4.2.6 Treatment Regimen

### 4.2.6.1 Treatment Arms

See Table 2 above.

### 4.2.6.2 Sponsor's Justification for Doses

NA

*Reviewer's Comment: Reasonable if the proposed therapeutic schedule (e.g., 125 mg daily for 21 consecutive days followed by 7 days off to comprise a complete cycle of 28 days) is accepted by the review division.*

### 4.2.6.3 Instructions with Regard to Meals

Study A5481001

Oral PD 0332991 was administered QD on an empty stomach. No food or liquids other than water were to be consumed for 2 hours before and 2 hours following each dose. In addition, patients participating in the food-effect component of the study had to either fast overnight for 10 hours prior to the first dose in Cycle 1 or 2 (if they were randomized to receive PD 0332991 under "fasted" conditions), or were to consume a high-fat meal prior to dosing on Day 1 of Cycle 1 or 2, (if they were randomized to receive PD 0332991 under "fed" conditions). PD 0332991 was to be administered ~ 30 minutes after the start of the meal and the complete meal should have been consumed before dosing.

Study A5481002

PD 0332991 was administered orally once daily on an empty stomach. No food or liquids other than water was to be consumed for 2 hours before and 2 hours following each dose.

Study A5481003

#### Phase 1

In Cycle 1, PD 0332991 was administered once a day in the morning and, on Day 14 only (PK day), on an empty stomach (overnight fast of approximately 10 hours and 4 hours post-dose fasting). In Cycles 2 and beyond, PD 0332991 was administered once a day together with letrozole, in the morning and, on Cycle 2/Day 14 only (PK day), on an empty stomach (overnight fast of approximately 10 hours and 4 hours post-dose fasting).

#### Phase 2

In all cycles, PD 0332991 was administered together with letrozole in the morning without regard to food.

*Reviewer's Comment: Food increases the bioavailability of palbociclib. Sponsor analyzed the data collected under fasted and fed condition which enables better characterization of QT prolongation.*

### 4.2.6.4 ECG and PK Assessments

See the following table.

**Table 3: Timing of Plasma Pharmacokinetic and ECG Assessment**

	Visit/Schedule	Pharmacokinetic Samples (hr post dose)	ECG Measurements (hr post dose)	
A5481001	<b>21 day on/7 day off</b>			
	Baseline	-	Approx. same time as the scheduled Cycle 1 Day 1, 3 hr postdose ECG	
	Cycle 1, Day 1	0 (predose), 1, 2, 4, 7, 10	3	
	Cycle 1, Day 8	0 (trough), 1, 2, 4, 7, & 10 hr postdose. Patients who dose escalate, a trough and postdose (1-2 hr) plasma are required on Day 8 of the Cycle following dose escalation	3	
	Cycle 1, Day 15	At time of biopsy, ECG, and also at predose for NHL	3	
	<b>14 day on/7 day off</b>			
	Baseline	-	3	
	Cycle 1, Day 1	0 (predose), 1, 2, 4, 7, 10	3	
	Cycle 1, Day 8	0 (predose), 1, 2, 4, 7, 10 hr postdose. Patients who dose escalate, a trough and postdose (1-2 hr) plasma are required on Day 8 of the Cycle following dose escalation	3	
	Cycle 1, Day 15 (expanded cohort)	At time of biopsy, ECG, and also at predose for NHL	4	
	A5481002	Screening		≤21 Days Prior to Dosing
		Cycle 1 or 2 <sup>a</sup> , Day 1	0 (predose)	0 (predose)
		Cycle 1 or 2 <sup>a</sup> , Day 15	0 (predose)	
		Cycle 1 or 2, Day 21	At approximately the same time as the tumor biopsy	0 (predose)
End of treatment				
A5481003	<b>Phase 1</b>			
	Screening		Visit	
	Cycle 1, Day 1		0 (predose)	
	Cycle 1, Day 8	0 (predose)		
	Cycle 1, Day 12	0 (predose)		
	Cycle 1, Day 14	0, 1, 2, 4, 8, 12, 24, 48, 96, and 120	0 (predose) 2, 4, 8, 24, 48, and 96	
	Cycle 2, Day 1		0 (predose), 4	
	Cycle 2, Day 8	0 (predose)		

	Cycle 2, Day 12	0 (predose)	
	Cycle 2, Day 14	0, 1, 2, 4, 8, 12, 24	0 (predose), 4
	Cycle 2, Day 28	0, 1, 2, 4, 8, 12, 24	-
	End of treatment		Visit
	<b>Phase 2 (palbociclib plus letrozole arm)</b>		
	Screening		Visit
	Cycle 1, Day 1		0 (predose)
	Cycle 1, Day 14	0 (predose) and 1 to 8 hours after dosing	0 (predose)
	Cycle 2, Day 14	0 (predose) and 1 to 8 hours after dosing	0 (predose)
	Cycle 3, Day 1		0 (predose)
	End of treatment	Some time following last dose	0 (predose)

*Reviewer's Comment: Based on the Tmax of 7.9 hr (2.2-8.2 hr) for palbociclib and 4.0 hr (4.0-6.1 hr) for M17 (PF-05089326), the timing of ECGs are acceptable.*

#### 4.2.6.5 Baseline

The baseline observations used the measurements taken at the time closest to the administration of the first dose of palbociclib. When ECG measurements were available at both screening and just prior to the first dose, the ECG measurements prior to the first dose were used as baseline measurements in the RR-C and QTc-C analyses.

#### 4.2.7 ECG Collection

In all studies, three consecutive 12-lead ECGs were scheduled to be performed at least two minutes apart. ECGs were expected to be performed prior to PK blood draws.

#### 4.2.8 Sponsor's Results

##### 4.2.8.1 Study Subjects

A total of 3593 individual QT records and 1904 concentrations obtained from 185 patients were included in the analysis dataset. Among the 185 patients, 184 patients provided a total of 569 PK-ECG matched pairs for exploring RR-C and QTc-C relationships, suggesting that the PK-ECG matched data could well represent the patient population in these studies.

The majority of the patients were female (48 males, 136 females). The average age and baseline body weight of patients in the analysis data set including patients with both PK-ECG pairs and unmatched (ECG only) was 60.5 years (range: 22 to 89) and 74.1 kg (range: 37.9 to 123).

### Summary of Patients Data

			All Data	PK-ECG Matched Data
	Group	Level	N	N
Number of subjects	All	All	185	184
	Protocol	1001	73	72
		1002	17	17
		1003	95	95
	Sex	Males	49	48
		Females	136	136
PK-ECG matched pairs	All	All	---	569
	Protocol	1001	---	307
		1002	---	23
		1003	---	239

Source Data: ePharmacology Artifact ID Number 8120669.

ECG=Electrocardiography; N=number of subjects or the records of PK-ECG matched pair; PK=pharmacokinetics.

### Summary of Concentration Data

		All Data	PK-ECG Matched Data
	Statistic	Value	Value
Palbociclib concentration (ng/mL)	Number of records	1904	385
	Mean (Std Dev)	59.5 (48.3)	63.8 (45.4)
	Median (min-max)	51.3 (2.51-378)	55.2 (2.51-329)

Source Data: ePharmacology Artifact ID Number 8120669.

PK=pharmacokinetic; ECG=Electrocardiography; Std Dev=standard deviation; min=minimal; max=maximal.

Source: Clinical Study Report No., Section 6.1, Table 4, page 23/174

## 4.2.8.2 Statistical Analyses

### 4.2.8.2.1 Primary Analysis

A linear mixed effects model was used to assess RR-C and QTc-C with inter-individual variability on both the intercept and slope. Sex was tested as covariate on the intercept for analysis of the QTc-interval. An ANOVA test suggested that sex was not a significant covariate for intercept. Similarly, separate variances for singlet and mean of triplicate observations were not required for any of the dependent variables.

The final model for all QTc variables estimated intercept (baseline QTc), palbociclib effect on QTc changes (slope: msec/ng/mL), the inter-subject variability in intercept and the slope, and one residual variance term. Additive error models for inter- and intra-subject variances were adequate for the QTc endpoints. For the RR-C relationship, since palbociclib had no effect on the RR interval (slope no different from zero), and the model which included inter- subject variability on slope did not improve the model fit, the inter-subject variability on the intercept alone was included.

The slope (95% CI) of the RR-C relationship was 0.0420 msec/ng/mL, which is not statistically different from zero, suggesting that palbociclib did not have a concentration-dependent effect on heart rate in the examined patient population.

The slopes (95% CI) of QTcS-C, QTcF-C, and QTcB-C relationship were 0.0524 (0.0176-0.0871), 0.0531 (0.0185-0.0878), and 0.0428 (0.00680-0.0788) msec/ng/mL, respectively. All slopes were statistically significantly different from zero ( $p < 0.05$ ), suggesting that palbociclib caused a concentration dependent increase in QT interval as Table below.

### Summary of Final Model Parameters

	Parameter	Estimate (95% Confidence Interval)
RR-interval	Intercept (msec)	814 (793-834)
	Slope (msec/ng/mL)	0.0420 (-0.11-0.195)
	Standard deviation of intercept	130 (116-146)
	Residual error (standard deviation)	72.6 (67.7-77.8)
QTcS-interval	Intercept (msec)	413 (410-415)
	Slope (msec/ng/mL)	0.0524 ( 0.0176-0.0871)
	Standard deviation of intercept	15.6 (13.7-17.9)
	Standard deviation of slope	0.131 (0.0929-0.184)
	Correlation between slope and intercept	-0.144 (-0.467-0.212)
	Residual error	9.03 (8.27-9.86)
QTcF-interval	Intercept (msec)	410 (407-412)
	Slope (msec/ng/mL)	0.0531 (0.0185-0.0878)
	Standard deviation of intercept	15.9 (13.9-18.1)
	Standard deviation of slope	0.127 (0.0893-0.181)
	Correlation between slope and intercept	-0.120 (-0.433(-0.220)
	Residual error	9.25 (8.47-10.1)
QTcB-interval	Intercept (msec)	425 (423-428)
	Slope (msec/ng/mL)	0.0428 (0.00680-0.0788)
	Standard deviation of intercept	17.6 (15.5-20.0)
	Standard deviation of slope	0.129 (0.0900-0.185)
	Correlation between slope and intercept	-0.156 (-0.431-0.145)
	Residual error	9.93 (9.10-10.8)

Source Data: ePharmacology Artifact ID Numbers 8100625, 8100951, 8099948, and 8100128.

Source: Clinical Study Report No., Section 6.4, table 10, page 31/174

The sponsor's concluded that there was a slight positive linear relationship between palbociclib concentration and QTcS was observed (see Table below); however, at the mean or median maximal steady-state palbociclib concentrations following administration of therapeutic doses in cancer patients, the upper bound of the one-sided 95% confidence interval for the increase in QTcS did not exceed the threshold of 10

msec, thus suggesting QT prolongation is not a major safety concern for palbociclib at the recommended therapeutic dose.

**Summary of Mean ECG Data by Baseline and Treatment Period**

			<b>All Data</b>	<b>PK-ECG Matched Data</b>
QTcS (msec)	Baseline	Number of records	428	184
		Mean (Std Dev)	412 (18.5)	412 (17.5)
		Median (min-max)	413 (360-485)	413 (360-469)
	Treatment	Number of records	987	385
		Mean (Std Dev)	417(21.2)	417 (19.6)
		Median (min-max)	416 (323-545)	416 (364-485)

Source Data: ePharmacology Artifact ID Number 8120669.

PK=pharmacokinetic; ECG=Electrocardiography; Std Dev=standard deviation; min=minimal; max=maximal.

Source: *Clinical Study Report No.*, page 24/174

*Reviewer’s Comments We will provide our independent analysis result in Section 5.2.*

**4.2.8.2.2 Assay Sensitivity**

No assay sensitivity established in this study because there is no positive control arm includes in the study.

**4.2.8.2.3 Categorical Analysis**

No data point was considered as an outlier for exclusion.

**4.2.8.3 Clinical Pharmacology**

**4.2.8.3.1 Pharmacokinetic Analysis**

The mean Cmax on day 1 and 8 are shown in table below. Figure below shows the mean concentration-time profile of palbociclib.

**Table 4 Summary of PD 0332991 Mean and Median Plasma PK Parameters by Dose (Day 1 and Day 8 Data Combined)**

Treatment Description (QD)	Study Day	C <sub>max</sub> <sup>1</sup> (ng/mL)	T <sub>max</sub> <sup>2</sup> (hour)	AUC <sub>(0-10)</sub> <sup>1,3</sup> (ng.hour/mL)
25 mg	1 (n=3)	9.6 (63)	4.0 (4.0-4.0)	58 (51)
	8 (n=3)	15.9 (32)	4.0 (2.0-7.0)	119 (32)
50 mg	1 (n=3)	20.7 (3)	4.0 (4.0-4.3)	134 (5)
	8 (n=3)	35.7 (16)	4.1 (2.0-7.0)	274 (15)
75 mg	1 (n=7)	28.7 (24)	4.0 (4.0-10.0)	199 (20)
	8 (n=6)	58.6 (24)	4.0 (4.0-9.0)	492 (27)
100 mg	1 (n=6)	45.6 (45)	4.0 (2.0-10.0)	332 (34)
	8 (n=6)	71.2 (31)	5.5 (4.0-10.0)	513 (45)
125 mg	1 (n=22)	51.6 (43)	7.0 (2.0-24.4)	299 (44)
	8 (n=13)	86.2 (34)	4.0 (1.0-10.0)	724 (38)
150 mg	1 (n=7)	83.8 (17)	4.0 (4.0-10.0)	633 (9)
	8 (n=6)	161 (44)	7.0 (7.0-10.0)	1342 (42)
200 mg	1 (n=20)	80.8 (35)	5.7 (1.0-10.2)	525 (36)
	8 (n=8)	174 (17)	4.0 (2.0-7.0)	1395 (23)
225 mg	1 (n=6)	104 (58)	4.0 (4.0-7.0)	718 (55)
	8 (n=6)	186 (64)	4.5 (1.0-7.0)	1491 (64)

Source: Table 16.2.1

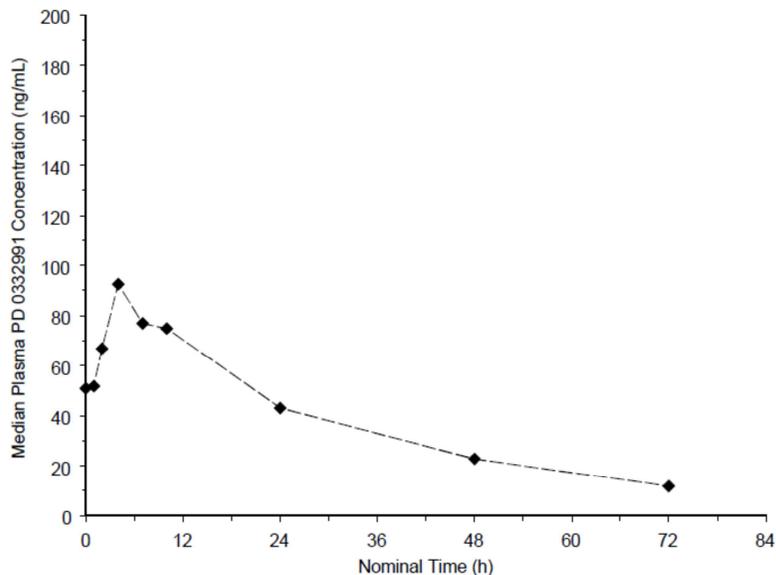
<sup>1</sup> C<sub>max</sub> and AUC<sub>(0-10)</sub>, mean (%CV)

<sup>2</sup> T<sub>max</sub>: Median (Range)

<sup>3</sup> For AUC<sub>(0-10)</sub>, the number of patients on Day 1 for the 100 mg, 125 mg, 150 mg and 200 mg groups were 5, 21, 5 and 19 respectively and on Day 8 for the 75 mg, 100 mg and 125 mg groups were 5, 4 and 12 respectively

Source: Table 17 on Page 77 in a5481001-report-body.pdf

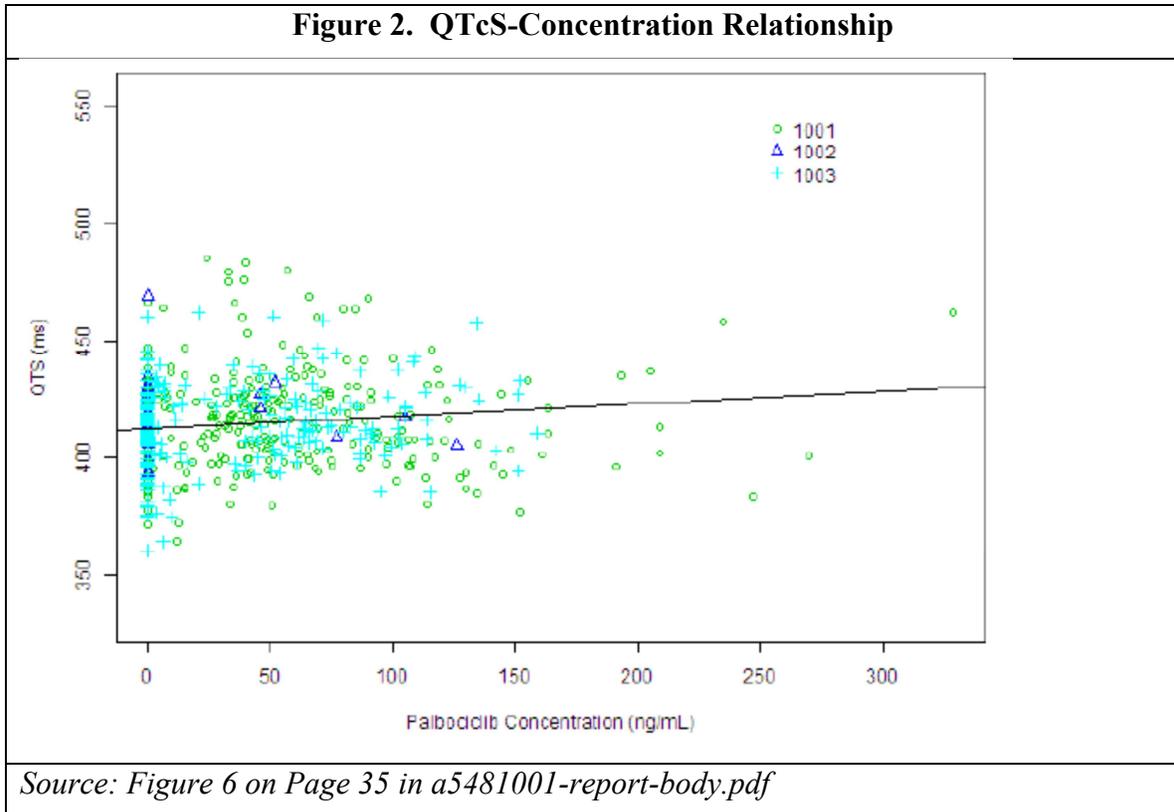
**Figure 1. Linear Plot of the Median Plasma Concentration-time Profile on Day 14(200 mg) and Day 21 (125 mg) Following Oral Administration of PD 0332991 Dose Corrected to the 125 mg Dose Level (N=13)**



Source: Figure 1 on Page 78 in a5481001-report-body.pdf

#### 4.2.8.3.2 Exposure-Response Analysis

Figure below shows the relationship between palbociclib concentration and QTcS.



Study 1003 provided the maximum palbociclib concentrations at steady state ( $C_{max,ss}$ ) in patients receiving a therapeutic regimen of 125 mg palbociclib QD for 3 weeks on/1 week off and in combination with 2.5 mg letrozole QD. In this study, the median and mean  $C_{max,ss}$  values were 107 and 112 ng/mL, respectively. The mean (95% CI) increase in QTcS, QTcF, and QTcB values compared to the baseline values at the median and mean  $C_{max,ss}$  values is shown below.

**Table 5. Summary of Estimated QTc Values at the Mean and Median Palbociclib C<sub>max,ss</sub> After the Therapeutic Dose Regimen in the Patient Population**

Dependent Variable		Palbociclib concentration (ng/mL)	Mean Drug Induced Change in QTc (msec)	90% Conf. Limits (msec)
QTcS	Mean	107	5.60	2.48-8.72
	Median	112	5.88	2.61-9.16
QTcF	Mean	107	5.69	2.58-8.80
	Median	112	5.97	2.71-9.24
QTcB	Mean	107	4.58	1.35-7.81
	Median	112	4.81	1.41-8.20

Source: Page 7 in a5481001-report-body.pdf

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcS and QTcF). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcS and QTcF distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcS or QTcF), and the interaction term of RR and correction type. The slopes of QTcS and QTcF versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 6, it appears that QTcF had smaller absolute slopes than QTcS. Therefore, QTcF is a better correction method for the study data.

**Table 6: Comparison of QTcS and QTcF Using the Mixed Model**

Treatment Groups	Slope of QTcS	Slope of QTcF	Diff P_Value
25 mg QD on the 3/1 schedule	0.18275	0.16464	0.72989
50 mg QD on the 3/1 schedule	0.10258	0.08992	0.33051
75 mg QD on the 3/1 schedule	0.00804	-.01026	0.25673
100 mg QD on the 3/1 schedule	-.01131	-.02901	0.56574
100 mg QD on the 2/1 schedule	0.13129	0.11370	0.39450
125 mg QD on the 3/1 schedule	0.01792	0.00181	0.00487
125 mg QD on the 2/1 schedule	0.04530	0.03403	0.25923
150 mg QD on the 3/1 schedule	0.03795	0.02040	0.27566
150 mg QD on the 2/1 schedule	0.00174	-.01883	0.19182
200 mg QD on the 2/1 schedule	0.01571	-.00089	0.02792
225 mg QD on the 2/1 schedule	0.01019	-.00389	0.16704

Treatment Groups	Slope of QTcS	Slope of QTcF	Diff P_Value
All	0.02773	0.01258	0.00001

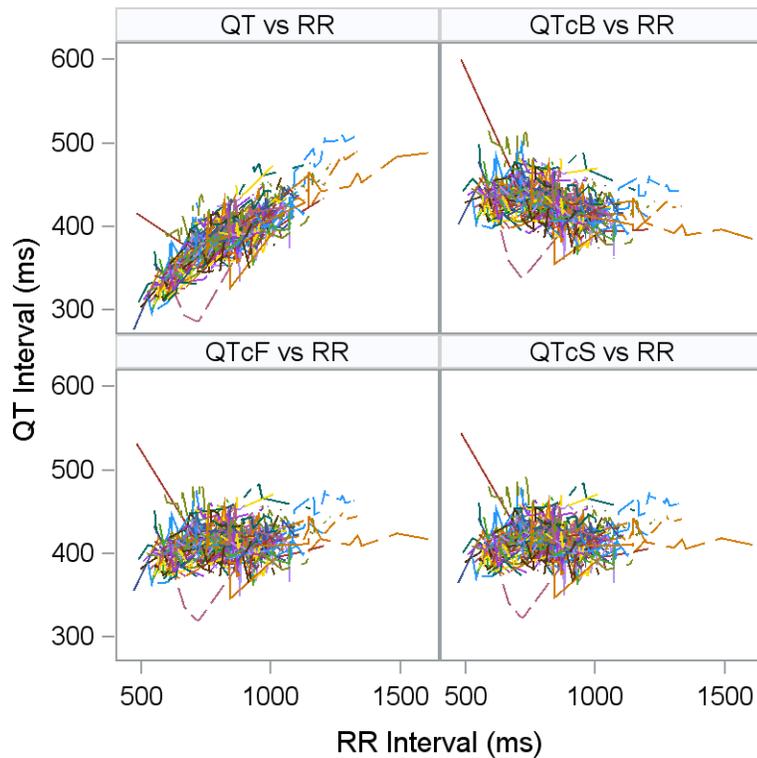
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 7, it appears that QTcF and QTcS are equally better QTcB. To be consistent with the sponsor's choice, this reviewer used QTcS for their primary analyses.

**Table 7: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

Treatment Group	QTcB		QTcF		QTcS	
	N	MSSS	N	MSSS	N	MSSS
25 mg QD on the 3/1 schedule	3	0.03503	3	0.03729	3	0.03617
50 mg QD on the 3/1 schedule	3	0.00432	3	0.02169	3	0.01712
75 mg QD on the 3/1 schedule	6	0.07010	6	0.04444	6	0.04768
100 mg QD on the 2/1 schedule	3	0.01001	3	0.02091	3	0.01809
100 mg QD on the 3/1 schedule	3	0.01249	3	0.00984	3	0.00906
125 mg QD on the 2/1 schedule	12	0.00311	12	0.00327	12	0.00243
125 mg QD on the 3/1 schedule	62	0.05295	62	0.05144	62	0.05065
150 mg QD on the 3/1 schedule	3	0.06496	3	0.03533	3	0.04008
150 mg QD on the 2/1 schedule	4	0.08584	4	0.09997	4	0.09571
200 mg QD on the 2/1 schedule	18	0.01008	18	0.00866	18	0.00800
225 mg QD on the 2/1 schedule	6	0.04175	6	0.02253	6	0.02549
All	94	0.04423	94	0.03983	94	0.03968

The relationship between different correction methods and RR is presented in Figure 3.

**Figure 3: QT, QTcB, QTcF, and QTcS vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 (STAT) STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for the Study Drug

The primary endpoints are changes from the baselines of QTcS. The descriptive statistics are listed in Table 8. For Study 1003 on Cycle 1 Day 14, the largest upper bounds of the 2-sided 90% CI for the mean changes from baseline of 125 mg QD for 2 weeks on/1 week off and 125 mg QD for 3 weeks on/1week off schedules are 14.2 and 7.8 ms, respectively. This reviewer also perform the analyses of QTcF, the descriptive statistics are listed in Table 9. No large change (i.e., > 20 ms) in the QTc interval was detected when administrated of therapeutic dosing regimen of palbociclib.

**Table 8: Analysis Results of  $\Delta$ QTcS for Palbociclib (Study 1003, Cycle 1 Day 14)**

Treatment	Time	N	Mean	Std Dev	90% CI for Mean
125 mg QD on the 2/1 schedule	2	12	4.6	13.6	(-2.4, 11.6)
	4	12	7.1	12.9	(0.4, 13.8)
	8	12	-3.6	14.1	(-10.9, 3.7)
	24	11	3.2	9.9	(-2.2, 8.6)
	48	11	3.0	16.4	(-6.0, 11.9)
125 mg QD on the 3/1 schedule	96	12	5.2	17.4	(-3.9, 14.2)
	4	22	2.7	13.7	(-2.3, 7.8)

**Table 9: Analysis Results of  $\Delta$ QTcF for Palbociclib (Study 1003, Cycle 1 Day 14)**

Treatment	Time	N	Mean	Std Dev	90% CI for Mean
125 mg QD on the 2/1 schedule	2	12	5.3	14.5	(-2.2, 12.7)
	4	12	7.4	13.9	(0.2, 14.6)
	8	12	-4.7	15.4	(-12.7, 3.3)
	24	11	3.4	10.8	(-2.5, 9.3)
	48	11	2.9	16.5	(-6.1, 11.9)
125 mg QD on the 3/1 schedule	96	12	4.7	19.3	(-5.3, 14.7)
	4	22	1.9	14.8	(-3.5, 7.3)

**5.2.1.2 Assay Sensitivity Analysis**

No assay sensitivity established in this study because there is no positive control arm includes in the study.

**5.2.1.3 Categorical Analysis**

lists the number of subjects as well as the number of observations whose QTcS values are  $\leq 450$  ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and  $>500$  ms. No subject's QTcS is above 500 ms.

**Table 10: Categorical Analysis for QTcS**

Treatment Group	Total N	Value $\leq 450$ ms	450 ms $<$ Value $\leq 480$ ms	480 ms $<$ Value $\leq 500$ ms
25 mg QD on the 3/1 schedule	3	2 (66.7%)	1 (33.3%)	0 (0.0%)
50 mg QD on the 3/1 schedule	3	3 (100%)	0 (0.0%)	0 (0.0%)
75 mg QD on the 3/1 schedule	6	5 (83.3%)	0 (0.0%)	1 (16.7%)
100 mg QD on the 2/1 schedule	3	2 (66.7%)	0 (0.0%)	1 (33.3%)

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms
100 mg QD on the 3/1 schedule	3	3 (100%)	0 (0.0%)	0 (0.0%)
125 mg QD on the 2/1 schedule	12	11 (91.7%)	1 (8.3%)	0 (0.0%)
125 mg QD on the 3/1 schedule	29	28 (96.6%)	1 (3.4%)	0 (0.0%)
150 mg QD on the 2/1 schedule	4	3 (75.0%)	1 (25.0%)	0 (0.0%)
150 mg QD on the 3/1 schedule	3	3 (100%)	0 (0.0%)	0 (0.0%)
200 mg QD on the 2/1 schedule	18	16 (88.9%)	2 (11.1%)	0 (0.0%)
225 mg QD on the 2/1 schedule	6	6 (100%)	0 (0.0%)	0 (0.0%)

Table 11 lists changes from baseline QTc  $\leq 30$  ms, between 30 and 60 ms, between 60 and 90 ms, and  $>90$  ms. No subject's change from baseline is above 90 ms.

**Table 11: Categorical Analysis of  $\Delta$ QTcS**

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms	60 ms<Value<=90 ms
25 mg QD on the 3/1 schedule	3	2 (66.7%)	1 (33.3%)	0 (0.0%)
50 mg QD on the 3/1 schedule	3	2 (66.7%)	1 (33.3%)	0 (0.0%)
75 mg QD on the 3/1 schedule	6	4 (66.7%)	1 (16.7%)	1 (16.7%)
100 mg QD on the 2/1 schedule	3	3 (100%)	0 (0.0%)	0 (0.0%)
100 mg QD on the 3/1 schedule	3	3 (100%)	0 (0.0%)	0 (0.0%)
125 mg QD on the 2/1 schedule	12	11 (91.7%)	1 (8.3%)	0 (0.0%)
125 mg QD on the 3/1 schedule	29	28 (96.6%)	0 (0.0%)	0 (0.0%)
150 mg QD on the 2/1 schedule	4	3 (75.0%)	1 (25.0%)	0 (0.0%)
150 mg QD on the 3/1 schedule	3	3 (100%)	0 (0.0%)	0 (0.0%)
200 mg QD on the 2/1 schedule	18	18 (100%)	0 (0.0%)	0 (0.0%)
225 mg QD on the 2/1 schedule	6	5 (83.3%)	1 (16.7%)	0 (0.0%)

### 5.2.2 HR Analysis

The primary endpoints are changes from the baselines of HR. The descriptive statistics are listed in Table 12. For Study 1003, the largest upper bounds of the 2-sided 90% CI for the mean changes from baseline for 125 mg QD for 2 weeks on/1 week off and 125 mg QD for 3 weeks on/1week off schedules are 12.5 and 8.4 bpm, respectively.

Table 13 presents the categorical analysis of HR. Four subjects who experienced HR interval greater than 100 bpm are in 125 mg QD for 3 weeks on/1 week off and 125 mg QD for 3 weeks on /1 week off dose-groups.

**Table 12: Analysis Results of  $\Delta$ HR for Palbociclib (Study 1003)**

Treatment	Time	N	Mean	Std Dev	90% CI for Mean
125 mg QD on the 2/1 schedule	2	12	-2.8	5.2	(-5.5, -0.1)
	4	12	-1.3	6.3	(-4.5, 2.0)
	8	12	6.7	11.2	(0.9, 12.5)
	24	11	-1.1	6.1	(-4.4, 2.3)
	48	11	-0.2	6.5	(-3.7, 3.4)
	96	12	2.6	10.1	(-2.6, 7.8)
125 mg QD on the 3/1 schedule	4	22	5.0	9.4	(1.5, 8.4)

**Table 13: Categorical Analysis for HR**

Treatment Group	Total N	HR $\leq$ 100 bpm	HR $>$ 100 bpm
25 mg QD on the 3/1 schedule	3	2 (66.7%)	1 (33.3%)
50 mg QD on the 3/1 schedule	3	3 (100%)	0 (0.0%)
75 mg QD on the 3/1 schedule	6	4 (66.7%)	2 (33.3%)
100 mg QD on the 2/1 schedule	3	2 (66.7%)	1 (33.3%)
100 mg QD on the 3/1 schedule	3	3 (100%)	0 (0.0%)
125 mg QD on the 2/1 schedule	12	12 (100%)	0 (0.0%)
125 mg QD on the 3/1 schedule	29	25 (86.2%)	4 (13.8%)
150 mg QD on the 2/1 schedule	4	3 (75.0%)	1 (25.0%)
150 mg QD on the 3/1 schedule	3	3 (100%)	0 (0.0%)
200 mg QD on the 2/1 schedule	18	16 (88.9%)	2 (11.1%)
225 mg QD on the 2/1 schedule	6	6 (100%)	0 (0.0%)

**5.2.3 PR Analysis**

No PR intervals provided in study 1003.

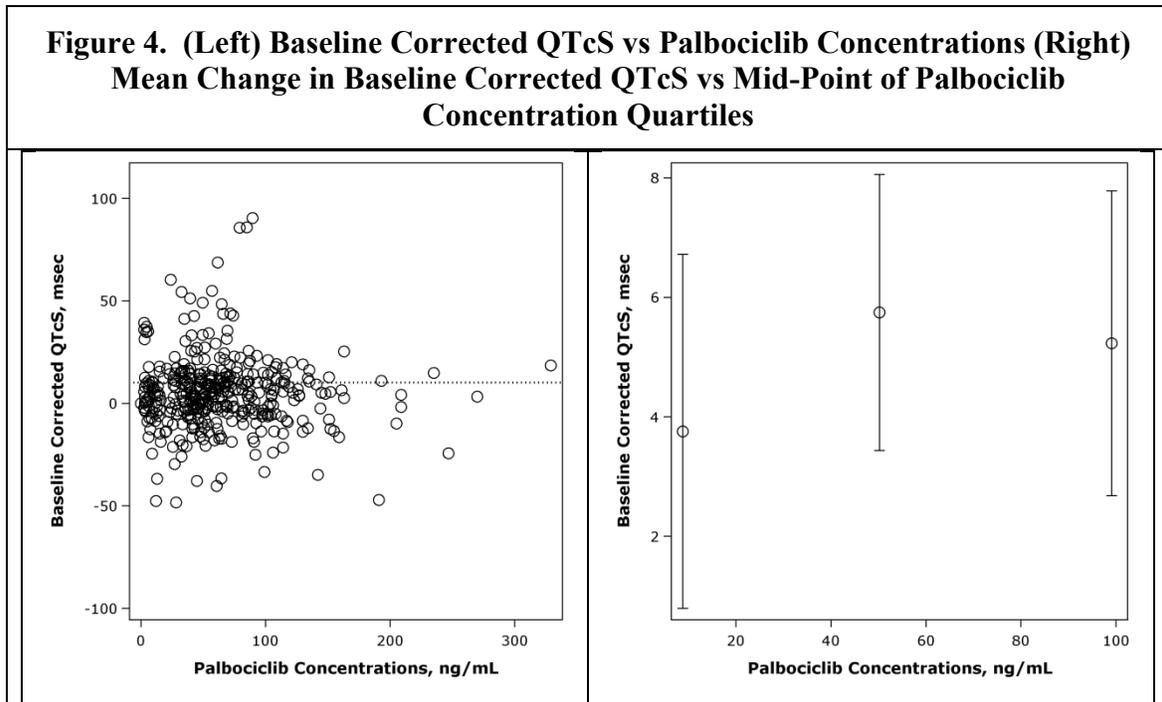
**5.2.4 QRS Analysis**

No QRS intervals provided in study 1003.

**5.3 CLINICAL PHARMACOLOGY ASSESSMENTS**

The mean drug concentration-time profile is illustrated in Figure 1.

The relationship between  $\Delta$ QTcS and palbociclib concentrations is visualized in Figure 4 with a positive but relatively flat exposure-response relationship.



## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

According to the NDA Safety Summary, there was one death from disease progression. Cardiovascular adverse events were not reported.

### 5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	<b>3/1 Schedule:</b> 125mg PO QD x 21 days on, 7 days off <b>2/1 Schedule:</b> 200mg PO QD x 14 days on, 7 days off	
Maximum tolerated dose	<b>3/1 Schedule:</b> 125mg PO QD x 21 days on, 7 days off <b>2/1 Schedule:</b> 200mg PO QD x 14 days on, 7 days off	
Principal adverse events	The most common adverse drug reactions of any grade reported in patients in palbociclib plus letrozole arm in the pivotal study were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis.  Overall, the most common dose limiting adverse events were hematologic toxicities.	
Maximum dose tested	Single Dose	225mg PO
	Multiple Dose	<b>3/1 Schedule:</b> 150mg PO QD x 21 days on, 7 days off <b>2/1 Schedule:</b> 225mg PO QD x 14 days on, 7 days off
Exposures Achieved at Maximum Tested Dose	Single Dose	<b>Geometric Mean (%CV): 225 mg Dose</b> <b>C<sub>max</sub>:</b> 89.3 ng/mL (58%) <b>AUC<sub>(0-10)</sub>:</b> 618 ng.hr/mL(55%)
	Multiple Dose	<b>Geometric Mean (%CV): 225 mg QD Dose</b> <b>C<sub>max</sub>:</b> 151 ng/mL (64%) <b>AUC<sub>(0-10)</sub>:</b> 1196 ng.hr/mL (64%)
Range of linear PK	Linear PK Range: 25 – 225mg PO QD	
Accumulation at steady state	Median (range): 2.4 (1.5 – 4.2)	
Metabolites	<b>Major circulating metabolite:</b> N-glucuronide of palbociclib (M22), which comprised 14.8% of total plasma radioactivity by AUC, in vitro activity towards CDK4/6 not evaluated; <b>Minor circulating oxidative metabolite:</b> lactam metabolite of palbociclib (M17, PF-05089326), which comprised 4.7% of total plasma radioactivity by AUC, in vitro inhibitory potency towards CDK4/6 similar to palbociclib; <b>Other minor circulating metabolites:</b> M11, M12, M16, M24, M25, M26 each comprised of 1.0% to 4.4% of total plasma radioactivity, in vitro activity towards CDK4/6 not evaluated due to low abundance.	
Absorption	Absolute/Relative Bioavailability	<b>Geometric mean ratio (90% CI):</b> Absolute oral bioavailability (F): 45.7% (39.3%-53.2%)
	T <sub>max</sub>	<b>Median (range):</b> • Palbociclib: 7.9 hrs (2.2-8.2 hrs) • M17 (PF-05089326): 4.0 hrs (4.0-6.1 hrs)
Distribution	V <sub>z</sub> /F	<b>Geometric Mean (%CV):</b> Palbociclib V <sub>z</sub> /F = 2583 L (26%)
	% bound	Mean: 85.3% (in vitro equilibrium dialysis assay at 500 to 5000 ng/mL)
Elimination	Route	• Primary by CYP3A and SULT2A1 metabolism • Following a single oral administration of 125 mg

		<p>[14C]palbociclib to healthy subjects (Study 1011), a median of 74.1% and 17.5% of the drug-related radioactivity was recovered in the feces and urine, respectively.</p> <ul style="list-style-type: none"> <li>Excretion of unchanged palbociclib in the feces and urine was 2.3% and 6.9% of dose, respectively, indicating that excretion plays a minor role in elimination of palbociclib.</li> </ul>
	Terminal t <sub>1/2</sub>	<p><b>Mean (Std Dev):</b></p> <ul style="list-style-type: none"> <li>Palbociclib: 28.8 hrs (±5 hrs)</li> </ul>
	CL/F	<p><b>Geometric Mean (%CV):</b></p> <p>Palbociclib CL/F: 63.1 L/hr (29%)</p>
Intrinsic Factors	Age	Population PK analysis suggests that age has no clinically important effect on the exposure of palbociclib.
	Sex	Population PK analysis suggests that sex has no effect on the exposure of palbociclib.
	Race	The effect of race on the exposure of palbociclib could not be evaluated due to limited data.
	Hepatic & Renal Impairment	<p>Population PK analysis indicates that mild hepatic impairment, as defined by the NCI scale, has no impact on the exposure of palbociclib. Palbociclib has not been studied in patients with moderate or severe hepatic impairment.</p> <p>Population PK analysis indicates that mild or moderate renal impairment has no impact on the exposure of palbociclib. Palbociclib has not been studied in patients with severe renal impairment or conditions requiring hemodialysis.</p>
Extrinsic Factors	Drug interactions	<p><b><u>Midazolam (Sensitive CYP3A substrate):</u></b></p> <ul style="list-style-type: none"> <li>Coadministration of palbociclib and midazolam increased midazolam AUC<sub>inf</sub> and C<sub>max</sub> by 61% and 37%, respectively, relative to midazolam given alone.</li> <li>The ratios (90% CIs) of the adjusted geometric means for midazolam AUC<sub>inf</sub> and C<sub>max</sub> were 161% (146%-177%) and 137% (124%-152%), respectively, following administration of midazolam with multiple doses of palbociclib (Test), relative to midazolam administered alone (Reference).</li> <li>These results indicate that palbociclib is a weak time-dependent inhibitor of CYP3A.</li> </ul> <p><b><u>Rifampin (Strong CYP3A Inducer):</u></b></p> <ul style="list-style-type: none"> <li>Coadministration of rifampin and palbociclib decreased palbociclib AUC<sub>inf</sub> and C<sub>max</sub> by approximately 85% and 70%, respectively, relative to palbociclib given alone.</li> <li>The ratios (90% CIs) of the adjusted geometric means for palbociclib AUC<sub>inf</sub> and C<sub>max</sub> were 15.5% (12.0%-19.9%) and 30.2% (23.5%-38.7%), respectively, following administration of palbociclib with multiple doses of rifampin (Test), relative to palbociclib administered alone (Reference).</li> </ul> <p><b><u>Rabeprazole (Proton-pump Inhibitor):</u></b></p> <p><u>Under the fasted conditions</u></p>

		<ul style="list-style-type: none"> <li>• Coadministration of PPI rabeprazole and single-dose palbociclib decreased the palbociclib geometric mean AUC<sub>inf</sub> and C<sub>max</sub> values by 62% and 80%, respectively, relative to palbociclib given alone.</li> <li>• The ratios (90% CIs) of the adjusted geometric means for palbociclib AUC<sub>inf</sub> and C<sub>max</sub> were 37.7% (33.5%-42.5%) and 19.7% (16.8%-23.2%), respectively, following administration of palbociclib with multiple doses of rabeprazole (Test), relative to palbociclib administered alone (Reference).</li> </ul> <p style="text-align: right;"><b>Section 2.7.2.3.5.6</b></p> <p><u>Under the fed conditions</u></p> <ul style="list-style-type: none"> <li>• Coadministration of PPI rabeprazole and single-dose palbociclib decreased the palbociclib geometric mean C<sub>max</sub> by 41%, but had limited effect (13%) on AUC<sub>inf</sub>.</li> <li>• The ratios (90% CIs) of the adjusted geometric means for palbociclib AUC<sub>inf</sub> and C<sub>max</sub> were 86.85% (79.50%, 94.87%) and 59.18% (49.36%, 70.95%), respectively, following administration of palbociclib with rabeprazole (Test), relative to palbociclib administered alone (Reference).</li> </ul> <p><u>Famotidine (an H2-receptor antagonist)</u></p> <ul style="list-style-type: none"> <li>• Famotidine (an H2-receptor antagonist) given 10 hours before and 2 hours after palbociclib under fed conditions had no impact on the exposure of palbociclib compared to palbociclib given alone.</li> <li>• The ratios of the adjusted geometric means (Test/Reference) of palbociclib AUC<sub>inf</sub> and C<sub>max</sub> (90% CI) were 96.02% (87.90%, 104.89%) and 95.00% (79.23%, 113.90%), respectively, following administration of palbociclib with famotidine (Test), relative to palbociclib administered alone (Reference).</li> </ul> <p><u>Mi-Acid Maximum Strength Liquid (local antacid)</u></p> <ul style="list-style-type: none"> <li>• Mi-Acid Maximum Strength Liquid given 2 hours before or 2 hours after palbociclib under fed conditions had no impact on the exposure of palbociclib compared to palbociclib given alone.</li> <li>• <u>The ratios of the adjusted geometric means (Test/Reference) of palbociclib AUC<sub>inf</sub> and C<sub>max</sub> (90% CI) were 105.86% (100.53%, 111.47%) and 96.07% (89.93%, 102.62%), respectively, following administration of palbociclib with a local antacid 2 hours before palbociclib administration (Test), relative to palbociclib administered alone (Reference).</u></li> <li>• <u>The ratios of the adjusted geometric means (Test/Reference) of palbociclib AUC<sub>inf</sub> and C<sub>max</sub> (90% CI) were 105.15% (99.86%, 110.72%) and 95.79% (89.67%, 102.32%), respectively, following administration of palbociclib with a local antacid 2 hours after palbociclib administration (Test), relative to palbociclib administered alone (Reference).</u></li> </ul>
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	<p><b><u>Tamoxifen:</u></b></p> <ul style="list-style-type: none"> <li>• Administration of palbociclib in the presence of tamoxifen and its metabolites at steady state (4-hydroxy-tamoxifen, N-desmethyl-tamoxifen, and 4-hydroxy-N-desmethyl-tamoxifen) showed that palbociclib exposure was comparable with that when palbociclib was given alone.</li> <li>• The ratios (90% CIs) of the adjusted geometric means of palbociclib AUC<sub>inf</sub> and C<sub>max</sub> were 108% (104%-111%) and 116% (105%-129%), respectively, following administration of palbociclib with multiple doses of tamoxifen (Test) relative to palbociclib administered alone (Reference).</li> </ul> <p><b><u>Letrozole:</u></b></p> <ul style="list-style-type: none"> <li>• The exposure of palbociclib in Study 1003 was similar in the absence and presence of letrozole (geometric mean ratios [90% CIs]: 97.5% [90.2%-106%] for AUC[0-24] and 93.6% [84.2%-104%] for C<sub>max</sub>).</li> <li>• In addition, the exposure of letrozole was similar in the absence and presence of palbociclib (geometric mean ratios [90% CIs]: 89.8% [84.5%-95.5%] for AUC[0-24] and 91.3% [85.2%-97.8%] for C<sub>max</sub>).</li> <li>• Therefore, there is no DDI between palbociclib and letrozole when the 2 drugs are coadministered.</li> </ul>
Food Effects	<p><b><u>Free Base Final Ph3/Commercial Formulation:</u></b></p> <ul style="list-style-type: none"> <li>•The ratios (90% CIs) of the adjusted geometric means for C<sub>max</sub> of palbociclib 125 mg after a high-fat meal, a low-fat meal, and moderate-fat meals 1 hour before and 2 hours after dose administration relative to palbociclib administration after an overnight fasting were 138% (121%-158%), 127% (111%-146%), and 124% (108%-142%), respectively. The corresponding ratios (90% CIs) of the adjusted geometric means for AUC<sub>inf</sub> were 121% (113%-129%), 112% (104%-120%), and 113% (106%-121%), respectively.</li> <li>•Administration of palbociclib with or in between meals significantly reduced the intersubject variability (%CV) of AUC<sub>inf</sub> and C<sub>max</sub>, from 39% for AUC<sub>inf</sub> and 73% for C<sub>max</sub> under the overnight fasted condition to 23%-27% for AUC<sub>inf</sub> and 21%-24% for C<sub>max</sub> under fed conditions irrespective of the fat and calorie content of the food. Administering palbociclib free base capsule formulations with or in between meals should also substantially reduce the intrasubject variability in palbociclib AUC<sub>inf</sub> and C<sub>max</sub>.</li> <li>•Based on these study results, palbociclib should be taken with food.</li> </ul> <p><b><u>Isethionate Capsule Formulation:</u></b></p> <ul style="list-style-type: none"> <li>• Administration of palbociclib under a minimal fasted condition (ie, 1 hour after and 2 hours before 2 separate moderate-fat, standard-calorie meals) relative to that under an overnight fasted condition in healthy subjects had</li> </ul>

		no effect on palbociclib AUC <sub>inf</sub> and C <sub>max</sub> . The 90% CIs for both AUC <sub>inf</sub> and C <sub>max</sub> fell within the established bioequivalence limits (80%-125%).
Expected High Clinical Exposure Scenario	<p>In theory, high clinical exposure scenarios include:</p> <ol style="list-style-type: none"> <li>1. Palbociclib is administered with potent CYP3A inhibitors in patients with severe hepatic impairment. Clinical studies for such interactions have not been conducted. However, such supra-therapeutic exposure is not expected to occur as recommended labeling for palbociclib is to avoid concomitant use of strong CYP3A inhibitors.</li> <li>2. Overdose of palbociclib. There is no known antidote for palbociclib. The treatment of overdose of palbociclib should consist of general supportive measures.</li> </ol>	
Preclinical Cardiac Safety	<p><i>Summarize in vitro and in vivo results per S7B guidance.</i></p> <p>The potential for QT prolongation and hemodynamic effects were identified from in vitro assays and/or in vivo cardiovascular dog studies. Palbociclib caused a small but statistically significant increase on APD<sub>90</sub> at 10 μM (4475 ng/mL) in the dog Purkinje fiber assay, and had an IC<sub>50</sub> of 3.2 μM (1432 ng/mL) in a hERG assay. The potential for QTc interval prolongation was identified from conscious telemetered dogs at unbound plasma concentrations ≥67 ng/mL, while QT interval prolongation was not noted in dogs given doses up to 2 mg/kg/day in the 3- or 15-week toxicity studies, with unbound C<sub>max</sub> values of up to 80 and 42 ng/mL, respectively. In addition to the potential for QT prolongation, hemodynamic effects were noted in conscious telemetered dogs, where decreases in HR (up to 8 bpm) that correlated with increases in RR interval (up to 73 msec) and modest increases in systolic blood pressure (up to 6 mmHg) were observed at unbound plasma concentrations ≥140 ng/mL. No cardiovascular effects are anticipated at plasma concentrations &lt;4 times those associated with the unbound C<sub>max</sub> at the human clinical dose of 125 mg QD (17 ng/mL).</p>	
Clinical Cardiac Safety	<p>The safety of palbociclib was investigated in 18 clinical studies in which 659 subjects/patients received either palbociclib or a comparator and 126 patients were randomized to blinded therapy in dosing ranging from 25 to 225 mg on a 14/21 or 21/28 cycle.</p> <p>The available safety data for studies A5481001, A5481002, A5481003, A5481004, A5481008 and A5481010 were reviewed and there were few cardiac safety events (per ICHE14 criteria) identified. There were three fatal cardiac arrests (in setting of: (1) progressive disease (2) prior CABG and angina (3) blinded case: thrombophlebitis with possible PE). There was one case of “grade one” syncope that spontaneously resolved. There were no adverse events of seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or QT prolongation (QTcS) &gt;500 msec and/or postbaseline maximum mean QTcF.</p>	

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/s/  
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VENKATESH A BHATTARAM  
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# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 207103

**Application Type:** NDA NME

**Name of Drug/Dosage Form:** Ibrance<sup>®</sup> (palbociclib) capsules, for oral use 125 mg, 100 mg, and 75 mg

**Applicant:** Pfizer, Inc.

**Receipt Date:** August 13, 2014

**Goal Date:** April 13, 2015

## 1. Regulatory History and Applicant's Main Proposals

NDA 207103 Ibrance (palbociclib) is a rolling submission NME with a Breakthrough Therapy development program for ER-positive, HER2-negative breast cancer. The sponsor requested Priority Review and is seeking Accelerated Approval.

The Palbociclib capsule is for oral use and is a highly selective, reversible, small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. The CDK4/6 is a downstream of multiple signaling pathways which lead to cellular proliferation.

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

# Selected Requirements of Prescribing Information

## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

## Selected Requirements of Prescribing Information

• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:** *In the Product Title the route of administration is missing after the dosage form.*

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:**

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

## Selected Requirements of Prescribing Information

### Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

### Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

### Comment:

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

### Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

### Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

### Comment:

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

### Comment:

### Contraindications in Highlights

**YES**

## Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

*Comment:*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

*Comment:*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

*Comment:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

#### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

#### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

#### DOSAGE AND ADMINISTRATION

- [text]
- [text]

#### DOSAGE FORMS AND STRENGTHS

[text]

#### CONTRAINDICATIONS

- [text]
- [text]

#### WARNINGS AND PRECAUTIONS

- [text]
- [text]

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- [text]
- [text]

#### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

#### 6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

#### 7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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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.**  
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/s/  
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AMY R TILLEY  
10/07/2014

ALICE KACUBA  
10/07/2014

MEMORANDUM

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

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DATE: September 18, 2014

TO: Director, Investigations Branch  
New England District Office  
One Montvale Ave., 4<sup>th</sup> Floor  
Stoneham, MA 02180

FROM: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGLPC)  
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2014, CDER High Priority Pre-Approval Data  
Validation Inspection**, Bioresearch Monitoring, Human  
Drugs, CP 7348.001

RE: NDA 207-103  
DRUG: Palbociclib  
SPONSOR: Pfizer, Inc., New York, NY

This memo requests that you arrange for an inspection of the clinical portion of the following bioequivalence (BE) study.

Please provide the name of the ORA investigator, once identified, to the DBGLPC point of contact (POC) listed at the end of the assignment. Background material will be available in ECMS under the ORA folder. **The inspection should be completed prior to January 15, 2015.**

**Do not reveal the applicant, application number, study to be inspected, drug name, or the study investigators to the site prior to the start of the inspection.** The site will receive this information during the inspection opening meeting. The inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

**At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the DBGLPC POC.**

**Study #:** A5481036  
**Study Title:** "A Phase 1, Open-Label 6-Sequence 3-Period Crossover Study of Palbociclib (PD-0332991) in Healthy Volunteers to Estimate Relative Bioavailability of Palbociclib Formulations"

**Clinical Site #1:** New Haven Clinical Research Unit  
One Howe Street  
New Haven, CT 06511  
TEL: (203) 401-0365

**Investigator:** Sylvester S. Pawlak

**SECTION A - RESERVE SAMPLES**

Because this bioequivalence study is subject to 21 CFR 320.38, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the Applicant for subject dosing.

The final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies (<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

**During the clinical site inspection, please:**

- Verify that the site retained reserve samples according to the regulations. If the site did not retain reserve samples or the samples are not adequate in quantity, notify the DBGLPC POC immediately.
- If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve

samples are representative of those used in the specific bioequivalence studies, and that samples were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a Affidavit.

- Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.  
Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis (DPA)  
Center for Drug Analysis (HFH-300)  
645 S. Newstead Ave  
St. Louis, MO 63110  
TEL: 1-314-539-2135

#### **SECTION B - CLINICAL DATA AUDIT**

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

#### **During the clinical site inspection, please:**

- Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.
- Compare the study report in the NDA submission to the original documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
- o Number of subject records reviewed during the inspection:\_\_\_\_\_
  - o Number of subjects screened at the site:\_\_\_\_\_
  - o Number of subjects enrolled at the site:\_\_\_\_\_
  - o Number of subjects completing the study:\_\_\_\_\_

- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:

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**Additional instructions to the ORA Investigator:**

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

**If you issue Form FDA 483, please forward a copy to the DBGLPC POC. If it appears that the observations may warrant an OAI classification, notify the DBGLPC POC as soon as possible.**

**Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the DBGLPC POC.**

DBGLPC POC: Kara A. Scheibner, Ph.D.  
Pharmacologist  
Office of Scientific Investigations  
Tel: (240) 402-6520  
Fax: (301) 847-8748  
E-mail: [Kara.Scheibner@fda.hhs.gov](mailto:Kara.Scheibner@fda.hhs.gov)

DARRTS cc:

OSI/DBGLPC/Taylor/Bonapace/Haidar/Choi/Dasgupta/Skelly/Scheibner  
OSI/DBGLPC/Fenty-Stewart/Nkah/Dejernett/Johnson  
CDER/OND/OHOP/DOPI/Tilley

Email cc:

ORA DO BIMO mailbox

Draft: KAS 9/18/2014

Edit: MFS 9/18/2014

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical  
Sites/New Haven Clinical Research Unit, New Haven, Connecticut

OSI file #: BE6758

**FACTS: 11473478**

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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.**  
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/s/  
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KARA A SCHEIBNER  
09/30/2014

MICHAEL F SKELLY  
09/30/2014  
Skelly signing on behalf of Dr. Haidar

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 207103 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Ibrance Established/Proper Name: palbociclib Dosage Form: Capsule Strengths: 75 mg, 100 mg, and 125 mg		
Applicant: Pfizer, Inc. Agent for Applicant (if applicable):		
Date of Application: 8-13-14 Date of Receipt: 8-13-14 Date clock started after UN:		
PDUFA Goal Date: 4-13-15		Action Goal Date (if different):
Filing Date: 10-12-14		Date of Filing Meeting: 9-11-14
Chemical Classification: (1,2,3 etc.) (original NDAs only) NME		
Proposed indication(s)/Proposed change(s): Advanced Breast Cancer		
Type of Original NDA: AND (if applicable)	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>.</i>		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 069324				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  If yes, # years requested: 5  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>For BLAs:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Format and Content</b>	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
<b>If electronic submission, does it follow the eCTD guidance?</b> <sup>1</sup> <b>If not, explain (e.g., waiver granted).</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>PREA</b> Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		PeRC Mtg = 2-25-15
<b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</b>  <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</b>  <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels			
	<input checked="" type="checkbox"/> Immediate container labels			
	<input type="checkbox"/> Diluent			
	<input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT 8-6-14
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 9-15-14

**NDA #:** 207103

**PROPRIETARY NAME:** Ibrance

**ESTABLISHED/PROPER NAME:** palbociclib

**DOSAGE FORM/STRENGTH:** Capsule 75 mg, 100 mg, and 125 mg

**APPLICANT:** Pfizer, Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Advanced Breast Cancer

**BACKGROUND:** IBRANCE is an NME and is a cyclin-dependent kinases (CDK) 4/6 inhibitor indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease. This application has Breakthrough Designation.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Amy Tilley	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	Patricia Cortazar		Y
Clinical	Reviewers:	Laleh Amiri-Kordestani Julia Beaver	Y
	TL:	Patricia Cortazar	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Jeanne Fourie-Zirkelbach	Y
	TL:	Qi Lu	Y
Biostatistics	Reviewer:	Erik Bloomquist	Y
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wei Chen	Y
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Joyce Crich Xiao Chen	N Y
	TL:	Haripada Sarker	Y
	Branch Chief:	Ali Al Hakim,	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Jessica Cole	Y
	TL:	Bryon Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Robert Wittorf	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Davis Mathew	N
	TL:	Alice Tu	N
OSE/DRISK (REMS)	Reviewer:	Naomi Redd	Y
	TL:	Doris Auth	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Lauren Iacono-Connor	N
	TL:	Susan Thompson	N

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Liang Zhao / Jingyu Yu Rosane Charlab-Orbach Jenna Lyndly / Tracy Salaam Minerva Hughes / Angelica Dorantes	Y (Yu) Y N Y (Hughes)	
Other attendees	Susan Jenney	Y	

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p> </li> </ul>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>If no, explain:</b>	
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b> Possible dates: 2-11 or 12, 2015</p> <p><b>If no, for an NME NDA or original BLA , include the reason. For example:</b></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed? (Not yet requested)</li> </ul>	<input checked="" type="checkbox"/> YES Study 1036 <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b>  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b><u>Environmental Assessment</u></b>  <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?   <b>If no</b>, was a complete EA submitted?   <b>If EA submitted</b>, consulted to EA officer (OPS)?</li> </ul> <b>Comments:</b> Branch Chief stated no consult needed.	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b><u>Quality Microbiology (for sterile products)</u></b>  <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? EER Requested</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b> None at this time.</p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input type="checkbox"/> N/A <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Richard Pazdur, M.D.</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): TBS</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:  <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]</p>
<input type="checkbox"/>	Other

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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.**  
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/s/  
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AMY R TILLEY  
09/15/2014

ALICE KACUBA  
09/15/2014