

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### ***APPLICATION NUMBER:***

**207103Orig1s004**

***Trade Name:*** IBRANCE

***Generic or Proper Name:*** palbociclib

***Sponsor:*** Pfizer, Inc.

***Approval Date:*** March 31, 2017

***Indication:*** Ibrance is a kinase inhibitor indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or
- fulvestrant in women with disease progression following endocrine therapy.

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## 207103Orig1s004

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*APPLICATION NUMBER:*

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**APPROVAL LETTER**



NDA 207103/S-004

**SUPPLEMENT APPROVAL  
POSTMARKETING REQUIREMENT  
FULFILLED**

Pfizer, Inc.  
Attention: Bethany Rappoli  
Director, Worldwide Safety and Regulatory  
235 East 42<sup>nd</sup> Street  
New York, NY 10017

Dear Ms. Rappoli:

Please refer to your Supplemental New Drug Application (sNDA) dated October 27, 2016, received October 27, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ibrance<sup>®</sup> (palbociclib) Capsules, 75 mg, 100 mg, and 125 mg.

This Prior Approval supplemental new drug application provides for the use of Ibrance<sup>®</sup> (palbociclib) for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or
- fulvestrant in women with disease progression following endocrine therapy.

**APPROVAL & LABELING**

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at: <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for the package insert and patient package insert, with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at: <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.”

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed immediate container labels that are identical to the enclosed immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 207103/S-004.**” Approval of this submission by FDA is not required before the labeling is used.

### **SUBPART H FULFILLED**

We approved this NDA under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses, which required further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. A description of the clinical trial is below.

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

Approval of this supplement fulfills your commitments made under Subpart H.

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable, as breast cancer does not occur in the pediatric population.

### **POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitment:

3192-1: Submit the overall survival (OS) data and results from 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”.

The timetable you submitted on March 13, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2020

Submit clinical protocols to your IND 069324 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

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

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

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at: <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at: <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see: <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Amy Tilley, Regulatory Project Manager, at 301-796-3994 or [amy.tilley@fda.hhs.gov](mailto:amy.tilley@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURES:

Content of Labeling  
Container Labeling

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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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GEOFFREY S KIM  
03/31/2017

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**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use IBRANCE safely and effectively. See full prescribing information for IBRANCE.

**IBRANCE® (palbociclib) capsules, for oral use**  
Initial U.S. Approval: 2015

**RECENT MAJOR CHANGES**

Indications and Usage (1)	03/2017
Dosage and Administration (2.1, 2.2)	03/2017
Warnings and Precautions (5.1, 5.2)	03/2017
Warnings and Precautions, Pulmonary Embolism (5) Removed	03/2017

**INDICATIONS AND USAGE**

IBRANCE is a kinase inhibitor indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or
- fulvestrant in women with disease progression following endocrine therapy. (1)

**DOSAGE AND ADMINISTRATION**

IBRANCE capsules are taken orally with food in combination with an aromatase inhibitor or fulvestrant. (2)

- Recommended starting dose: 125 mg once daily taken with food for 21 days followed by 7 days off treatment. (2.1)
- Dosing interruption and/or dose reductions are recommended based on individual safety and tolerability. (2.2)

**DOSAGE FORMS AND STRENGTHS**

Capsules: 125 mg, 100 mg, and 75 mg. (3)

**CONTRAINDICATIONS**

None. (4)

**WARNINGS AND PRECAUTIONS**

- Neutropenia: Monitor complete blood count prior to start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. (2.2, 5.1)
- Embryo-Fetal Toxicity: IBRANCE can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.2, 8.1, 8.3)

**ADVERSE REACTIONS**

Most common adverse reactions (incidence ≥10%) were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, and pyrexia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

- CYP3A Inhibitors: Avoid concurrent use of IBRANCE with strong CYP3A inhibitors. If the strong inhibitor cannot be avoided, reduce the IBRANCE dose. (2.2, 7.1)
- CYP3A Inducers: Avoid concurrent use of IBRANCE with strong CYP3A inducers. (7.2)
- CYP3A Substrates: The dose of sensitive CYP3A4 substrates with narrow therapeutic indices may need to be reduced when given concurrently with IBRANCE. (7.3)

**USE IN SPECIFIC POPULATIONS**

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/31/2017

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

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

IBRANCE is indicated for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or
- fulvestrant in women with disease progression following endocrine therapy.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dose and Schedule

The recommended dose of IBRANCE is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. IBRANCE should be taken with food [see *Clinical Pharmacology* (12.3)].

Administer the recommended dose of an aromatase inhibitor when given with IBRANCE. Please refer to the Full Prescribing Information for the aromatase inhibitor being used.

When given with IBRANCE, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, 29, and once monthly thereafter. Please refer to the Full Prescribing Information of fulvestrant.

Patients should be encouraged to take their dose of IBRANCE at approximately the same time each day.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. IBRANCE capsules should be swallowed whole (do not chew, crush, or open them prior to swallowing). Capsules should not be ingested if they are broken, cracked, or otherwise not intact.

Pre/perimenopausal women treated with the combination IBRANCE plus fulvestrant therapy should be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to current clinical practice standards.

#### 2.2 Dose Modification

The recommended dose modifications for adverse reactions are listed in Tables 1, 2, and 3.

**Table 1. Recommended Dose Modification for Adverse Reactions**

Dose Level	Dose
Recommended starting dose	125 mg/day
First dose reduction	100 mg/day
Second dose reduction	75 mg/day*

\*If further dose reduction below 75 mg/day is required, discontinue.

**Table 2. Dose Modification and Management – Hematologic Toxicities<sup>a</sup>**

Monitor complete blood counts prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated.	
For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated.	
CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3	<p><u>Day 1 of cycle:</u> Withhold IBRANCE, repeat complete blood count monitoring within 1 week. When recovered to Grade <math>\leq 2</math>, start the next cycle at the <i>same dose</i>.</p> <p><u>Day 15 of first 2 cycles:</u> If Grade 3 on Day 15, continue IBRANCE at current dose to complete cycle and repeat complete blood count on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below.</p> <p>Consider dose reduction in cases of prolonged (&gt;1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.</p>
Grade 3 neutropenia <sup>b</sup> with fever $\geq 38.5$ °C and/or infection	<p><u>At any time:</u> Withhold IBRANCE until recovery to Grade <math>\leq 2</math>. Resume at the <i>next lower dose</i>.</p>
Grade 4	<p><u>At any time:</u> Withhold IBRANCE until recovery to Grade <math>\leq 2</math>. Resume at the <i>next lower dose</i>.</p>

Grading according to CTCAE 4.0.

CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal.

<sup>a</sup> Table applies to all hematologic adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

<sup>b</sup> Absolute neutrophil count (ANC): Grade 1: ANC < LLN - 1500/mm<sup>3</sup>; Grade 2: ANC 1000 - <1500/mm<sup>3</sup>; Grade 3: ANC 500 - <1000/mm<sup>3</sup>; Grade 4: ANC <500/mm<sup>3</sup>.

**Table 3. Dose Modification and Management – Non-Hematologic Toxicities**

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade $\geq 3$ non-hematologic toxicity (if persisting despite optimal medical treatment)	<p>Withhold until symptoms resolve to:</p> <ul style="list-style-type: none"> <li>• Grade <math>\leq 1</math>;</li> <li>• Grade <math>\leq 2</math> (if not considered a safety risk for the patient)</li> </ul> <p>Resume at the <i>next lower dose</i>.</p>

Grading according to CTCAE 4.0.

CTCAE=Common Terminology Criteria for Adverse Events.

Refer to the Full Prescribing Information for coadministered endocrine therapy dose adjustment guidelines in the event of toxicity and other relevant safety information or contraindications.

## Dose Modifications for Use With Strong CYP3A Inhibitors

Avoid concomitant use of strong CYP3A inhibitors and consider an alternative concomitant medication with no or minimal CYP3A inhibition. If patients must be coadministered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg once daily. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3 to 5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

### 3 DOSAGE FORMS AND STRENGTHS

125 mg capsules: opaque, hard gelatin capsules, size 0, with caramel cap and body, printed with white ink “Pfizer” on the cap, “PBC 125” on the body.

100 mg capsules: opaque, hard gelatin capsules, size 1, with caramel cap and light orange body, printed with white ink “Pfizer” on the cap, “PBC 100” on the body.

75 mg capsules: opaque, hard gelatin capsules, size 2, with light orange cap and body, printed with white ink “Pfizer” on the cap, “PBC 75” on the body.

### 4 CONTRAINDICATIONS

None.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Neutropenia

Neutropenia was the most frequently reported adverse reaction in Study 1 (PALOMA-2) with an incidence of 80% and Study 2 (PALOMA-3) with an incidence of 83%. A Grade  $\geq 3$  decrease in neutrophil counts was reported in 66% of patients receiving IBRANCE plus letrozole in Study 1 and 66% of patients receiving IBRANCE plus fulvestrant in Study 2. In Study 1 and 2, the median time to first episode of any grade neutropenia was 15 days and the median duration of Grade  $\geq 3$  neutropenia was 7 days [see *Adverse Reactions (6.1)*].

Monitor complete blood counts prior to starting IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia [see *Dosage and Administration (2.2)*].

Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across Studies 1 and 2. One death due to neutropenic sepsis was observed in Study 2. Physicians should inform patients to promptly report any episodes of fever [see *Patient Counseling Information (17)*].

#### 5.2 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at maternal exposures that were  $\geq 4$  times the human clinical exposure based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective

contraception during treatment with IBRANCE and for at least 3 weeks after the last dose [see *Use in Specific Populations (8.1 and 8.3) and Clinical Pharmacology (12.1)*].

## 6 ADVERSE REACTIONS

The following topic is described below and elsewhere in the labeling:

- Neutropenia [see *Warnings and Precautions (5.1)*]

### 6.1 Clinical Studies Experience

Because clinical trials are conducted under varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

#### **Study 1: IBRANCE plus Letrozole**

##### **Patients with estrogen receptor (ER)-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy**

The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus placebo plus letrozole was evaluated in Study 1 (PALOMA-2). The data described below reflect exposure to IBRANCE in 444 out of 666 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE plus letrozole in Study 1. The median duration of treatment for IBRANCE plus letrozole was 19.8 months while the median duration of treatment for placebo plus letrozole arm was 13.8 months.

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving IBRANCE plus letrozole. No dose reduction was allowed for letrozole in Study 1.

Permanent discontinuation associated with an adverse reaction occurred in 43 of 444 (9.7%) patients receiving IBRANCE plus letrozole and in 13 of 222 (5.9%) patients receiving placebo plus letrozole. Adverse reactions leading to permanent discontinuation for patients receiving IBRANCE plus letrozole included neutropenia (1.1%) and alanine aminotransferase increase (0.7%).

The most common adverse reactions ( $\geq 10\%$ ) of any grade reported in patients in the IBRANCE plus letrozole arm by descending frequency were neutropenia, infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia.

The most frequently reported Grade  $\geq 3$  adverse reactions ( $\geq 5\%$ ) in patients receiving IBRANCE plus letrozole by descending frequency were neutropenia, leukopenia, infections, and anemia.

Adverse reactions ( $\geq 10\%$ ) reported in patients who received IBRANCE plus letrozole or placebo plus letrozole in Study 1 are listed in Table 4.

**Table 4. Adverse Reactions (≥10%) in Study 1**

Adverse Reaction	IBRANCE plus Letrozole (N=444)			Placebo plus Letrozole (N=222)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections <sup>a</sup>	60 <sup>b</sup>	6	1	42	3	0
Blood and lymphatic system disorders						
Neutropenia	80	56	10	6	1	1
Leukopenia	39	24	1	2	0	0
Anemia	24	5	<1	9	2	0
Thrombocytopenia	16	1	<1	1	0	0
Metabolism and nutrition disorders						
Decreased appetite	15	1	0	9	0	0
Nervous system disorders						
Dysgeusia	10	0	0	5	0	0
Gastrointestinal disorders						
Stomatitis <sup>c</sup>	30	1	0	14	0	0
Nausea	35	<1	0	26	2	0
Diarrhea	26	1	0	19	1	0
Vomiting	16	1	0	17	1	0
Skin and subcutaneous tissue disorders						
Alopecia	33 <sup>d</sup>	N/A	N/A	16 <sup>e</sup>	N/A	N/A
Rash <sup>f</sup>	18	1	0	12	1	0
Dry skin	12	0	0	6	0	0
General disorders and administration site conditions						
Fatigue	37	2	0	28	1	0
Asthenia	17	2	0	12	0	0
Pyrexia	12	0	0	9	0	0

Grading according to CTCAE 4.0.

CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable;

<sup>a</sup> Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.

<sup>b</sup> Most common infections (≥1%) include: nasopharyngitis, upper respiratory tract infection, urinary tract infection, oral herpes, sinusitis, rhinitis, bronchitis, influenza, pneumonia, gastroenteritis, conjunctivitis, herpes zoster, pharyngitis, cellulitis, cystitis, lower respiratory tract infection, tooth infection, gingivitis, skin infection, gastroenteritis viral, respiratory tract infection, respiratory tract infection viral, and folliculitis.

<sup>c</sup> Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oral discomfort, oropharyngeal pain, and stomatitis.

<sup>d</sup> Grade 1 events – 30%; Grade 2 events – 3%.

<sup>e</sup> Grade 1 events – 15%; Grade 2 events – 1%.

<sup>f</sup> Rash includes the following PTs: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of <10.0% of patients receiving IBRANCE plus letrozole in Study 1 included alanine aminotransferase increased (9.9%), aspartate aminotransferase increased (9.7%), epistaxis (9.2%), lacrimation increased (5.6%), dry eye (4.1%), vision blurred (3.6%), and febrile neutropenia (2.5%).

**Table 5. Laboratory Abnormalities in Study 1**

Laboratory Abnormality	IBRANCE plus Letrozole (N=444)			Placebo plus Letrozole (N=222)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
WBC decreased	97	35	1	25	1	0
Neutrophils decreased	95	56	12	20	1	1
Anemia	78	6	0	42	2	0
Platelets decreased	63	1	1	14	0	0
Aspartate aminotransferase increased	52	3	0	34	1	0
Alanine aminotransferase increased	43	2	<1	30	0	0

N=number of patients; WBC=white blood cells.

### **Study 2: IBRANCE plus Fulvestrant**

#### **Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy**

The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in Study 2 (PALOMA-3). The data described below reflect exposure to IBRANCE in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of IBRANCE plus fulvestrant in Study 2. The median duration of treatment for IBRANCE plus fulvestrant was 10.8 months while the median duration of treatment for placebo plus fulvestrant arm was 4.8 months.

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving IBRANCE plus fulvestrant. No dose reduction was allowed for fulvestrant in Study 2.

Permanent discontinuation associated with an adverse reaction occurred in 19 of 345 (6%) patients receiving IBRANCE plus fulvestrant, and in 6 of 172 (3%) patients receiving placebo plus fulvestrant. Adverse reactions leading to discontinuation for those patients receiving IBRANCE plus fulvestrant included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%).

The most common adverse reactions ( $\geq 10\%$ ) of any grade reported in patients in the IBRANCE plus fulvestrant arm by descending frequency were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, diarrhea, thrombocytopenia, vomiting, alopecia, rash, decreased appetite, and pyrexia.

The most frequently reported Grade  $\geq 3$  adverse reactions ( $\geq 5\%$ ) in patients receiving IBRANCE plus fulvestrant in descending frequency were neutropenia and leukopenia.

Adverse reactions ( $\geq 10\%$ ) reported in patients who received IBRANCE plus fulvestrant or placebo plus fulvestrant in Study 2 are listed in Table 6.

**Table 6. Adverse Reactions (≥10%) in Study 2**

Adverse Reaction	IBRANCE plus Fulvestrant (N=345)			Placebo plus Fulvestrant (N=172)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	%	%	%	%	%	%
Infections and infestations						
Infections <sup>a</sup>	47 <sup>b</sup>	3	1	31	3	0
Blood and lymphatic system disorders						
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	4	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	8	1	0
Gastrointestinal disorders						
Nausea	34	0	0	28	1	0
Stomatitis <sup>c</sup>	28	1	0	13	0	0
Diarrhea	24	0	0	19	1	0
Vomiting	19	1	0	15	1	0
Skin and subcutaneous tissue disorders						
Alopecia	18 <sup>d</sup>	N/A	N/A	6 <sup>e</sup>	N/A	N/A
Rash <sup>f</sup>	17	1	0	6	0	0
General disorders and administration site conditions						
Fatigue	41	2	0	29	1	0
Pyrexia	13	<1	0	5	0	0

Grading according to CTCAE 4.0.

CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable.

<sup>a</sup> Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.

<sup>b</sup> Most common infections (≥1%) include: nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis, rhinitis, influenza, conjunctivitis, sinusitis, pneumonia, cystitis, oral herpes, respiratory tract infection, gastroenteritis, tooth infection, pharyngitis, eye infection, herpes simplex, and paronychia.

<sup>c</sup> Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.

<sup>d</sup> Grade 1 events – 17%; Grade 2 events – 1%.

<sup>e</sup> Grade 1 events – 6%.

<sup>f</sup> Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of <10.0% of patients receiving IBRANCE plus fulvestrant in Study 2 included asthenia (7.5%), aspartate aminotransferase increased (7.5%), dysgeusia (6.7%), epistaxis (6.7%), lacrimation increased (6.4%), dry skin (6.1%), alanine aminotransferase increased (5.8%), vision blurred (5.8%), dry eye (3.8%), and febrile neutropenia (0.9%).

**Table 7. Laboratory Abnormalities in Study 2**

Laboratory Abnormality	IBRANCE plus Fulvestrant (N=345)			Placebo plus Fulvestrant (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
WBC decreased	99	45	1	26	0	1
Neutrophils decreased	96	56	11	14	0	1
Anemia	78	3	0	40	2	0
Platelets decreased	62	2	1	10	0	0
Aspartate aminotransferase increased	43	4	0	48	4	0
Alanine aminotransferase increased	36	2	0	34	0	0

N=number of patients; WBC=white blood cells.

## 7 DRUG INTERACTIONS

Palbociclib is primarily metabolized by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. In vivo, palbociclib is a time-dependent inhibitor of CYP3A.

### 7.1 Agents That May Increase Palbociclib Plasma Concentrations

#### Effect of CYP3A Inhibitors

Coadministration of a strong CYP3A inhibitor (itraconazole) increased the plasma exposure of palbociclib in healthy subjects by 87%. Avoid concomitant use of strong CYP3A inhibitors (e.g., clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole). Avoid grapefruit or grapefruit juice during IBRANCE treatment. If coadministration of IBRANCE with a strong CYP3A inhibitor cannot be avoided, reduce the dose of IBRANCE [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

### 7.2 Agents That May Decrease Palbociclib Plasma Concentrations

#### Effect of CYP3A Inducers

Coadministration of a strong CYP3A inducer (rifampin) decreased the plasma exposure of palbociclib in healthy subjects by 85%. Avoid concomitant use of strong CYP3A inducers (e.g., phenytoin, rifampin, carbamazepine, enzalutamide, and St John's Wort) [see *Clinical Pharmacology (12.3)*].

### 7.3 Drugs That May Have Their Plasma Concentrations Altered by Palbociclib

Coadministration of midazolam with multiple doses of IBRANCE increased the midazolam plasma exposure by 61%, in healthy subjects, compared to administration of midazolam alone. The dose of the sensitive CYP3A substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimeozide, quinidine, sirolimus, and tacrolimus) may need to be reduced, as IBRANCE may increase its exposure [see *Clinical Pharmacology (12.3)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on findings from animal studies and its mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryofetal toxicity at maternal exposures that were  $\geq 4$  times the human clinical exposure based on AUC [see *Data*]. Advise pregnant women of the potential risk to a fetus.

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

#### 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 of palbociclib up to 300 mg/kg/day and 20 mg/kg/day, respectively, during the period of organogenesis. The maternally toxic dose of 300 mg/kg/day was fetotoxic in rats, resulting in reduced fetal body weights. At doses  $\geq 100$  mg/kg/day in rats, there was an increased incidence of a skeletal variation (increased incidence of a rib present at the seventh cervical vertebra). At the maternally toxic dose of 20 mg/kg/day in rabbits, there was an increased incidence of skeletal variations, including small phalanges in the forelimb. At 300 mg/kg/day in rats and 20 mg/kg/day in rabbits, the maternal systemic exposures were approximately 4 and 9 times the human exposure (AUC) at the recommended dose, respectively.

CDK4/6 double knockout mice have been reported to die in late stages of fetal development (gestation Day 14.5 until birth) due to severe anemia. However, knockout mouse data may not be predictive of effects in humans due to differences in degree of target inhibition.

### 8.2 Lactation

#### Risk Summary

There is no information regarding the presence of palbociclib in human milk, its effects on milk production, or the breastfed infant. Because of the potential for serious adverse reactions in breastfed infants from IBRANCE, advise a lactating woman not to breastfeed during treatment with IBRANCE and for 3 weeks after the last dose.

## 8.3 Females and Males of Reproductive Potential

### Pregnancy Testing

Based on animal studies, IBRANCE can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Females of reproductive potential should have a pregnancy test prior to starting treatment with IBRANCE.

### Contraception

#### Females

IBRANCE can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 weeks after the last dose.

#### Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with IBRANCE and for 3 months after the last dose [*see Nonclinical Toxicology (13.1)*].

### Infertility

#### Males

Based on animal studies, IBRANCE may impair fertility in males of reproductive potential [*see Nonclinical Toxicology (13.1)*].

## 8.4 Pediatric Use

The safety and efficacy of IBRANCE in pediatric patients have not been studied. Altered glucose metabolism (glycosuria, hyperglycemia, decreased insulin) associated with changes in the pancreas (islet cell vacuolation), eye (cataracts, lens degeneration), kidney (tubule vacuolation, chronic progressive nephropathy) and adipose tissue (atrophy) were identified in a 27 week repeat-dose toxicology study in rats that were immature at the beginning of the studies and were most prevalent in males at oral palbociclib doses  $\geq 30$  mg/kg/day (approximately 11 times the adult human exposure [AUC] at the recommended dose). Some of these findings (glycosuria/hyperglycemia, pancreatic islet cell vacuolation, and kidney tubule vacuolation) were present with lower incidence and severity in a 15 week repeat-dose toxicology study in immature rats. Altered glucose metabolism or associated changes in the pancreas, eye, kidney and adipose tissue were not identified in a 27-week repeat-dose toxicology study in rats that were mature at the beginning of the study and in dogs in repeat-dose toxicology studies up to 39 weeks duration.

Toxicities in teeth independent of altered glucose metabolism were observed in rats. Administration of 100 mg/kg palbociclib for 27 weeks (approximately 15 times the adult human exposure [AUC] at the recommended dose) resulted in abnormalities in growing incisor teeth (discolored, ameloblast degeneration/necrosis, mononuclear cell infiltrate). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

## 8.5 Geriatric Use

Of 444 patients who received IBRANCE in Study 1, 181 patients (41%) were  $\geq 65$  years of age and 48 patients (11%) were  $\geq 75$  years of age. Of 347 patients who received IBRANCE in Study 2, 86 patients (25%) were  $\geq 65$  years of age and 27 patients (8%) were  $\geq 75$  years of age. No overall differences in safety or effectiveness of IBRANCE were observed between these patients and younger patients.

## 8.6 Hepatic Impairment

Based on a population pharmacokinetic analysis that included 183 patients, where 40 patients had mild hepatic impairment (total bilirubin  $\leq$  ULN and AST  $>$  ULN, or total bilirubin  $>1.0$  to  $1.5 \times$  ULN and any AST), mild hepatic impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with moderate or severe hepatic impairment (total bilirubin  $>1.5 \times$  ULN and any AST) [see *Clinical Pharmacology* (12.3)].

Review the Full Prescribing Information for the aromatase inhibitor or fulvestrant for dose modifications related to hepatic impairment.

## 8.7 Renal Impairment

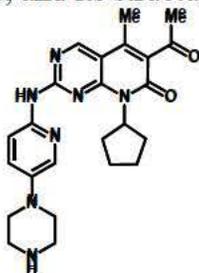
Based on a population pharmacokinetic analysis that included 183 patients, where 73 patients had mild renal impairment ( $60 \text{ mL/min} \leq \text{CrCl} < 90 \text{ mL/min}$ ) and 29 patients had moderate renal impairment ( $30 \text{ mL/min} \leq \text{CrCl} < 60 \text{ mL/min}$ ), mild and moderate renal impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with severe renal impairment [see *Clinical Pharmacology* (12.3)].

## 10 OVERDOSAGE

There is no known antidote for IBRANCE. The treatment of overdose of IBRANCE should consist of general supportive measures.

## 11 DESCRIPTION

IBRANCE capsules for oral administration contain 125 mg, 100 mg, or 75 mg of palbociclib, a kinase inhibitor. The molecular formula for palbociclib is  $\text{C}_{24}\text{H}_{29}\text{N}_7\text{O}_2$ . The molecular weight is 447.54 daltons. The chemical name is 6-acetyl-8-cyclopentyl-5-methyl-2-[[5-(piperazin-1-yl)pyridin-2-yl]amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one, and its structural formula is:



Palbociclib is a yellow to orange powder with pKa of 7.4 (the secondary piperazine nitrogen) and 3.9 (the pyridine nitrogen). At or below pH 4, palbociclib behaves as a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly.

*Inactive ingredients:* Microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and hard gelatin capsule shells. The light orange, light orange/caramel, and caramel opaque capsule shells contain gelatin, red iron oxide, yellow iron oxide, and titanium dioxide; the printing ink contains shellac, titanium dioxide, ammonium hydroxide, propylene glycol, and simethicone.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Palbociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. In vitro, palbociclib reduced cellular proliferation of estrogen receptor (ER)-positive breast cancer cell lines by blocking progression of the cell from G1 into S phase of the cell cycle. Treatment of breast cancer cell lines with the combination of palbociclib and antiestrogens leads to decreased retinoblastoma (Rb) protein phosphorylation resulting in reduced E2F expression and signaling, and increased growth arrest compared to treatment with each drug alone. In vitro treatment of ER-positive breast cancer cell lines with the combination of palbociclib and antiestrogens led to increased cell senescence compared to each drug alone, which was sustained for up to 6 days following palbociclib removal and was greater if antiestrogen treatment was continued. In vivo studies using a patient-derived ER-positive breast cancer xenograft model demonstrated that the combination of palbociclib and letrozole increased the inhibition of Rb phosphorylation, downstream signaling, and tumor growth compared to each drug alone.

Human bone marrow mononuclear cells treated with palbociclib in the presence or absence of an anti-estrogen in vitro did not become senescent and resumed proliferation following palbociclib withdrawal.

### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

The effect of palbociclib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with breast cancer. Palbociclib had no large effect on QTc (i.e. > 20 ms) at 125 mg once daily (Schedule 3/1).

### 12.3 Pharmacokinetics

The pharmacokinetics (PK) of palbociclib were characterized in patients with solid tumors including advanced breast cancer and in healthy subjects.

#### Absorption

The mean maximum observed concentration ( $C_{max}$ ) of palbociclib is generally observed between 6 to 12 hours (time to reach maximum concentration,  $T_{max}$ ) following oral administration. The mean absolute bioavailability of IBRANCE after an oral 125 mg dose is 46%. In the dosing range of 25 mg to 225 mg, the AUC and  $C_{max}$  increased proportionally with dose in general. Steady state was achieved within 8 days following repeated once daily dosing. With repeated once daily administration, palbociclib accumulated with a median accumulation ratio of 2.4 (range 1.5 to 4.2).

Food effect: Palbociclib absorption and exposure were very low in approximately 13% of the population under the fasted condition. Food intake increased the palbociclib exposure in this small subset of the

population, but did not alter palbociclib exposure in the rest of the population to a clinically relevant extent. Therefore, food intake reduced the intersubject variability of palbociclib exposure, which supports administration of IBRANCE with food. Compared to IBRANCE given under overnight fasted conditions, the population average area under the concentration-time curve from zero to infinity ( $AUC_{INF}$ ) and  $C_{max}$  of palbociclib increased by 21% and 38%, respectively, when given with high-fat, high-calorie food (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively), by 12% and 27%, respectively, when given with low-fat, low-calorie food (approximately 400 to 500 calories with 120, 250, and 28 to 35 calories from protein, carbohydrate, and fat, respectively), and by 13% and 24%, respectively, when moderate-fat, standard calorie food (approximately 500 to 700 calories with 75 to 105, 250 to 350 and 175 to 245 calories from protein, carbohydrate, and fat, respectively) was given 1 hour before and 2 hours after IBRANCE dosing.

## **Distribution**

Binding of palbociclib to human plasma proteins *in vitro* was approximately 85%, with no concentration dependence over the concentration range of 500 ng/mL to 5000 ng/mL. The geometric mean apparent volume of distribution ( $V_z/F$ ) was 2583 L with a coefficient of variation (CV) of 26%.

## **Metabolism**

*In vitro* and *in vivo* studies indicated that palbociclib undergoes hepatic metabolism in humans. Following oral administration of a single 125 mg dose of [ $^{14}C$ ]palbociclib to humans, the primary metabolic pathways for palbociclib involved oxidation and sulfonation, with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-derived entity in plasma (23%). The major circulating metabolite was a glucuronide conjugate of palbociclib, although it only represented 1.5% of the administered dose in the excreta. Palbociclib was extensively metabolized with unchanged drug accounting for 2.3% and 6.9% of radioactivity in feces and urine, respectively. In feces, the sulfamic acid conjugate of palbociclib was the major drug-related component, accounting for 26% of the administered dose. *In vitro* studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant SULT enzymes indicated that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

## **Elimination**

The geometric mean apparent oral clearance (CL/F) of palbociclib was 63.1 L/hr (29% CV), and the mean ( $\pm$  standard deviation) plasma elimination half-life was 29 ( $\pm 5$ ) hours in patients with advanced breast cancer. In 6 healthy male subjects given a single oral dose of [ $^{14}C$ ]palbociclib, a median of 91.6% of the total administered radioactive dose was recovered in 15 days; feces (74.1% of dose) was the major route of excretion, with 17.5% of the dose recovered in urine. The majority of the material was excreted as metabolites.

## **Age, Gender, and Body Weight**

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age range from 22 to 89 years, and body weight range from 37.9 to 123 kg), gender had no effect on the exposure of palbociclib, and age and body weight had no clinically important effect on the exposure of palbociclib.

## Pediatric Population

Pharmacokinetics of IBRANCE have not been evaluated in patients <18 years of age.

## Drug Interactions

In vitro data indicate that CYP3A and SULT enzyme SULT2A1 are mainly involved in the metabolism of palbociclib. Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing to steady state in humans. In vitro, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations.

*CYP3A Inhibitors:* Data from a drug interaction trial in healthy subjects (N=12) indicate that coadministration of multiple 200 mg daily doses of itraconazole with a single 125 mg IBRANCE dose increased palbociclib AUC<sub>INF</sub> and the C<sub>max</sub> by approximately 87% and 34%, respectively, relative to a single 125 mg IBRANCE dose given alone [see *Drug Interactions (7.1)*].

*CYP3A Inducers:* Data from a drug interaction trial in healthy subjects (N=15) indicate that coadministration of multiple 600 mg daily doses of rifampin, a strong CYP3A inducer, with a single 125 mg IBRANCE dose decreased palbociclib AUC<sub>INF</sub> and C<sub>max</sub> by 85% and 70%, respectively, relative to a single 125 mg IBRANCE dose given alone. Data from a drug interaction trial in healthy subjects (N=14) indicate that coadministration of multiple 400 mg daily doses of modafinil, a moderate CYP3A inducer, with a single 125 mg IBRANCE dose decreased palbociclib AUC<sub>INF</sub> and C<sub>max</sub> by 32% and 11%, respectively, relative to a single 125 mg IBRANCE dose given alone [see *Drug Interactions (7.2)*].

*CYP3A Substrates:* Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing to steady state in humans. In a drug interaction trial in healthy subjects (N=26), coadministration of midazolam with multiple doses of IBRANCE increased the midazolam AUC<sub>INF</sub> and the C<sub>max</sub> values by 61% and 37%, respectively, as compared to administration of midazolam alone [see *Drug Interactions (7.3)*].

*Gastric pH Elevating Medications:* In a drug interaction trial in healthy subjects, coadministration of a single 125 mg dose of IBRANCE with multiple doses of the proton pump inhibitor (PPI) rabeprazole under fed conditions decreased palbociclib C<sub>max</sub> by 41%, but had limited impact on AUC<sub>INF</sub> (13% decrease), when compared to a single dose of IBRANCE administered alone. Given the reduced effect on gastric pH of H<sub>2</sub>-receptor antagonists and local antacids compared to PPIs, the effect of these classes of acid-reducing agents on palbociclib exposure under fed conditions is expected to be minimal. Under fed conditions there is no clinically relevant effect of PPIs, H<sub>2</sub>-receptor antagonists, or local antacids on palbociclib exposure. In another healthy subject study, coadministration of a single dose of IBRANCE with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib AUC<sub>INF</sub> and C<sub>max</sub> by 62% and 80%, respectively, when compared to a single dose of IBRANCE administered alone.

*Letrozole:* Data from a clinical trial in patients with breast cancer showed that there was no drug interaction between palbociclib and letrozole when the 2 drugs were coadministered.

*Fulvestrant:* Data from a clinical trial in patients with breast cancer showed that there was no clinically relevant drug interaction between palbociclib and fulvestrant when the 2 drugs were coadministered.

*Goserelin*: Data from a clinical trial in patients with breast cancer showed that there was no clinically relevant drug interaction between palbociclib and goserelin when the 2 drugs were coadministered.

*Anastrozole or exemestane*: No clinical data are available to evaluate drug interactions between anastrozole or exemestane and palbociclib. A clinically significant drug interaction between anastrozole or exemestane and palbociclib is not expected based on analyses of the effects of anastrozole, exemestane and palbociclib on or by metabolic pathways or transporter systems.

*Effect of Palbociclib on Transporters*: In vitro evaluations indicated that palbociclib has a low potential to inhibit the activities of drug transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, and organic anion transporting polypeptide (OATP)1B1, OATP1B3 at clinically relevant concentrations.

*Effect of Transporters on Palbociclib*: Based on in vitro data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of palbociclib at therapeutic doses.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with palbociclib.

Palbociclib was aneugenic in Chinese Hamster Ovary cells in vitro and in the bone marrow of male rats at doses  $\geq 100$  mg/kg/day for 3 weeks. Palbociclib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay and was not clastogenic in the in vitro human lymphocyte chromosome aberration assay.

In a fertility study in female rats, palbociclib did not affect mating or fertility at any dose up to 300 mg/kg/day (approximately 4 times human clinical exposure based on AUC) and no adverse effects were observed in the female reproductive tissues in repeat-dose toxicity studies up to 300 mg/kg/day in the rat and 3 mg/kg/day in the dog (approximately 6 times and similar to human exposure [AUC], at the recommended dose, respectively).

The adverse effects of palbociclib on male reproductive function and fertility were observed in the repeat-dose toxicology studies in rats and dogs and a male fertility study in rats. In repeat-dose toxicology studies, palbociclib-related findings in the testis, epididymis, prostate, and seminal vesicle at  $\geq 30$  mg/kg/day in rats and  $\geq 0.2$  mg/kg/day in dogs included decreased organ weight, atrophy or degeneration, hypospermia, intratubular cellular debris, and decreased secretion. Partial reversibility of male reproductive organ effects was observed in the rat and dog following a 4- and 12-week non-dosing period, respectively. These doses in rats and dogs resulted in approximately  $\geq 10$  and 0.1 times, respectively, the exposure [AUC] in humans at the recommended dose. In the fertility and early embryonic development study in male rats, palbociclib caused no effects on mating but resulted in a slight decrease in fertility in association with lower sperm motility and density at 100 mg/kg/day with projected exposure levels [AUC] of 20 times the exposure in humans at the recommended dose.

## 14 CLINICAL STUDIES

### Study 1: IBRANCE plus Letrozole

**Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy**

Study 1 (PALOMA-2) was an international, randomized, double-blind, parallel-group, multicenter study of IBRANCE plus letrozole versus placebo plus letrozole conducted in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. A total of 666 patients were randomized 2:1 to IBRANCE plus letrozole or placebo plus letrozole. Randomization was stratified by disease site (visceral versus non-visceral), disease-free interval (de novo metastatic versus  $\leq 12$  months from the end of adjuvant treatment to disease recurrence versus  $>12$  months from the end of adjuvant treatment to disease recurrence), and nature of prior (neo)adjuvant anticancer therapies (prior hormonal therapies versus no prior hormonal therapy). IBRANCE was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Patients received study treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. The major efficacy outcome of the study was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST).

Patients enrolled in this study had a median age of 62 years (range 28 to 89). The majority of patients were White (78%), and most patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 (98%). Forty-eight percent of patients had received chemotherapy and 56% had received antihormonal therapy in the neoadjuvant or adjuvant setting prior to their diagnosis of advanced breast cancer. Thirty-seven percent of patients had no prior systemic therapy in the neoadjuvant or adjuvant setting. The majority of patients (97%) had metastatic disease. Twenty-three percent of patients had bone only disease, and 49% of patients had visceral disease.

Major efficacy results from Study 1 are summarized in Table 8 and Figure 1. Consistent results were observed across patient subgroups of disease-free interval (DFI), disease site, and prior therapy. The treatment effect of the combination on PFS was also supported by an independent review of radiographs. The overall survival (OS) data were not mature at the time of the final PFS analysis (20% of patients had died). Patients will continue to be followed for the final analysis.

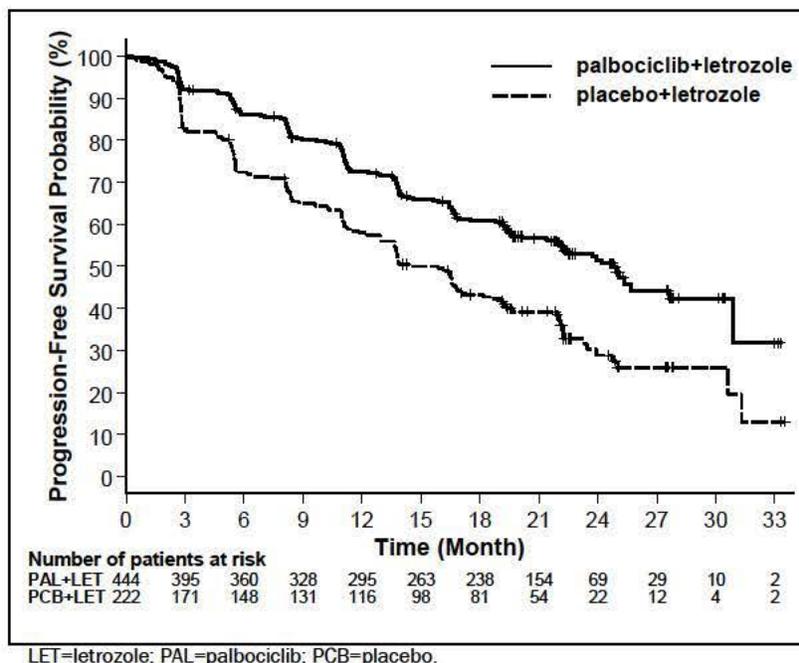
**Table 8. Efficacy Results – Study 1 (Investigator Assessment, Intent-to-Treat Population)**

	<b>IBRANCE plus Letrozole</b>	<b>Placebo plus Letrozole</b>
<b>Progression-free survival for ITT</b>	<b>N=444</b>	<b>N=222</b>
Number of PFS events (%)	194 (43.7)	137 (61.7)
Median progression-free survival (months, 95% CI)	24.8 (22.1, NE)	14.5 (12.9, 17.1)
Hazard ratio (95% CI) and p-value	0.576 (0.463, 0.718), p<0.0001	
<b>Objective Response for patients with measurable disease</b>	<b>N=338</b>	<b>N=171</b>
Objective response rate* (% , 95% CI)	55.3 (49.9, 60.7)	44.4 (36.9, 52.2)

\*Response based on confirmed responses

CI=confidence interval; ITT=Intent-to-Treat; N=number of patients; NE=not estimable.

**Figure 1. Kaplan-Meier Plot of Progression-Free Survival – Study 1 (Investigator Assessment, Intent-to-Treat Population)**



### **Study 2: IBRANCE plus Fulvestrant**

**Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy**

Study 2 (PALOMA-3) was an international, randomized, double-blind, parallel group, multicenter study of IBRANCE plus fulvestrant versus placebo plus fulvestrant conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy. A total of 521 pre/postmenopausal women were randomized 2:1 to IBRANCE plus fulvestrant or placebo plus fulvestrant and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri versus postmenopausal), and presence of visceral metastases. IBRANCE was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Pre/perimenopausal women were enrolled in the study and received the LHRH agonist goserelin for at least 4 weeks prior to and for the duration of Study 2. Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. The major efficacy outcome of the study was investigator-assessed PFS evaluated according to RECIST 1.1.

Patients enrolled in this study had a median age of 57 years (range 29 to 88). The majority of patients on study were White (74%), all patients had an ECOG PS of 0 or 1, and 80% were postmenopausal. All patients had received prior systemic therapy, and 75% of patients had received a previous chemotherapy regimen. Twenty-five percent of patients had received no prior therapy in the metastatic disease setting, 60% had visceral metastases, and 23% had bone only disease.

The results from the investigator-assessed PFS from Study 2 are summarized in Table 9 and Figure 2. Consistent results were observed across patient subgroups of disease site, sensitivity to prior hormonal therapy and menopausal status. The overall survival (OS) data were not mature at the time of the final PFS analysis (11% of patients had died). Patients will continue to be followed for the final analysis.

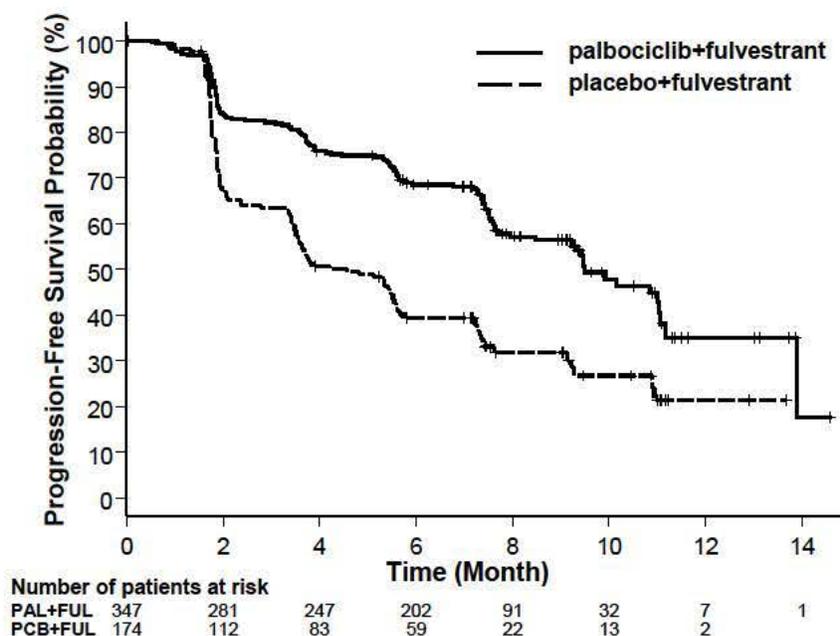
**Table 9. Efficacy Results – Study 2 (Investigator Assessment, Intent-to-Treat Population)**

	<b>IBRANCE plus Fulvestrant</b>	<b>Placebo plus Fulvestrant</b>
<b>Progression-free survival for ITT</b>	<b>N=347</b>	<b>N=174</b>
Number of PFS events (%)	145 (41.8%)	114 (65.5%)
Median progression-free survival (months, 95% CI)	9.5 (9.2, 11.0)	4.6 (3.5, 5.6)
Hazard ratio (95% CI) and p-value	0.461 (0.360, 0.591), p < 0.0001	
<b>Objective Response for patients with measurable disease</b>	<b>N=267</b>	<b>N=138</b>
Objective response rate* (%; 95% CI)	24.6 (19.6, 30.2)	10.9 (6.2, 17.3)

\* Response based on confirmed responses

CI=confidence interval; ITT=Intent-to-Treat; N=number of patients.

**Figure 2. Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, Intent-to-Treat Population) – Study 2**



FUL=fulvestrant; PAL=palbociclib; PCB=placebo.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

IBRANCE is supplied in the following strengths and package configurations:

<b>IBRANCE Capsules</b>			
<b>Package Configuration</b>	<b>Capsule Strength (mg)</b>	<b>NDC</b>	<b>Capsule Description</b>
Bottles of 21 capsules	125	NDC 0069-0189-21	opaque, hard gelatin capsules, size 0, with caramel cap and body, printed with white ink “Pfizer” on the cap,

IBRANCE Capsules			
Package Configuration	Capsule Strength (mg)	NDC	Capsule Description
			“PBC 125” on the body
Bottles of 21 capsules	100	NDC 0069-0188-21	opaque, hard gelatin capsules, size 1, with caramel cap and light orange body, printed with white ink “Pfizer” on the cap, “PBC 100” on the body
Bottles of 21 capsules	75	NDC 0069-0187-21	opaque, hard gelatin capsules, size 2, with light orange cap and body, printed with white ink “Pfizer” on the cap, “PBC 75” on the body

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) [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

### Myelosuppression/Infection

- Advise patients to immediately report any signs or symptoms of myelosuppression or infection, such as fever, chills, dizziness, shortness of breath, weakness, or any increased tendency to bleed and/or to bruise [see Warnings and Precautions (5.1)].

### Drug Interactions

- Grapefruit may interact with IBRANCE. Patients should not consume grapefruit products while on treatment with IBRANCE.
- Inform patients to avoid strong CYP3A inhibitors and strong CYP3A inducers.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions (7)].

### Dosing and Administration

- Advise patients to take IBRANCE with food.
- If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. IBRANCE capsules should be swallowed whole (do not chew, crush, or open them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

### Pregnancy, Lactation, and Fertility

- Embryo-Fetal Toxicity
  - Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with IBRANCE therapy and for at least 3 weeks after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.2) and Use in Specific Populations (8.1 and 8.3)].

- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 months after the last dose [*see Use in Specific Populations (8.3)*].
- Lactation: Advise women not to breastfeed during treatment with IBRANCE and for 3 weeks after the last dose [*see Use in Specific Populations (8.2)*].

This product's label may have been updated. For full prescribing information, please visit [www.IBRANCE.com](http://www.IBRANCE.com).



LAB-0723-2.1

**PATIENT INFORMATION**  
**IBRANCE® (EYE-brans)**  
**(palbociclib)**  
Capsules

**What is the most important information I should know about IBRANCE?**

**IBRANCE may cause serious side effects, including:**

**Low white blood cell counts (neutropenia).** Low white blood cell counts are very common when taking IBRANCE and may cause serious infections that can lead to death. Your healthcare provider should check your white blood cell counts before and during treatment.

If you develop low white blood cell counts during treatment with IBRANCE, your healthcare provider may stop your treatment, decrease your dose, or may tell you to wait to begin your treatment cycle. Tell your healthcare provider right away if you have signs and symptoms of low white blood cell counts or infections such as fever and chills.

**See “What are the possible side effects of IBRANCE?” for more information about side effects.**

**What is IBRANCE?**

IBRANCE is a prescription medicine used to treat hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has spread to other parts of the body (metastatic) in combination with:

- an aromatase inhibitor as the first hormonal based therapy in women who have gone through menopause, or
- fulvestrant in women with disease progression following hormonal therapy.

It is not known if IBRANCE is safe and effective in children.

**What should I tell my healthcare provider before taking IBRANCE?**

Before you take IBRANCE, tell your healthcare provider if you:

- have fever, chills, or any other signs or symptoms of infection.
- have liver or kidney problems.
- have any other medical conditions.
- are pregnant, or plan to become pregnant. IBRANCE can harm your unborn baby.
  - Females who are able to become pregnant and who take IBRANCE should use effective birth control during treatment and for at least 3 weeks after stopping IBRANCE.
  - Males who are taking IBRANCE, with female partners who can become pregnant should use effective birth control during treatment with IBRANCE for 3 months after the final dose of IBRANCE.
  - Talk to your healthcare provider about birth control methods that may be right for you during this time.
  - If you become pregnant or think you are pregnant, tell your healthcare provider right away.
- are breastfeeding or plan to breastfeed. It is not known if IBRANCE passes into your breast milk. You and your healthcare provider should decide if you will take IBRANCE or breastfeed. You should not do both.

**Tell your healthcare provider about all of the medicines you take, including** prescription and over-the-counter medicines, vitamins, and herbal supplements. IBRANCE and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

**How should I take IBRANCE?**

- Take IBRANCE exactly as your healthcare provider tells you.
- Take IBRANCE with food.
- Swallow IBRANCE capsules whole. Do not chew, crush or open IBRANCE capsules before swallowing them.
- Do not take any IBRANCE capsules that are broken, cracked, or that look damaged.
- Avoid grapefruit and grapefruit products during treatment with IBRANCE. Grapefruit may increase the amount of IBRANCE in your blood.
- Do not change your dose or stop taking IBRANCE unless your healthcare provider tells you.
- If you miss a dose of IBRANCE or vomit after taking a dose of IBRANCE, do not take another dose on that day. Take your next dose at your regular time.
- If you take too much IBRANCE, call your healthcare provider right away or go to the nearest hospital emergency room.

### What are the possible side effects of IBRANCE?

**IBRANCE may cause serious side effects. See “What is the most important information I should know about IBRANCE?”**

Common side effects of IBRANCE when used with either letrozole or fulvestrant include:

- Low red blood cell counts and low platelet counts are common with IBRANCE. Call your healthcare provider right away if you develop any of these symptoms during treatment:
  - dizziness
  - shortness of breath
  - weakness
  - bleeding or bruising more easily
  - nosebleeds
- infections (see “What is the most important information I should know about IBRANCE?”)
- tiredness
- nausea
- sore mouth
- abnormalities in liver blood tests
- diarrhea
- hair thinning or hair loss
- vomiting
- rash
- loss of appetite

IBRANCE may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if this is a concern for you.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of IBRANCE. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### How should I store IBRANCE?

- Store IBRANCE at 68 °F to 77 °F (20 °C to 25 °C).

**Keep IBRANCE and all medicines out of the reach of children.**

### General information about the safe and effective use of IBRANCE

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use IBRANCE for a condition for which it was not prescribed. Do not give IBRANCE to other people, even if they have the same symptoms you have. It may harm them.

If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for more information about IBRANCE that is written for health professionals.

For more information, go to [www.IBRANCE.com](http://www.IBRANCE.com) or call 1-800-438-1985.

### What are the ingredients in IBRANCE?

Active ingredient: palbociclib

Inactive ingredients: Microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and hard gelatin capsule shells.

Light orange, light orange/caramel and caramel opaque capsule shells contain: gelatin, red iron oxide, yellow iron oxide, and titanium dioxide.

Printing ink contains: shellac, titanium dioxide, ammonium hydroxide, propylene glycol, and simethicone.



LAB-0724-2.1

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: March 2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207103Orig1s004**

**SUMMARY REVIEW**

## Division Director Summary Review for Regulatory Action

<b>Date</b>	March 31, 2017
<b>From</b>	Geoffrey Kim
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	207103/S-004
<b>Supplement #</b>	
<b>Applicant</b>	Pfizer, Inc.
<b>Date of Submission</b>	October 7, 2016
<b>PDUFA Goal Date</b>	April 27, 2017
<b>Proprietary Name / Non-Proprietary Name</b>	Ibrance/palbociclib
<b>Dosage Form(s) / Strength(s)</b>	Capsules/ 75 mg, 100 mg, 125 mg
<b>Applicant Proposed Indication(s)/Population(s)</b>	IBRANCE is a (b) (4) kinase (b) (4) inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with: <ul style="list-style-type: none"> <li>• an aromatase inhibitor as initial endocrine based therapy in postmenopausal women or</li> <li>• fulvestrant in women with disease progression following endocrine therapy.</li> </ul>
<b>Action/Recommended Action for sNDA:</b>	<i>Approval</i>
<b>Approved/Recommended Indication/Population(s) (if applicable)</b>	IBRANCE is a kinase inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with: <ul style="list-style-type: none"> <li>• an aromatase inhibitor as initial endocrine based</li> </ul>

	therapy in postmenopausal women; or <ul style="list-style-type: none"> <li>fulvestrant in women with disease progression following endocrine therapy.</li> </ul>
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<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Suparna Wedam
Statistical Review	Erik Bloomquist; Shenghui Tang
Clinical Pharmacology Review	Wentao Fu, Qi Liu; Jerry Yu
OPDP	Nick Senior
OSI	Lauren Iacono-Connors
CDTL Review	Laleh Amiri-Kordestani

OND=Office of New Drugs  
 OPQ=Office of Pharmaceutical Quality  
 OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 CDTL=Cross-Discipline Team Leader  
 OSE= Office of Surveillance and Epidemiology  
 DEPI= Division of Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRISK=Division of Risk Management

# 1. Benefit-Risk Assessment

## Benefit-Risk Summary and Assessment

*I concur with the Benefit-Risk Assessment that was made by the clinical and statistical teams. Based on the results of Study 1008 (A5481008, PALOMA-2), a favorable benefit-risk profile of palbociclib has been demonstrated for patients with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women. The regulatory action for this supplement is approval. As summarized by the clinical review team:*

“The basis for this recommendation is a favorable benefit-risk profile for palbociclib when added to letrozole in women with HR-positive, HER2-negative advanced or metastatic breast cancer that have not been previously treated for their advanced/metastatic disease. In the randomized, double-blind, placebo- controlled Phase 3 study, Study 1008 (A5481008, PALOMA-2) a clinically meaningful and statistically significant 10 month improvement in estimated median progression free survival (PFS) was observed favoring the palbociclib plus letrozole treatment arm. Results of a blinded independent central review (BICR), subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results. The estimated median PFS in the palbociclib plus letrozole arm at the time of the final PFS analysis was 24.8 months compared to 14.5 months in the placebo plus letrozole arm with a Hazard Ratio (HR) of 0.58 (95%Confidence Interval (CI): 0.46, 0.72;  $p < 0.0001$ ). Overall survival (OS) analysis was not mature at the time of the PFS analysis.

The final PFS results from Study 1008 fulfill the postmarketing requirement (2860-1) from the accelerated approval of palbociclib in combination of letrozole and confirm the results observed in Study 1003 (PALOMA-1) which supported the accelerated approval. Study 1003 was an international, multicenter, open-label, randomized Phase 1/2 study in a population of postmenopausal HR-positive HER2- negative advanced breast cancer patients who had not been treated previously for their advanced disease who were randomized 1:1 to receive palbociclib plus letrozole or letrozole alone. In Study 1003, a 10 month improvement in estimated median PFS was also observed with a HR of 0.488 (95% CI: 0.319, 0.748, 1 sided  $p = 0.0004$ ) favoring the palbociclib plus letrozole treatment arm.

This indication for palbociclib will expand the indication to allow for the use with any aromatase inhibitor. No clinical data are available regarding drug interactions, safety or efficacy between anastrozole or exemestane and palbociclib. However, clinically significant drug interactions are not expected based on analyses of the effects of these drugs on or by metabolic pathways or transporter systems.

Overall, palbociclib was generally tolerable with adverse reactions manageable through the use of dose reduction, temporary treatment discontinuation, and/or standard medical care. Neutropenia was the most common adverse reaction in the palbociclib treatment arm, occurring in 80% of patients. Febrile neutropenia occurred in 2.5% of patients. Additional common adverse reactions ( $\geq 10\%$ ) with palbociclib include infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia. With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2. Permanent discontinuation associated with an adverse reaction occurred in 9.7% of patients receiving palbociclib plus letrozole. The safety profile is acceptable for this patient population with a serious and life-threatening disease.

In conclusion, based on a favorable risk-benefit profile for palbociclib in combination with letrozole, the reviewers recommend regular approval for the following indication “IBRANCE is a (b) (4) kinase (b) (4) inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women.”

*The Table below is from the combined clinical and statistical review. I concur with the findings and analysis.*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>In 2017, it is estimated that breast cancer will be diagnosed in 252,710 women in the United States and that approximately 40,000 women will die of their disease. MBC, where the original cancer in the breast has spread to distant organs in the body, is the most advanced stage of breast cancer and is incurable with a 5 year survival of approximately 20%.</li> </ul>	<ul style="list-style-type: none"> <li>Breast cancer is a serious and life-threatening condition.</li> <li>HR positive-tumors represent the most common form of breast cancer and account for most of the deaths from the disease.</li> </ul>
<a href="#">Current Treatment Options</a>	<ul style="list-style-type: none"> <li>The treatment of MBC is palliative in nature with a goal to prolong survival and improve quality of life by reducing cancer-related symptoms. Endocrine therapy options for postmenopausal women with HR-positive MBC include aromatase inhibitors (anastrozole, letrozole and exemestane), fulvestrant or tamoxifen. Endocrine therapy options for premenopausal women with HR-positive MBC that do not respond to first line therapy are similar to those for</li> </ul>	<ul style="list-style-type: none"> <li>Endocrine therapy represents the main initial therapeutic strategy for these patients. Although currently available ET agents are generally effective and well tolerated, not all patients benefit equally and many develop resistance.</li> <li>There is an unmet medical need to improve</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>postmenopausal women; however, aromatase inhibitors or fulvestrant need to be administered in combination with ovarian suppression therapy. Pre- and post-menopausal women may also receive chemotherapy as second or later lines of treatment, once they have had tumor progression on endocrine therapy. Patients whose tumors overexpress HER2 have separate prognoses and distinct treatment options.</p>	<p>the outcomes in patients with HR-positive, HER2-negative advanced or metastatic breast cancer.</p>
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> <li>The clinical data from a randomized, double-blind, placebo-controlled Phase 3 Trial (Study 1008, A5481008, PALOMA-2) in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease was not previously treated presented in this sNDA demonstrates an improvement in PFS for palbociclib plus letrozole compared to placebo plus letrozole. The median PFS in the palbociclib plus fulvestrant arm was 24.8 months compared to 14.5 months in the placebo plus fulvestrant arm (HR =0.58; 95% CI: 0.46, 0.72; p&lt;0.0001). OS results were immature at the time of analysis with only 20% of deaths having occurred. Objective response rate (ORR) was 55.3% in the palbociclib plus letrozole arm compared with 44.4% in the placebo plus letrozole arm for patients with measurable disease at baseline.</li> </ul>	<p>The PFS benefit derived from palbociclib is statistically significant and clinically meaningful. It is unclear if there will be an OS benefit.</p>
<p><u>Risk</u></p>	<ul style="list-style-type: none"> <li>Neutropenia was the most common adverse reaction in the palbociclib treatment arm, occurring in 80% of patients. Febrile neutropenia occurred in 2.5% of patients.</li> <li>Additional common adverse reactions (&gt;10%) with palbociclib include infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia. With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2. Permanent discontinuation associated with an adverse reaction occurred in 9.7% of patients receiving palbociclib plus letrozole.</li> </ul>	<ul style="list-style-type: none"> <li>The safety profile of palbociclib plus letrozole for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer is generally tolerable, with adverse reactions manageable through the use of palbociclib dose reduction, temporary treatment discontinuation, and/or standard medical care.</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• Neutropenia is the only adverse reactions being described in the warnings and precautions section of labeling.</li> </ul>	
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> <li>• Palbociclib is intended to be prescribed by oncologists.</li> <li>• Oncologists are well versed in the identification and management of the toxicities associated with palbociclib.</li> <li>• Labeling details dose interruption, reduction, or discontinuation</li> <li>• Laboratory monitoring is recommended before and during treatment.</li> </ul>	<ul style="list-style-type: none"> <li>• The safe use of palbociclib can be managed through accurate labeling and routine oncology care.</li> <li>• No REMS is indicated.</li> </ul>

## 2. Background

*From the clinical and statistical review:*

Palbociclib was granted accelerated approved by the FDA on February 3, 2015 for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. This accelerated approval had a postmarketing requirement (PMR) to confirm the clinical benefit observed in Study 1003 (PALOMA-1). This PMR required PFS and OS data and results from the ongoing Study 1008 (PALOMA-2).

On February 19, 2016, the FDA approved palbociclib in combination with fulvestrant for the treatment of women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.

*Intended Population*

*From the Clinical Review:*

FDA-approved endocrine therapies for patients with HR-receptor positive locally advanced or metastatic breast cancer as first line therapy are shown in **Error! Reference source not found.** .

**Table 1: Available Therapy for the Proposed Patient Population**

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Drug Class
<b>FDA Approved Treatments</b>						
Ribociclib	In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer	2017	600mg daily by mouth, 21 days on/7 days off	Ribociclib+letrozole vs placebo+letrozole PFS: NR vs 14.7 months, HR 0.556 (95% CI: 0.429, 0.720; p<0.0001)	Myelosuppression, abnormal liver function tests, vomiting, QT prolongation	CDK 4/6 inhibitor
Letrozole	First and second-line treatment of postmenopausal women with hormone	1997	2.5mg daily by mouth	Vs tamoxifen TTP: 9.4 months vs 6.4 months HR 0.72 (p<0.0001) OS: 35 months vs 32 months	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor

	receptor positive or unknown advanced breast cancer			(p=0.5136)		
Anastrozole	First-line treatment of postmenopausal women with HR-positive or unknown locally advanced or metastatic breast cancer	1995	1mg daily by mouth	Vs. tamoxifen TTP: 11.1 vs 5.6 months (p=0.006) and 8.2 vs 8.3 months (p=0.92)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor
Tamoxifen	In the treatment of metastatic breast cancer in women and men. Patients whose tumors are estrogen receptor positive are more likely to benefit.	1977	20mg daily by mouth	Response rate in 14 phase 2 studies and nine literature reports. The overall database included 1164 patients.	Uterine malignancies, stroke, pulmonary embolism and hot flashes	Selective estrogen receptor modulator
<b>Other Treatments</b>						
Exemestane	Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy	1999	25mg daily by mouth	Vs megestrol acetate TTP: 20.3 weeks vs 16.6 weeks (HR 0.84)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor

### 3. Product Quality

From the CMC Reviewer:

“No CMC changes have been proposed in the supplement. Pfizer Inc. claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR Part 25.31 (a) applicable for action on a supplemental NDA when the action does not increase the use of the active moiety. Pfizer Inc. claims that to their knowledge, no extraordinary circumstances exist. The claim for a categorical exclusion to the environmental assessment is deemed acceptable.”

## 4. Nonclinical Pharmacology/Toxicology

I agree with the recommendation for approval of this application from the pharmacology/toxicology team. Major findings from the review that resulted in changes to the label are summarized as follows:

“Section (b) (4) was updated based on the re-evaluation of altered glucose metabolism in a 27-week study using aged rats. The absence of effects on glucose metabolism, the pancreas, eyes, and kidney in aged rats at the systemic exposures at which effects were observed in young rats, together with the absence of similar clinical signals in patients suggested that these risks may not be relevant to adult patients. However, these potential risks still remain for a younger patient population. Therefore, the results from the repeat-dose toxicity study in young rats were moved to section 8.4 Pediatric Use, consistent with FDA guidance documents recommending of pediatric information into labeling of human pharmaceuticals.

Section 12.1 was updated based on the in vitro pharmacology study results (NDA 207103/S-02, 2/8/2016). The in vitro pharmacology studies suggested that the mechanism of palbociclib-induced bone marrow suppression was different from that induced by cytotoxic chemotherapeutic agents, and the mechanisms of palbociclib induced cell growth inhibition are different in human bone marrow mononuclear cells and human breast cancer cells.”

## 5. Clinical Pharmacology

I agree with the assessment from the clinical pharmacology and Pharmacometrics team as stated: “The current submission is acceptable from a clinical pharmacology perspective (Divisions of Clinical Pharmacology V and Pharmacometrics).”

Major findings from the review are as follows:

“In support of full approval, results from a confirmatory, randomized, double-blind, placebo controlled, parallel-group Phase 3 Study 1008 (PALOMA-2), comparing the efficacy and safety of palbociclib + letrozole (N=444) versus placebo + letrozole (N=222) in postmenopausal women with ER-positive/HER2-negative advanced breast cancer who had not received any prior systemic anticancer therapies for their advanced disease. In the Phase 3 Study, 125 mg palbociclib or placebo was administered orally once daily on Days 1 to 21 of each 28-day cycle and 2.5 mg letrozole was administered orally once daily. The addition of palbociclib to letrozole resulted in a statistically significant improvement in the primary endpoint, investigator-assessed progression free survival (PFS). The median PFS was 24.8 months (95% CI: 22.1, not estimable) in the palbociclib + letrozole arm and 14.5 months (95% CI: 12.9, 17.1) in the placebo + letrozole arm. The hazard ratio was 0.576 (95% CI: 0.463, 0.718). In a ECG subgroup analysis (N=77), no large QTc prolongation effect of palbociclib + letrozole was detected on from the Phase 3 Study 1008. The largest upper bound of the 2-sided 90% CI for the mean difference between palbociclib + letrozole and placebo + letrozole was below 10 ms. In an exposure response (E-R) analysis using Study 1008 results, investigator-assessed PFS prolongation was not significantly associated with palbociclib exposure at the fixed dose of 125 mg palbociclib.

Palbociclib is proposed in combination with an aromatase inhibitor (letrozole, anastrozole or exemestane). However, the Phase 3 Study 1008 only evaluated letrozole in combination with palbociclib. For aromatase inhibitors anastrozole or exemestane, no clinical data are available to evaluate drug interactions between anastrozole or exemestane and palbociclib. A clinically significant drug interaction between anastrozole or exemestane and palbociclib is not expected based on mechanistic understandings of the potentials of palbociclib, anastrozole, and exemestane as a perpetrator or a victim.”

## **6. Clinical Microbiology**

Not Applicable

## **7. Clinical/Statistical-Efficacy**

This efficacy supplement is supported by a single, well-controlled, randomized, multicenter, multinational trial Study 1008 (A5481008, PALOMA-2) conducted in 666 postmenopausal women with HR-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. The following is excerpted from the clinical studies section (14) of the agreed upon text in the palbociclib package insert regarding the design and efficacy results of PALOMA-2:

### **Study 1: IBRANCE plus Letrozole**

#### **Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy**

Study 1 (PALOMA-2) was an international, randomized, double-blind, parallel-group, multicenter study of IBRANCE plus letrozole versus placebo plus letrozole conducted in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. A total of 666 patients were randomized 2:1 to IBRANCE plus letrozole or placebo plus letrozole. Randomization was stratified by disease site (visceral versus non-visceral), disease-free interval (de novo metastatic versus  $\leq 12$  months from the end of adjuvant treatment to disease recurrence versus  $> 12$  months from the end of adjuvant treatment to disease recurrence), and nature of prior (neo)adjuvant anticancer therapies (prior hormonal therapies versus no prior hormonal therapy). IBRANCE was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Patients received study treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. The major efficacy outcome of the study was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST).

Patients enrolled in this study had a median age of 62 years (range 28 to 89). The majority of patients were White (78%), and most patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 (98%). Forty-eight percent of patients had received chemotherapy and 56% had received antihormonal therapy in the neoadjuvant or adjuvant setting prior to their diagnosis of advanced breast cancer. Thirty-seven percent of patients had no prior systemic therapy in the neoadjuvant or adjuvant setting. The majority of patients (97%) had metastatic disease. Twenty-three percent of patients had bone only disease, and 49% of patients had visceral disease.

Major efficacy results from Study 1 are summarized in Table 8 and Figure 1. Consistent results were observed across patient subgroups of disease-free interval (DFI), disease site, and prior therapy. The treatment effect of the combination on PFS was also supported by an independent review of radiographs. The overall survival (OS) data were not mature at the time of the final PFS analysis (20% of patients had died). Patients will continue to be followed for the final analysis.

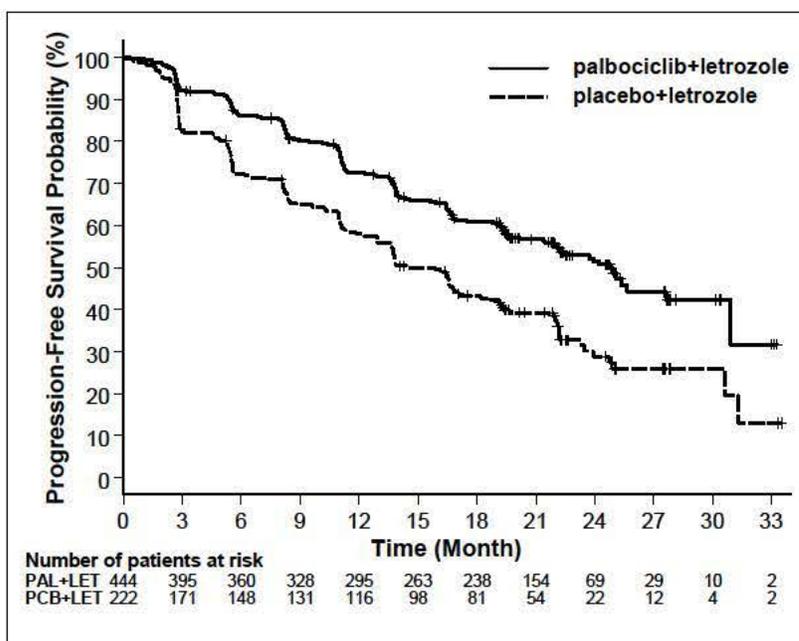
**Table 8. Efficacy Results – Study 1 (Investigator Assessment, Intent-to-Treat Population)**

	<b>IBRANCE plus Letrozole</b>	<b>Placebo plus Letrozole</b>
<b>Progression-free survival for ITT</b>	<b>N=444</b>	<b>N=222</b>
Number of PFS events (%)	194 (43.7)	137 (61.7)
Median progression-free survival (months, 95% CI)	24.8 (22.1, NE)	14.5 (12.9, 17.1)
Hazard ratio (95% CI) and p-value	0.576 (0.463, 0.718), p<0.0001	
<b>Objective Response for patients with measurable disease</b>	<b>N=338</b>	<b>N=171</b>
Objective response rate* (% , 95% CI)	55.3 (49.9, 60.7)	44.4 (36.9, 52.2)

\*Response based on confirmed responses

CI=confidence interval; ITT=Intent-to-Treat; N=number of patients; NE=not estimable.

**Figure 1. Kaplan-Meier Plot of Progression-Free Survival – Study 1 (Investigator Assessment, Intent-to-Treat Population)**



LET=letrozole; PAL=palbociclib; PCB=placebo.

## 8. Safety

The safety results from this trial are summarized below in the following excerpt from section 6.1 of the agreed-upon package insert.

### **Study 1: IBRANCE plus Letrozole**

#### **Patients with estrogen receptor (ER)-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy**

The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus placebo plus letrozole was evaluated in Study 1 (PALOMA-2). The data described below reflect exposure to IBRANCE in 444 out of 666 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE plus letrozole in Study 1. The median duration of treatment for IBRANCE plus letrozole was 19.8 months while the median duration of treatment for placebo plus letrozole arm was 13.8 months.

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving IBRANCE plus letrozole. No dose reduction was allowed for letrozole in Study 1.

Permanent discontinuation associated with an adverse reaction occurred in 43 of 444 (9.7%) patients receiving IBRANCE plus letrozole and in 13 of 222 (5.9%) patients receiving placebo plus letrozole. Adverse reactions leading to permanent discontinuation for patients receiving IBRANCE plus letrozole included neutropenia (1.1%) and alanine aminotransferase increase (0.7%).

The most common adverse reactions ( $\geq 10\%$ ) of any grade reported in patients in the IBRANCE plus letrozole arm by descending frequency were neutropenia, infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia.

The most frequently reported Grade  $\geq 3$  adverse reactions ( $\geq 5\%$ ) in patients receiving IBRANCE plus letrozole by descending frequency were neutropenia, leukopenia, infections, and anemia.

Adverse reactions ( $\geq 10\%$ ) reported in patients who received IBRANCE plus letrozole or placebo plus letrozole in Study 1 are listed in Table 4.

**Table 4. Adverse Reactions (≥10%) in Study 1**

Adverse Reaction	IBRANCE plus Letrozole (N=444)			Placebo plus Letrozole (N=222)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections <sup>a</sup>	60 <sup>b</sup>	6	1	42	3	0
Blood and lymphatic system disorders						
Neutropenia	80	56	10	6	1	1
Leukopenia	39	24	1	2	0	0
Anemia	24	5	<1	9	2	0
Thrombocytopenia	16	1	<1	1	0	0
Metabolism and nutrition disorders						
Decreased appetite	15	1	0	9	0	0
Nervous system disorders						
Dysgeusia	10	0	0	5	0	0
Gastrointestinal disorders						
Stomatitis <sup>c</sup>	30	1	0	14	0	0
Nausea	35	<1	0	26	2	0
Diarrhea	26	1	0	19	1	0
Vomiting	16	1	0	17	1	0
Skin and subcutaneous tissue disorders						
Alopecia	33 <sup>d</sup>	N/A	N/A	16 <sup>e</sup>	N/A	N/A
Rash <sup>f</sup>	18	1	0	12	1	0
Dry skin	12	0	0	6	0	0
General disorders and administration site conditions						
Fatigue	37	2	0	28	1	0
Asthenia	17	2	0	12	0	0
Pyrexia	12	0	0	9	0	0

Grading according to CTCAE 4.0.

CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable;

<sup>a</sup> Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.

<sup>b</sup> Most common infections (≥1%) include: nasopharyngitis, upper respiratory tract infection, urinary tract infection, oral herpes, sinusitis, rhinitis, bronchitis, influenza, pneumonia, gastroenteritis, conjunctivitis, herpes zoster, pharyngitis, cellulitis, cystitis, lower respiratory tract infection, tooth infection, gingivitis, skin infection, gastroenteritis viral, respiratory tract infection, respiratory tract infection viral, and folliculitis.

<sup>c</sup> Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oral discomfort, oropharyngeal pain, and stomatitis.

<sup>d</sup> Grade 1 events – 30%; Grade 2 events – 3%.

<sup>e</sup> Grade 1 events – 15%; Grade 2 events – 1%.

<sup>f</sup> Rash includes the following PTs: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of <10.0% of patients receiving IBRANCE plus letrozole in Study 1 included alanine aminotransferase increased (9.9%), aspartate aminotransferase increased (9.7%), epistaxis (9.2%), lacrimation increased (5.6%), dry eye (4.1%), vision blurred (3.6%), and febrile neutropenia (2.5%).

**Table 5. Laboratory Abnormalities in Study 1**

Laboratory Abnormality	IBRANCE plus Letrozole (N=444)			Placebo plus Letrozole (N=222)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
WBC decreased	97	35	1	25	1	0
Neutrophils decreased	95	56	12	20	1	1
Anemia	78	6	0	42	2	0
Platelets decreased	63	1	1	14	0	0
Aspartate aminotransferase increased	52	3	0	34	1	0
Alanine aminotransferase increased	43	2	<1	30	0	0

N=number of patients; WBC=white blood cells.

I concur with the review team’s recommendation to remove “Pulmonary Embolism” as a stand-alone warning and precaution in section 5 of the product label. From the clinical/statistical review: *“Thromboembolism rates are similar in both treatment arms for Study 1008. Pulmonary embolism had a higher rate in the placebo arm compared to the palbociclib treatment arm despite patients being on treatment longer in the palbociclib treatment arm. There was one treatment related SAE of pulmonary embolism (in Study 1003) in the palbociclib treatment arms of Study 1003, Study 1034, Study 1027 and Study 1023.*

*The findings above support removal of “pulmonary embolism” from the Warnings and Precautions section in the label as it is not clear that pulmonary embolism is a clear adverse reaction of palbociclib. In addition, thrombotic events (including pulmonary embolism) are complications often observed in patients with metastatic disease.”*

## 9. Advisory Committee Meeting

This efficacy supplement was not referred to a meeting of the Oncologic Drugs Advisory Committee.

## 10. Pediatrics

A pediatric waiver was granted by the PeRC.

## 11. Other Relevant Regulatory Issues

### OSI

The OSI consultants conclude: “The data from Study A5481008 were submitted to the Agency in support of sNDA 7103 S-004. Three clinical sites, Dr. Richard Finn (Site 1009), Dr. Oleg Lipatov (Site 1056), and Dr. Hope S. Rugo (Site 1078) were selected for audit.

The primary efficacy endpoint, Progression Free Survival (PFS) as determined by the clinical investigators, was verified with the source records generated at the inspected clinical sites. There were no significant inspectional findings for clinical investigators Dr. Richard Finn, Dr. Oleg Lipatov, and Dr. Hope S. Rugo. The data from all inspected sites associated with Study A5481008 appear reliable.”

There are no other unresolved relevant regulatory issues.

## **12. Labeling**

Agreement has been reached on the physician labeling. The final indication is as follows:

*IBRANCE is a kinase inhibitor indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:*

- *an aromatase inhibitor as initial endocrine based therapy in postmenopausal women;*  
*or*
- *fulvestrant in women with disease progression following endocrine therapy*

The changes to the efficacy (14) and safety (5, 6) sections of the package insert are discussed in prior sections of this review.

## **13. Postmarketing**

There was no recommendation for Postmarketing Risk Evaluation and Mitigation Strategies.

This application fulfills the postmarketing requirement (2860-1) from the accelerated approval of palbociclib in combination of letrozole.

The applicant has agreed to the following post marketing commitment:

- Submit the overall survival (OS) data and results from 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”

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/s/  
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GEOFFREY S KIM  
03/31/2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207103Orig1s004**

**OFFICER/EMPLOYEE LIST**

**Officer / Employee List**  
**Application: NDA 207103/004**

The Following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Amiri-Kordestani, Laleh  
Beaver, Julia  
Bloomquist, Erik  
Brave, Michael  
Chen, Xiao  
Chen, Wei  
Cottrell, Christy  
Dang, Qianyu  
Fedenko, Kathy  
Fu, Wentao  
Garnett, Christine  
Huang, Dalong  
Iacono-Connor, Lauren  
Ibrahim, Amna  
Johannesen, Lars  
Kim, Geoff  
Li, Michelle  
Li, Zhong  
Liu, Chao  
Liu, Qi  
Marshall, Christina  
Palmby, Todd  
Pierce, William  
Qiu, Peter  
Tang, Shenghui  
Thompson, Susan  
Tilley, Amy  
Wedam, Suparna

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207103Orig1s004**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

Cross Discipline Team Leader Review  
sNDA 207103/004 IBRANCE® (Palbociclib)

## Cross-Discipline Team Leader Review

<b>Date</b>	March 30, 2017
<b>From</b>	Laleh Amiri-Kordestani, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	207103
<b>Supplement#</b>	004
<b>Applicant</b>	Pfizer, Inc.
<b>Date of Submission</b>	October 27, 2016
<b>PDUFA Goal Date</b>	April 27, 2017
<b>Proprietary Name / Non-Proprietary Name</b>	Ibrance® / palbociclib
<b>Dosage form(s) / Strength(s)</b>	Capsules: 75 mg, 100 mg and 125 mg
<b>Applicant Proposed Indication(s)/Population(s)</b>	<p>IBRANCE is a (b) (4) kinase (b) (4) inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with:</p> <ul style="list-style-type: none"> <li>• an aromatase inhibitor as initial endocrine based therapy in postmenopausal women or</li> <li>• fulvestrant in women with disease progression following endocrine therapy.</li> </ul>
<b>Recommendation on Regulatory Action</b>	Regular Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	<p>IBRANCE is a kinase inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with:</p> <ul style="list-style-type: none"> <li>• an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or</li> <li>• fulvestrant in women with disease progression following endocrine therapy.</li> </ul>

## 1. Benefit-Risk Assessment

*Source: Clinical and Statistical Review (Drs. Suparna Wedam and Erik Bloomquist)*

APPEARS THIS WAY ON  
ORIGINAL

### Benefit-Risk Summary and Assessment

Breast cancer is the most common cancer among US women (excluding cancers of the skin), accounting for 29% of newly diagnosed cancers. In 2017, it is estimated that breast cancer will be diagnosed in 252,710 women in the United States and that approximately 40,000 women will die of their disease. Breast cancer can be categorized into different histopathologic subtypes based on expression of estrogen receptor (ER), progesterone receptor (PR) and HER2 overexpression. HR-positive/HER2-negative breast cancer is the most common subset of breast cancer. Most patients are diagnosed at an early stage and treated with endocrine therapy with or without chemotherapy. About one-third of all HR-positive/HER2-negative patients, diagnosed initially with early stage disease, experience metastatic or recurrent disease. Endocrine therapy is the preferred option at the time of disease recurrence. Not all patients respond to first-line endocrine therapy (primary or de novo resistance), and even patients who have a response will eventually relapse (acquired resistance). Further treatment options at the time of recurrence include subsequent endocrine therapy or chemotherapy. Metastatic breast cancer (MBC), where the original cancer in the breast has spread to distant organs in the body, is the most advanced stage of breast cancer and is incurable with a 5 year survival of approximately 20%. Therefore, there is an unmet medical need to improve the outcomes in patients with advanced or metastatic breast cancer.

The Applicant submitted a sNDA application for palbociclib with a proposed indication for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have not received prior therapy for their advanced disease. Palbociclib is a reversible inhibitor of cyclin-dependent kinase (CDK) 4 and CDK6 and thus acts to prevent cellular proliferation by blocking G1 to S phase transition of the cell cycle. Palbociclib was granted accelerated approval by the FDA on February 3, 2015 for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. On February 19, 2016, the U. S. Food and Drug Administration approved palbociclib in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.

The basis for this recommendation is a favorable benefit-risk profile for palbociclib when added to letrozole in women with HR-positive, HER2-negative advanced or metastatic breast cancer that have not been previously treated for their advanced/metastatic disease. In the randomized, double-blind, placebo- controlled Phase 3 study, Study 1008 (A5481008, PALOMA-2) a clinically meaningful and statistically significant 10 month improvement in estimated median progression free survival (PFS) was observed favoring the palbociclib plus letrozole treatment arm. Results of a blinded independent central review (BICR), subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results. The estimated median PFS in the palbociclib plus letrozole arm at the time of the final PFS analysis was 24.8 months compared to 14.5 months in the placebo plus letrozole arm with a Hazard Ratio (HR) of 0.58 (95%Confidence Interval (CI): 0.46, 0.72; p<0.0001).

Overall survival (OS) analysis was not mature at the time of the PFS analysis.

The final PFS results from Study 1008 fulfill the postmarketing requirement (2860-1) from the accelerated approval of palbociclib in combination of letrozole and confirm the results observed in Study 1003 (PALOMA-1) which supported the accelerated approval. Study 1003 was an international, multicenter, open-label, randomized Phase 1/2 study in a population of postmenopausal HR-positive HER2- negative advanced breast cancer patients who had not been treated previously for their advanced disease who were randomized 1:1 to receive palbociclib plus letrozole or letrozole alone. In Study 1003, a 10 month improvement in estimated median PFS was also observed with a HR of 0.488 (95% CI: 0.319, 0.748, 1 sided p=0.0004) favoring the palbociclib plus letrozole treatment arm.

This indication for palbociclib will expand the indication to allow for the use with any aromatase inhibitor. The Applicant evaluated the drug-drug interaction (DDI) potential of combining palbociclib with the aromatase inhibitors, anastrozole and exemestane, based on their known metabolic pathways. Clinically significant drug interactions are not expected based on the results of these analyses. In addition, studies evaluating the safety and efficacy of the combination of palbociclib and anastrozole or exemestane are ongoing or completed. No new safety signals have been identified to date. All three aromatase inhibitors (letrozole, anastrozole, exemestane) are used as first-line treatment of postmenopausal women with HR-positive advanced/metastatic breast cancer. Broadening the indication to use palbociclib in combination with any aromatase inhibitor provides flexibility to make therapeutic decisions based on the individual patient's prior adjuvant endocrine therapy, time to progression on prior therapy, and tolerance of the therapies' known potential side effects.

Overall, palbociclib was generally tolerable with adverse reactions manageable through the use of dose reduction, temporary treatment discontinuation, and/or standard medical care. Neutropenia was the most common adverse reaction in the palbociclib treatment arm, occurring in 80% of patients. Febrile neutropenia occurred in 2.5% of patients. Additional common adverse reactions ( $\geq 10\%$ ) with palbociclib include infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia. With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2. Permanent discontinuation associated with an adverse reaction occurred in 9.7% of patients receiving palbociclib plus letrozole. The safety profile is acceptable for this patient population with a serious and life-threatening disease.

In conclusion, based on a favorable risk-benefit profile for palbociclib in combination with letrozole, the reviewers recommend regular approval for the following indication "IBRANCE is a (b) (4) kinase (b) (4) inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>In 2017, it is estimated that breast cancer will be diagnosed in 252,710 women in the United States and that approximately 40,000 women will die of their disease. MBC, where the original cancer in the breast has spread to distant organs in the body, is the most advanced stage of breast cancer and is incurable with a 5 year survival of approximately 20%.</li> </ul>	<ul style="list-style-type: none"> <li>Breast cancer is a serious and life-threatening condition.</li> <li>HR positive-tumors represent the most common form of breast cancer and account for most of the deaths from the disease.</li> <li>There is an unmet medical need to improve the outcomes in patients with HR-positive, HER2-negative advanced or metastatic breast cancer.</li> </ul>
<a href="#">Current Treatment Options</a>	<ul style="list-style-type: none"> <li>The treatment of MBC is palliative in nature with a goal to prolong survival and improve quality of life by reducing cancer-related symptoms. First-line endocrine based treatment options for postmenopausal women with HR-positive, human epidermal growth factor receptor 2 (HER2)-negative MBC include ribociclib + aromatase inhibitor, palbociclib + letrozole (accelerated approval), aromatase inhibitors (anastrozole, letrozole and exemestane) or tamoxifen. Endocrine therapy options for premenopausal women with HR-positive MBC that do not respond to first line therapy are similar to those for postmenopausal women; however, aromatase inhibitors or fulvestrant need to be administered in combination with ovarian suppression therapy. Pre- and post-menopausal women may also receive chemotherapy as second or later lines of treatment, once they have had tumor progression on endocrine therapy. Patients whose tumors overexpress HER2 have separate prognoses and distinct treatment options.</li> </ul>	<ul style="list-style-type: none"> <li>Endocrine therapy (ET) represents the main initial therapeutic strategy for patients HR-positive, HER2-negative MBC.</li> <li>Although currently available ET agents are generally effective and very well tolerated, not all patients benefit equally and many develop resistance.</li> <li>Other approved therapies include ribociclib + aromatase inhibitor, palbociclib + letrozole (accelerated approval).</li> </ul>
<a href="#">Benefit</a>	<ul style="list-style-type: none"> <li>The clinical data from a randomized, double-blind, placebo- controlled Phase 3 Trial (Study 1008, A5481008, PALOMA-2) in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease was not previously treated presented in this sNDA demonstrates an improvement in PFS for palbociclib plus letrozole compared to placebo</li> </ul>	<ul style="list-style-type: none"> <li>The PFS benefit derived from palbociclib is statistically significant and clinically meaningful.</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>plus letrozole. The estimated median PFS in the palbociclib plus fulvestrant arm was 24.8 months compared to 14.5 months in the placebo plus fulvestrant arm (HR =0.58; 95% CI: 0.46, 0.72; p&lt;0.0001). OS results were immature at the time of analysis with only 20% of deaths having occurred. Objective response rate (ORR) was 55.3% in the palbociclib plus letrozole arm compared with 44.4% in the placebo plus letrozole arm for patients with measurable disease at baseline.</p>	
<p><a href="#">Risk</a></p>	<ul style="list-style-type: none"> <li>• Neutropenia was the most common adverse reaction in the palbociclib treatment arm, occurring in 80% of patients. Febrile neutropenia occurred in 2.5% of patients.</li> <li>• Additional common adverse reactions (&gt;10%) with palbociclib include infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia. With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2. Permanent discontinuation associated with an adverse reaction occurred in 9.7% of patients receiving palbociclib plus letrozole.</li> <li>• Neutropenia is the only adverse reactions being described in the warnings and precautions section of labeling.</li> </ul>	<ul style="list-style-type: none"> <li>• The safety profile of palbociclib plus letrozole for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer is generally tolerable, with adverse reactions manageable through the use of palbociclib dose reduction, temporary treatment discontinuation, and/or standard medical care.</li> </ul>
<p><a href="#">Risk Management</a></p>	<ul style="list-style-type: none"> <li>• Palbociclib is intended to be prescribed by oncologists.</li> <li>• Oncologists are well versed in the identification and management of the toxicities associated with palbociclib.</li> <li>• Labeling details dose interruption, reduction, or discontinuation</li> <li>• Laboratory monitoring is recommended before and during treatment.</li> </ul>	<ul style="list-style-type: none"> <li>• The safe use of palbociclib can be managed through accurate labeling and routine oncology care.</li> <li>• No REMS is indicated.</li> </ul>

## 2. Background

Breast cancer is the leading cause of cancer death and the second leading cause of death in women in United States. Hormone receptor (HR)-positive/ human epidermal growth factor receptor (HER2)-negative breast cancer is the most common subtype of breast cancer. About one-third of all HR-positive/HER2-negative patients, diagnosed initially with early stage disease, experience metastatic or recurrent disease. Although survival rates among patients with stage IV breast cancer have improved in recent years, the 5-year survival rate remains around 20%. While endocrine therapy is considered the preferred treatment for first-line therapy in HR-positive/HER2-negative breast cancer, drug resistance frequently develops. Premenopausal women with HR-positive MBC generally are treated similar to postmenopausal women; however, aromatase inhibitors or fulvestrant need to be administered in combination with ovarian suppression therapy.

Guidelines for first-line treatment in HR-positive/HER2-negative disease depend on patient and tumor characteristics. The aromatase inhibitors with or without ribociclib and tamoxifen are FDA approved therapies for this setting. Chemotherapy is generally recommended when there is no clinical benefit after two or three consecutive endocrine therapies, or in patients who have symptomatic visceral disease. A number of single-agent chemotherapy regimens have shown efficacy in the treatment of advanced breast cancer, including anthracyclines (doxorubicin, epirubicin, and pegylated liposomal doxorubicin), taxanes (paclitaxel, docetaxel, and albumin-bound paclitaxel), antimetabolites (capecitabine and gemcitabine), and microtubule inhibitors (vinorelbine and eribulin). While there are multiple treatment options available for patients with HR-positive, HER2-negative advanced or metastatic breast cancer, there is still a need for effective yet tolerable new therapy.

Palbociclib is an oral reversible inhibitor of CDK 4 and CDK6 and thus acts to prevent cellular proliferation by preventing G1 to S phase progression of the cell cycle. Palbociclib was granted accelerated approval in combination with letrozole in February 2015. This accelerated approval had a postmarketing requirement (PMR) in which the PFS and OS data from the ongoing PALOMA-2, 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] had to be submitted within a timeline agreed upon with the Agency.

On February 19, 2016, the FDA approved palbociclib in combination with fulvestrant for the treatment of women with hormone receptor–positive, HER2–negative advanced or metastatic breast cancer with disease progression following endocrine therapy based on PALOMA-3 study results.

On October 27, 2016, Applicant submitted Supplement 004 to NDA 207103 for palbociclib (Ibrance®) to the Division of Oncology Products, 1. The recommended dose and schedule is 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment with food and in combination with endocrine therapy. The application was complete upon submission and was filed as a priority review because the topline results indicated that palbociclib plus letrozole combination therapy provided an advantage over available therapy. Pfizer proposes a new indication, “IBRANCE® (palbociclib), is indicated in combination with [REDACTED] (b)(4) with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.”

### **Background of Clinical Program:**

The following summarizes the key milestones in the regulatory history:

- March 10, 2004: IND 69324 for PD-0332991 (palbociclib) was submitted in the United States for the treatment of advanced cancers.
- November 27, 2012: The protocol for Study 1008 was submitted to the IND (SDN 171, eCTD 160). There was no special protocol assessment requested for Study 1008.
- April 9, 2013: FDA granted Breakthrough Designation to palbociclib for the treatment of patients with breast cancer.
- February 3, 2015: Palbociclib was granted accelerated approval in combination with letrozole. This accelerated approval had a postmarketing requirement (PMR) in which the PFS and OS data from the ongoing PALOMA-2, 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] had to be submitted within a timeline agreed upon with the Agency.
- June 16, 2015: A Type B Pre-sNDA Meeting was held to primarily discuss the top line summary of the interim analysis for Study 1023. In addition, the format and content of the NDA submission was discussed.

- February 19, 2016: Palbociclib was approved in combination with fulvestrant for the treatment of women with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
- July 11, 2016: Preliminary comments received for a Type B pre-sNDA meeting, scheduled for July 20, 2016, to discuss the top line summary of the final analysis for Study 1008. FDA agreed with the Sponsor’s format and content plans to submit a sNDA seeking full approval based on Study 1008, and the meeting was subsequently canceled.
- October 27, 2016: sNDA 207103/004 was submitted to FDA.

### 3. Product Quality

*Source: CMC Review (Dr. Xiao Hong Chen)*

**CMC Team Recommendation:** Approval

There were no CMC modules submitted in this sNDA. Pfizer Inc. claimed a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR Part 25.31 (a) applicable for action on a supplemental NDA when the action does not increase the use of the active moiety. Per Dr. Xiao Hong Chen (CMC reviewer) this claim is acceptable.

### 4. Nonclinical Pharmacology/Toxicology

*Source: Pharmacology and Toxicology Review (Drs. Wei Chen and Todd Palmby)*

**Pharmacology Toxicology Team Recommendation:** Approval

The original NDA submission for palbociclib included a 27-week rat study that showed that administration of palbociclib to rats resulted in increased serum glucose levels, glucosuria and other adverse effects possibly associated with increased glucose, including pancreatic islet cell vacuolation, eye lens degeneration, degeneration of tooth ameloblasts, and renal tubuloepithelial cell vacuolation. To further investigate the altered glucose metabolism in rats, Applicant conducted a GLP 27-week repeat-dose toxicology study in aged male rats (12 months

old at initiation of dosing). The observed adverse effects in young rats associated with increase of glucose were not observed in aged rats. Odontopathy in the incisor teeth was observed in both young rats and aged rat, suggesting independent of the endocrine/metabolic changes. Toxicokinetic (TK) studies showed that the systemic exposures were similar in young and aged rats. The absence of dysregulated glucose and pancreatic or renal effects in aged rats suggest that young rats maybe susceptible to the development of dysregulated glucose in response to palbociclib administration, potentially related to differences in beta cell proliferation capacity or beta cell biology.

*I agree with the nonclinical reviewer's conclusion that the absence of effects on glucose metabolism, the pancreas, eyes, and kidney in aged rats at the systemic exposures at which effects were observed in young rats, together with the absence of similar clinical signals in patients suggested that these risks may not be relevant to adult patients. However, these potential risks still remain for a younger patient population. Therefore, the results from the repeat-dose toxicity study in young rats were moved to section 8.4 Pediatric Use, consistent with FDA guidance documents recommending of pediatric information into labeling of human pharmaceuticals. In addition, Section (b) (4) of PI was updated.*

## 5. Clinical Pharmacology

Source: Clinical Pharmacology Review (Drs. Wentao Fu, Jingyu Yu, Qi Liu)

**Clinical Pharmacology Team Recommendation:** Approval

### **Exposure-response Analysis:**

In an exposure-response (E-R) analysis using Study 1008 results, investigator-assessed PFS prolongation was not significantly associated with palbociclib exposure at the fixed dose of 125 mg palbociclib.

*I agree with the Clinical pharmacology reviewer that the flat E-R relationship for PFS and positive E-R relationship for lower neutrophil counts in other studies (see Pharmacometrics Review section in clinical pharmacology review in DARRTs dated 02/05/2016 and 01/25/2015 for detail) supports the palbociclib's proposed dose regimen.*

### **Drug-drug interactions:**

In Study 1008 only letrozole in combination with palbociclib was studied. An information request was sent on December 16, 2016 and response received on December 23, 2016 (SDN

473). At this time, for aromatase inhibitors anastrozole or exemestane, no clinical data are available to evaluate drug interactions between anastrozole or exemestane and palbociclib.

Palbociclib (recommended dose 125 mg once daily (QD)):

- As a perpetrator: A weak CYP3A time dependent inhibitor (TDI). Palbociclib 125 mg QD increased midazolam (a sensitive CYP3A substrate) AUC by 61% and Cmax by 37%.
- As a victim: Mainly metabolized by CYP3A and SULT2A1

Anastrozole (recommended dose 1 mg QD): Anastrozole has a wide therapeutic window. Recommended dose is 1 mg QD for postmenopausal women with advanced breast cancer. Up to 10 mg QD dose of anastrozole given to postmenopausal women with advanced breast cancer were well tolerated

- As a perpetrator: Anastrozole (1mg QD) is unlikely affect other drugs by inhibition of cytochrome P450. *In vitro* anastrozole inhibits CYP1A2, 2C8, 2C9, and 3A4 with Ki values ~30 fold higher than the steady-state Cmax values observed at 1mg QD.
- As a victim: It is not a sensitive CYP3A substrate and is cleared by CYP3A and other pathways.

Exemestane (recommended dose 25 mg QD)

- As a perpetrator: *In vitro* does not inhibit any of the major isoenzymes, including CYP1A2, 2C9, 2D6, 2E1, and 3A4.
- As a victim: It is primarily metabolized by CYP3A4 and aldoketoreductases. However, in vivo concomitant use of ketoconazole, a strong inhibitor of CYP3A4, had no significant effect on exemestane pharmacokinetics

*I agree with the Clinical pharmacology reviewer conclusion that based on mechanistic understandings of the potentials of palbociclib, anastrozole, and exemestane as a perpetrator or a victim (noted above), a clinically significant drug interaction between anastrozole or exemestane and palbociclib is not expected.*

### **ECG subgroup analysis for QTc prolongation:**

In an ECG subgroup analysis (N=77), no large QTc prolongation effect of palbociclib + letrozole was detected. The largest upper bound of the 2-sided 90% CI for the mean difference between palbociclib + letrozole and placebo + letrozole was 5.1 ms, which is below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. Palbociclib had no large effect on QTc (i.e. > 20 ms) at 125 mg once daily.

## 6. Efficacy

*Source: Statistical and Clinical Reviews (Drs. Suparna Wedam, and Erik Bloomquist)*

### **Statistical and Clinical Team Recommendation:** Approval

*I agree with the overall conclusions of primary FDA Clinical Reviewer for efficacy, Suparna Wedam, and of the primary FDA statistical Reviewer, Dr Erik Bloomquist, pertaining to the efficacy data submitted in the sNDA to support an indication for palbociclib in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women.*

### **Efficacy Summary**

Study 1008 or PALOMA-2 Design:

This sNDA contains data from Study 1008, entitled “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”.

Patients were treated with either palbociclib 125 mg/day or placebo orally for 3 of 4 weeks. Patients also received letrozole 2.5mg orally continuously. Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first.

The primary objective was to demonstrate an improvement in investigator-assessed progression free survival with palbociclib plus letrozole over placebo plus letrozole. Key secondary objectives include overall survival, objective response rates, duration of response, and clinical benefit response (CR or PR or SD  $\geq$  24 weeks).

### Statistical Assumptions:

The study was originally designed to enroll 450 patients with a primary endpoint of progression free survival determined through primary investigator assessment. The trial was to have a final

PFS analysis at 267 events. The study had approximately 90% power to detect a hazard ratio of 0.64 which equates to an approximate 5 month difference in PFS (9 vs 14 months).

The applicant submitted 7 protocol amendments. Per statistical review, the protocol amendments did not affect the conclusions reached from the study.

In protocol amendment 2 (January 2014), the study changed the drug administration from fasting to with food. Because of this change, the sponsor decided to increase the sample size to 650 patients with a final PFS analysis to occur at 347 events. When determining the new sample size, the sponsor revised their intended hazard ratio target from 0.64 to 0.69.

The study originally included an interim analysis of PFS with an O'Brien-Fleming stopping boundary. In protocol amendment 3 (December 2014), however, the sponsor changed their stopping rule to a Haybittle-Peto boundary where the minimum hazard ratio to declare efficacy at the interim boundary was approximately 0.56. The interim analysis was planned to occur when 226 PFS events had been observed (approximately 65% of the total PFS events). The efficacy boundary was suggested by the agency in order to provide consistent advice across the CDK 4/6 drug class.

For the primary PFS endpoint patients were considered as censored under the following scenarios. One, if new anti-cancer therapy was started prior to progression, patients were censored at last available follow-up. Two, if patients withdrew consent or were lost to follow-up, patients were censored at last available follow-up. Finally, in patients with documented progression after 2 more missed visits, patients were censored at the last available visit that documented no progression.

The sponsor included overall survival as a key secondary endpoint. An interim analysis of OS was to be conducted at the primary PFS analysis. Based upon a request by the agency, the sponsor also added a second interim analysis of OS with a cutoff date of November 24, 2016. The sponsor modified their SAP so that a nominal level of alpha was spent at the second interim analysis (0.0001). The final OS analysis is to occur when 347 deaths have happened.

#### Study 1008 Efficacy Results:

The primary analysis of PFS occurred when 331 progression events occurred in both arms. The results are displayed in Table 1 below. Figure 1 shows a Kaplan-Meier plot of PFS.

The results displayed in Table 1 correspond to the final PFS analysis. In addition to the PFS analysis conducted by the investigator, the sponsor subjected the PFS data to an independent review committee (BICR). The results of this analysis are shown in Table 2. A Kaplan-Meier plot of the BIRC results is shown in Figure 2.

**Table 1: Primary Endpoint Results (PFS by investigator) for Study 1008**

	<b>Palbociclib plus Letrozole N=444</b>	<b>Placebo plus Letrozole N=222</b>
Events, n (%)	194 (43.7)	137 (61.7)
Censored, n (%)	250 (46.3)	85 (38.3)
Median, months (95% CI)	24.8 (22.1, NE)	14.5 (12.9, 17.1)
Hazard ratio, estimate (95% CI)	0.576 (0.463, 0.718)	
p-value	<0.0001	

Source: Study 1008 CSR Table 20

1. NE = not estimable
2. The data cutoff for this analysis was February 26, 2016.

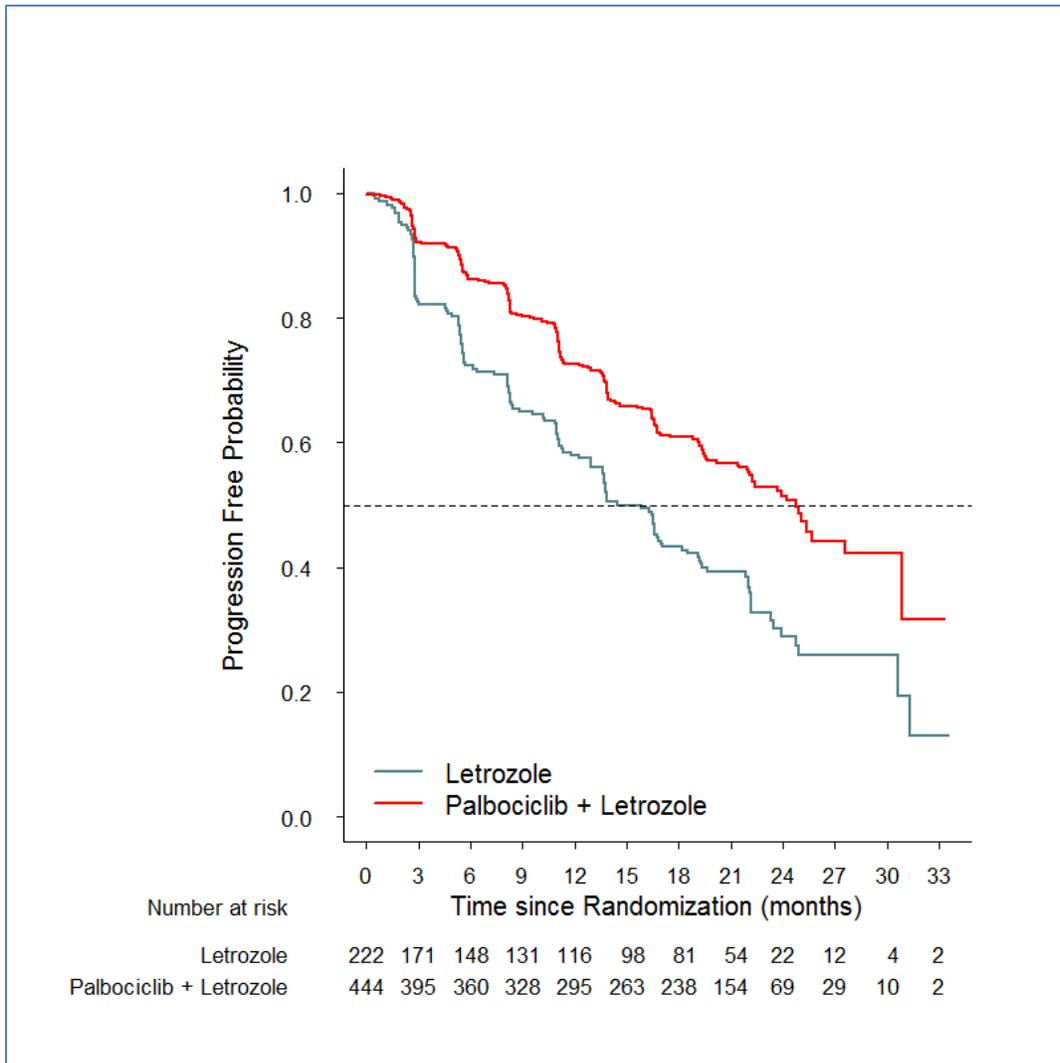
**Table 2: Supportive PFS Results (PFS by BICR) for Study 1008**

	<b>Palbociclib plus Letrozole N=444</b>	<b>Placebo plus Letrozole N=222</b>
Events, n (%)	152 (34.2)	96 (43.2)
Censored, n (%)	292 (65.8)	126 (56.8)
Median, months (95% CI)	30.5 (27.4, NE)	19.3 (16.4, 30.6)
Hazard ratio, estimate (95% CI)	0.653 (0.505, 0.844)	
p-value	0.0005	

Source: CSR Table 23

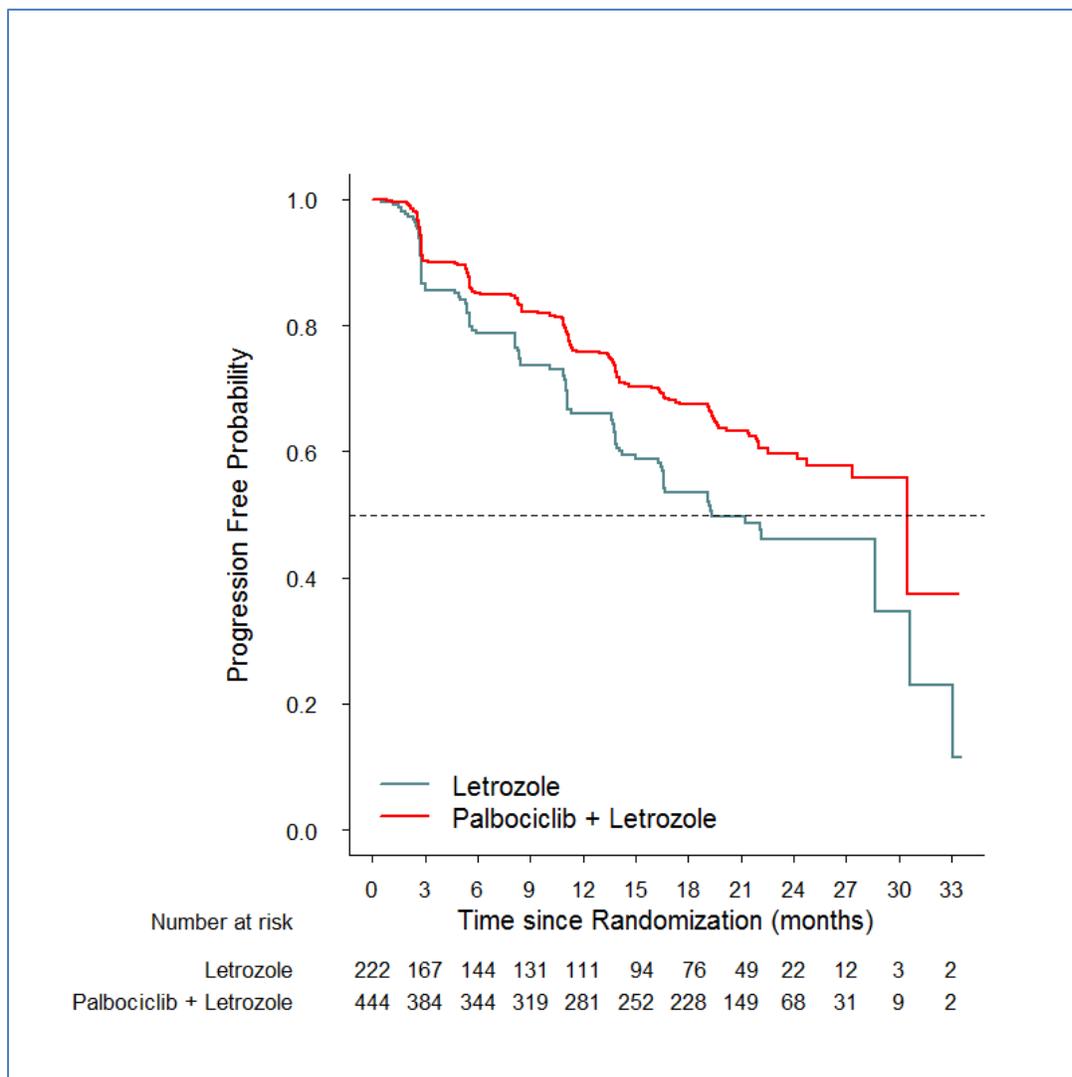
1. NE = not estimable

**Figure 1: Kaplan-Meier Plot of Primary Analysis Results (PFS by investigator)**



Source: Reviewer's Analysis (dataset: eedrsp.xpt)

**Figure 2: Kaplan-Meier Plot of Supportive PFS Results (PFS by BICR)**



Source: Reviewer's Analysis (dataset: eeiotb.xpt)

**Conclusions on the Substantial Evidence of Effectiveness:**

The efficacy results of clinical trial 1008 provide substantial evidence of effectiveness. Study 1008 demonstrated a statistically significant and clinically meaningful improvement in the primary efficacy endpoint of PFS. The BICR results showed good concordance with the primary PFS results.

In addition, following information are to support the expansion of indication of palbociclib with aromatase inhibitors ( Information Request dated 12/23/2016) :

#### Palbociclib in combination with anastrozole:

A single-arm Phase 2 neoadjuvant study of palbociclib in combination with anastrozole has completed. Fifty patients were treated in this study with 45 patients evaluable for the primary endpoint. The most common all-causality AEs with the combination of palbociclib plus anastrozole was neutropenia (all grades: 56%; Grades 3 or 4: 26%), leukopenia (all grades; 46%; Grades 3 or 4: 0%), and fatigue (all grades: 40%; Grades 3 or 4: 0%). There were no reports of febrile neutropenia. Seven patients (14%) required 1 palbociclib dose reduction associated with AEs.

A second study evaluating the palbociclib plus anastrozole combination is the ongoing double-blind Phase 3 CRC study PENELOPE-B (GBG 078/NSABP B 54 1/BIG 1 13, NCT01864746), a study in patients with HR-positive, HER2 negative primary breast cancer with high relapse risk after neoadjuvant chemotherapy (N=366 as of February 2016). On January 25, 2016, the Applicant received confirmation that the external data monitoring committee (E-DMC) had evaluated the ongoing study and recommended it proceed as planned. A review of the Sponsor's safety database for this study has not identified any new safety signals.

#### Palbociclib in combination with exemestane:

PEARL (Spanish Breast Cancer Research Group, NCT02028507), is an ongoing study evaluating the safety and efficacy of the combination of exemestane and palbociclib (N=229 as of February 2016). In December 2016, the Sponsor received confirmation that the E-DMC has recommended the study proceed as planned. A review of the Sponsor's safety database for this study has not identified any new safety signals. All other safety and efficacy data are not anticipated to be available during the 1008 sNDA submission review cycle.

*I agree with the clinical reviewer's conclusion that replacing "letrozole" with "aromatase inhibitor" and broadening the indication appears acceptable based on the minimal potential for clinically significant DDI between aromatase inhibitors and palbociclib and results from the ongoing clinical studies (as outlined above). All three aromatase inhibitors (letrozole, anastrozole, exemestane) are used as first-line treatment of postmenopausal women with HR-positive advanced/metastatic breast cancer. Broadening the indication to use palbociclib in combination with any aromatase inhibitor provides flexibility to both patients and physicians to make therapeutic decisions based on the individual patient's prior adjuvant endocrine therapy, time to progression on prior therapy, and tolerance of the therapies' known potential side effects.*

## **8. Safety**

Source: Clinical Review (Dr. Suparna Wedam)

**Clinical Team Recommendation:** Approval

*I concur with the clinical reviewer's (Dr. Suparna Wedam's) conclusions regarding the relative safety of palbociclib. The safety profile observed in Study 1008 was generally well-tolerated and consistent with the known safety profiles of palbociclib and letrozole.*

Neutropenia was the most common adverse reaction in the palbociclib treatment arm, occurring in 80% of patients. Febrile neutropenia occurred in 2.5% of patients. Additional common adverse reactions ( $\geq 10\%$ ) with palbociclib include infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia. With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2. Permanent discontinuation associated with an adverse reaction occurred in 9.7% of patients receiving palbociclib plus letrozole. The safety profile is acceptable for this patient population with a serious and life-threatening disease.

With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2, and rates of treatment discontinuation due to adverse reactions were generally low. Please see Table 3 for details on Deaths on study and Table 4 for serious adverse events.

**Table 3: Deaths on Study 1008 (2/26/2016 Data Cut-off)**

	<b>Palbociclib+ Letrozole N=444 n (%)</b>	<b>Placebo + Letrozole N=222 n (%)</b>
<b>Patients who Died</b>	95	38
Disease Progression	81	34
Other	14	4
<b>Within 28 Days of Last Dose</b>		
Disease Progression	3	2
Study Drug Toxicity	1	1
Other	7	2
<b>After 28 days of Last Dose</b>		
Disease Progression	78	32
Other	7	2

**Table 4: SAEs Occurring in ≥2 Patients by Descending Frequency in the Palbociclib plus Letrozole Arm of Study 1008 as of 8/31/2016**

	<b>Palbociclib plus Letrozole N=444 (%)</b>	<b>Placebo plus Letrozole N=222 (%)</b>
Any <sup>1</sup>	95 (21.4)	31 (14)
Infections	22 (5)	9 (4.1)
Febrile neutropenia	6 (1.4)	0
Acute kidney injury	4 (0.9)	0
Pleural Effusion	4 (0.9)	1 (0.5)
Pulmonary embolism	4 (0.9)	3 (1.4)
Pyrexia	4 (0.9)	0
Disease progression	3 (0.7)	0
Malignant melanoma <sup>2</sup>	3 (0.7)	0
ALT increased	2 (0.5)	0
Anemia	2 (0.5)	0
AST increased	2 (0.5)	0
Atrial fibrillation	2 (0.5)	0
Constipation	2 (0.5)	0
Deep vein thrombosis	2 (0.5)	1 (0.5)
Neutropenia	2 (0.5)	0
Pain	2 (0.5)	1 (0.5)
Acute pancreatitis	2 (0.5)	0
Pathological fracture	2 (0.5)	0
Pericardial effusion	2 (0.5)	0
Rash	2 (0.5)	0
Syncope	2 (0.5)	0
Vomiting	2 (0.5)	2 (0.9)

Source: 90-Day Safety Update, Table 26, pages 76

<sup>1</sup>Any SAE without consideration for the minimum 2 patient cutoff used in this table

<sup>2</sup>New primary cancer

## 9. Patient Reported Outcome Results:

PROs were listed as secondary endpoints in Study 1008 but there was no alpha allocation for PRO analyses. PRO endpoints included: FACT-G total score, FACT-G subscales, BC subscale (BCS), FACT-B total score, trial outcome index (TOI), EQ-5D index score, EQ-VAS general health status score.

The FACT-B includes 5 subscale scores: physical well-being (PWB), social/family wellbeing (SWB), emotional well-being (EWB), functional well-being (FWB), and a breast cancer subscale (BCS). The EQ-5D index was derived by combining 1 level from each of the 5 dimensions and converting it to a single summary index or health utility value.

In nearly all cycles (except for one), 95-100% of patients answered at least one question on both the FACT-B and EQ-5D instruments. There was no difference in any of the PRO endpoints between treatment arms.

*I concur with the clinical/stat review that since there was no alpha allocation for PRO analyses in the statistical analysis plan, any PRO results should be considered exploratory.*

## 10. Advisory Committee Meeting

An advisory committee meeting was not held for this sNDA because the application provided a clearly favorable benefit:risk, and the endpoints used have been previously used in this setting.

## 11. Pediatrics

A Pediatric Study Plan was submitted under IND 69,324 Serial Number 0327 on 25 April 2014 to request a waiver for ER-positive, HER2-negative advanced breast cancer. Pfizer requested a disease-specific waiver for pediatric patients based on the intended indication of breast cancer because breast cancer rarely occurs in the pediatric population. Thus, studies in children would be impossible or highly impractical to conduct because the patient population is too small. The full waiver was granted.

## 12. Other Relevant Regulatory Issues

This section may include discussion on other issues (if not addressed in previous sections):

- Application Integrity Policy (AIP): No issues
- Financial disclosures: No issues

- Other Good Clinical Practice (GCP) issues : No issues
- Office of Scientific Investigations (OSI) audits

The review division chose three clinical sites for inspection based on the size of the enrolled study population.

According to the OSI review (Lauren Iacono-Connors, Reviewer) , the primary efficacy endpoint of PFS as determined by the clinical investigators was verified with the source records generated at the inspected clinical sites. There were no significant inspectional findings from any of three inspected sites and the data from all inspected sites associated with Study 1008 appear reliable.

### 13. Labeling

#### Prescribing Information

The following are the key clinical labeling recommendations:

- INDICATIONS AND USAGE (section 1):

*IBRANCE is a (b) (4) kinase (b) (4) inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with:*

- *an aromatase inhibitor as initial endocrine based therapy in postmenopausal women or*
- *fulvestrant in women with disease progression following endocrine therapy.*

Removed the Accelerated approval phrase” The indication in combination with letrozole is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.”

In addition the indication for palbociclib was broadened from in combination with “letrozole” to “aromatase therapy”.

- WARNINGS AND PRECAUTIONS (Section 5):

Recommended deletion of “pulmonary embolism” from the WARNINGS AND PRECAUTIONS section, as the incidence was low.

- ADVERSE REACTIONS (Section 6):

Updated Study 1 to refer to results from PALOMA-2 (Study 1008) and remove PALOMA-1 (Study 1003) results.

- CLINICAL PHARMACOLOGY (Section 12):

Updated “Cardiac Electrophysiology” section based on the new ECG subgroup analysis for QTc prolongation.

Section 12.1 (Mechanism of Action) was updated based on the *in vitro* pharmacology study results (NDA 207103/S-02, 2/8/2016) based on nonclinical reviewer’s recommendation.

- NONCLINICAL TOXICOLOGY (Section 13):

Based on the nonclinical data submitted to this sNDA, the following labeling changes were implemented:

Section (b) (4) was updated based on the re-evaluation of altered glucose metabolism in a 27-week study using aged rats. Since there is a potential risk for a younger patient population. The results from the repeat-dose toxicity study in young rats were moved to section 8.4 Pediatric Use.

- CLINICAL STUDIES (section 14):

Updated Study 1 to refer to results from PALOMA-2 (Study 1008) and remove PALOMA-1 (Study 1003) results. (b) (4)

## 14. Postmarketing Recommendations

### Risk Evaluation and Management Strategies (REMS)

I agree with the recommendations of the sNDA review team that a REMS is not required to ensure safe use of palbociclib. Risk mitigation will occur through product labeling.

### Postmarketing Requirements (PMRs) and Commitments (PMCs)

No PMRs were requested.

The original postmarketing requirement (2860-1) from the accelerated approval of palbociclib in combination of letrozole has been fulfilled with the final PFS analysis submitted in this supplement. However, the OS data was not available and is expected 11/2020. This is important information to include in Section 14 of the package insert.

I agree with the primary reviewers' recommendation for the following new PMC:

*Submit the final overall survival analysis with datasets from Trial A5481023, PALOMA-3 “A double-blind, phase III trial of fulvestrant with or without palbociclib in pre- and post-menopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer that progressed on prior endocrine therapy.”*

## 15. Recommended Comments to the Applicant

None

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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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LALEH AMIRI KORDESTANI  
03/30/2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207103Orig1s004**

**MEDICAL REVIEW(S)**

**CLINICAL REVIEW**

<b>Application Type</b>	sNDA 505 (b) (1)
<b>Application Number(s)</b>	207103/S-004
<b>Priority or Standard</b>	Priority
<b>Submit Date(s)</b>	October 27, 2016
<b>Received Date(s)</b>	October 27, 2016
<b>PDUFA Goal Date</b>	April 27, 2017
<b>Division/Office</b>	DOP1/OHOP
<b>Reviewer Name(s)</b>	Suparna Wedam (Clinical) Laleh Amiri-Kordestani (Clinical Team Leader) Erik Bloomquist (Statistical) Shenghui Tang (Statistical Team Leader)
<b>Review Completion Date</b>	March 30, 2017
<b>Established Name</b>	Palbociclib
<b>(Proposed) Trade Name</b>	Ibrance®
<b>Applicant</b>	Pfizer Inc.
<b>Formulation(s)</b>	125 mg, 100 mg, and 75 mg
<b>Dosing Regimen</b>	Capsules taken orally with food in combination with an aromatase inhibitor or fulvestrant
<b>Applicant Proposed Indication(s)/Population(s)</b>	IBRANCE is a (b) (4) kinase (b) (4) inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with: <ul style="list-style-type: none"> <li>• an aromatase inhibitor as initial endocrine based therapy in postmenopausal women or</li> <li>• fulvestrant in women with disease progression following endocrine therapy.</li> </ul>
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	IBRANCE is a kinase inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with: <ul style="list-style-type: none"> <li>• an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or</li> <li>• fulvestrant in women with disease progression following endocrine therapy.</li> </ul>

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Statistical – Erik Bloomquist / Shenghui Tang

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## Glossary

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AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

Clinical and Statistical Review NDA 207103/S-004 Ibrance (palbociclib)

Clinical – Suparna Wedam / Laleh Amiri-Kordestani

Statistical – Erik Bloomquist / Shenghui Tang

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

## 1 Executive Summary

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### 1.1. Product Introduction

This is a supplemental New Drug Application (sNDA) for IBRANCE in patients with advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2) negative breast cancer.

The Applicant proposed the following indication for the IBRANCE label:

*“IBRANCE is a (b) (4) kinase (b) (4) inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with:*

- *an aromatase inhibitor as initial endocrine based therapy in postmenopausal women or*
- *fulvestrant in women with disease progression following endocrine therapy.”*

The recommended indication is:

*“IBRANCE is a kinase inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with:*

- *an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or*
- *fulvestrant in women with disease progression following endocrine therapy.”*

In February 2015, FDA granted accelerated approval for palbociclib in combination with letrozole for the treatment of HR-positive, HER2-negative advanced breast cancer as initial endocrine based therapy in postmenopausal women. Regular approval was granted in February, 2016, for palbociclib in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. This indication would provide regular approval for palbociclib as initial endocrine based therapy and would expand the indication from allowing palbociclib in combination with only letrozole to allowing it in combination with any aromatase inhibitor.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical review team recommends regular approval of IBRANCE (palbociclib) for the following indication:

*“IBRANCE is a (b) (4) kinase (b) (4) inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative*

*advanced or metastatic breast cancer in combination with:*

- *an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or*
- *fulvestrant in women with disease progression following endocrine therapy.”*

The basis for this recommendation is a favorable benefit-risk profile for palbociclib when added to letrozole in women with HR-positive, HER2-negative advanced or metastatic breast cancer that have not been previously treated for their advanced/metastatic disease. In the randomized, double-blind, placebo- controlled Phase 3 study, Study 1008 (A5481008, PALOMA-2) a clinically meaningful and statistically significant 10 month improvement in estimated median progression free survival (PFS) was observed favoring the palbociclib plus letrozole treatment arm. Results of a blinded independent central review (BICR), subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results. The median PFS in the palbociclib plus letrozole arm at the time of the final PFS analysis was 24.8 months compared to 14.5 months in the placebo plus letrozole arm with a Hazard Ratio (HR) of 0.58 (95% Confidence Interval (CI): 0.46, 0.72;  $p < 0.0001$ ). Overall survival (OS) analysis was not mature at the time of the PFS analysis.

The final PFS results from Study 1008 fulfill the postmarketing requirement (2860-1) from the accelerated approval of palbociclib in combination of letrozole and confirm the results observed in Study 1003 (PALOMA-1) which supported the accelerated approval in 2015. Study 1003 was an international, multicenter, open-label, randomized Phase 1/2 study in a population of postmenopausal HR-positive HER2- negative advanced breast cancer patients who had not been treated previously for their advanced disease who were randomized 1:1 to receive palbociclib plus letrozole or letrozole alone. In Study 1003, a 10 month improvement in estimated median PFS was also observed with a HR of 0.488 (95% CI: 0.319, 0.748, 1 sided  $p = 0.0004$ ) favoring the palbociclib plus letrozole treatment arm.

This indication for palbociclib will expand the indication to allow for the use with any aromatase inhibitor. The Applicant evaluated the drug-drug interaction (DDI) potential of combining palbociclib with the aromatase inhibitors, anastrozole and exemestane, based on their known metabolic pathways. Clinically significant drug interactions are not expected based on the results of these analyses. In addition, studies evaluating the safety and efficacy of the combination of palbociclib and anastrozole or exemestane are ongoing or completed. No new safety signals have been identified to date. All three aromatase inhibitors (letrozole, anastrozole, exemestane) are used as first-line treatment of postmenopausal women with HR-positive advanced/metastatic breast cancer. Broadening the indication to use palbociclib in combination with any aromatase inhibitor provides flexibility to both the patients and physicians to make therapeutic decisions based on the individual patient’s prior adjuvant endocrine therapy, time to progression on prior therapy, and tolerance of the therapies’ known potential side effects.

Palbociclib was generally tolerable with adverse reactions manageable through the use of dose

reduction, temporary treatment discontinuation, and/or standard medical care. Neutropenia was the most common adverse reaction in the palbociclib treatment arm, occurring in 80% of patients. Febrile neutropenia occurred in 2.5% of patients. Additional common adverse reactions ( $\geq 10\%$ ) with palbociclib include infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia. With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2. Permanent discontinuation associated with an adverse reaction occurred in 9.7% of patients receiving palbociclib plus letrozole. The safety profile is acceptable for this patient population with a serious and life-threatening disease.

### 1.3. **Benefit-Risk Assessment**

### Benefit-Risk Summary and Assessment

Breast cancer is the most common cancer among US women (excluding cancers of the skin), accounting for 29% of newly diagnosed cancers. In 2017, it is estimated that breast cancer will be diagnosed in 252,710 women in the United States and that approximately 40,000 women will die of their disease. Breast cancer can be categorized into different histopathologic subtypes based on expression of estrogen receptor (ER), progesterone receptor (PR) and HER2 overexpression. HR-positive/HER2-negative breast cancer is the most common subset of breast cancer. Most patients are diagnosed at an early stage and treated with endocrine therapy with or without chemotherapy. About one-third of all HR-positive/HER2-negative patients, diagnosed initially with early stage disease, experience metastatic or recurrent disease. Endocrine therapy is the preferred option at the time of disease recurrence. Not all patients respond to first-line endocrine therapy (primary or de novo resistance), and even patients who have a response will eventually relapse (acquired resistance). Further treatment options at the time of recurrence include subsequent endocrine therapy or chemotherapy. Metastatic breast cancer (MBC), where the original cancer in the breast has spread to distant organs in the body, is the most advanced stage of breast cancer and is incurable with a 5 year survival of approximately 20%. Therefore, there is an unmet medical need to improve the outcomes in patients with advanced or metastatic breast cancer.

The Applicant submitted a sNDA application for palbociclib with a proposed indication for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have not received prior therapy for their advanced disease. Palbociclib is a reversible inhibitor of cyclin-dependent kinase (CDK) 4 and CDK6 and thus acts to prevent cellular proliferation by blocking G1 to S phase transition of the cell cycle. Palbociclib was granted accelerated approval by the FDA on February 3, 2015 for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. On February 19, 2016, the U. S. Food and Drug Administration approved palbociclib in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.

The basis for this recommendation is a favorable benefit-risk profile for palbociclib when added to letrozole in women with HR-positive, HER2-negative advanced or metastatic breast cancer that have not been previously treated for their advanced/metastatic disease. In the randomized, double-blind, placebo- controlled Phase 3 study, Study 1008 (A5481008, PALOMA-2) a clinically meaningful and statistically significant 10 month improvement in estimated median PFS was observed favoring the palbociclib plus letrozole treatment arm. Results of a BICR, subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results. The estimated median PFS in the palbociclib plus letrozole arm at the time of the final PFS analysis was 24.8 months compared to 14.5 months in the placebo plus letrozole arm with a HR of 0.58 (95% CI: 0.46, 0.72;  $p < 0.0001$ ). OS analysis was not mature at the time of the PFS analysis.

The final PFS results from Study 1008 fulfill the postmarketing requirement (2860-1) from the accelerated approval of palbociclib in combination of letrozole and confirm the results observed in Study 1003 (PALOMA-1) which supported the accelerated approval. Study 1003 was an international, multicenter, open-label, randomized Phase 1/2 study in a population of postmenopausal HR-positive HER2- negative advanced breast cancer patients who had not been treated previously for their advanced disease who were randomized 1:1 to receive palbociclib plus letrozole or letrozole alone. In Study 1003, a 10 month improvement in estimated median PFS was also observed with a HR of 0.488 (95% CI: 0.319, 0.748, 1 sided p=0.0004) favoring the palbociclib plus letrozole treatment arm.

This indication for palbociclib will expand the indication to allow for the use with any aromatase inhibitor. The Applicant evaluated the drug-drug interaction (DDI) potential of combining palbociclib with the aromatase inhibitors, anastrozole and exemestane, based on their known metabolic pathways. Clinically significant drug interactions are not expected based on the results of these analyses. In addition, studies evaluating the safety and efficacy of the combination of palbociclib and anastrozole or exemestane are ongoing or completed. No new safety signals have been identified to date. All three aromatase inhibitors (letrozole, anastrozole, exemestane) are used as first-line treatment of postmenopausal women with HR-positive advanced/metastatic breast cancer. Broadening the indication to use palbociclib in combination with any aromatase inhibitor provides flexibility to make therapeutic decisions based on the individual patient's prior adjuvant endocrine therapy, time to progression on prior therapy, and tolerance of the therapies' known potential side effects.

Overall, palbociclib was generally tolerable with adverse reactions manageable through the use of dose reduction, temporary treatment discontinuation, and/or standard medical care. Neutropenia was the most common adverse reaction in the palbociclib treatment arm, occurring in 80% of patients. Febrile neutropenia occurred in 2.5% of patients. Additional common adverse reactions ( $\geq 10\%$ ) with palbociclib include infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia. With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2. Permanent discontinuation associated with an adverse reaction occurred in 9.7% of patients receiving palbociclib plus letrozole. The safety profile is acceptable for this patient population with a serious and life-threatening disease.

In conclusion, based on a favorable risk-benefit profile for palbociclib in combination with letrozole, the reviewers recommend regular approval for the following indication "IBRANCE is a (b) (4) kinase (b) (4) inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>In 2017, it is estimated that breast cancer will be diagnosed in 252,710 women in the United States and that approximately 40,000 women will die of their disease. MBC, where the original cancer in the breast has spread to distant organs in the body, is the most advanced stage of breast cancer and is incurable with a 5 year survival of approximately 20%.</li> </ul>	<ul style="list-style-type: none"> <li>Breast cancer is a serious and life-threatening condition.</li> <li>HR positive-tumors represent the most common form of breast cancer and account for most of the deaths from the disease.</li> </ul>
<a href="#">Current Treatment Options</a>	<ul style="list-style-type: none"> <li>The treatment of MBC is palliative in nature with a goal to prolong survival and improve quality of life by reducing cancer-related symptoms. First-line endocrine based treatment options for postmenopausal women with HR-positive, human epidermal growth factor receptor 2 (HER2)-negative MBC include ribociclib + aromatase inhibitor, palbociclib + letrozole (accelerated approval), aromatase inhibitors (anastrozole, letrozole and exemestane) or tamoxifen. Endocrine therapy options for premenopausal women with HR-positive MBC that do not respond to first line therapy are similar to those for postmenopausal women; however, aromatase inhibitors or fulvestrant need to be administered in combination with ovarian suppression therapy. Pre- and post-menopausal women may also receive chemotherapy as second or later lines of treatment, once they have had tumor progression on endocrine therapy. Patients whose tumors overexpress HER2 have separate prognoses and distinct treatment options.</li> </ul>	<ul style="list-style-type: none"> <li>Endocrine therapy (ET) represents the main initial therapeutic strategy for these patients. Although currently available ET agents are generally effective and well tolerated, not all patients benefit equally and many develop resistance.</li> <li>There is an unmet medical need to improve the outcomes in patients with HR-positive, HER2-negative advanced or metastatic breast cancer.</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#">Benefit</a></p>	<ul style="list-style-type: none"> <li>The clinical data from a randomized, double-blind, placebo-controlled Phase 3 Trial (Study 1008, A5481008, PALOMA-2) in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease was not previously treated presented in this sNDA demonstrates an improvement in PFS for palbociclib plus letrozole compared to placebo plus letrozole. The median PFS in the palbociclib plus fulvestrant arm was 24.8 months compared to 14.5 months in the placebo plus fulvestrant arm (HR =0.58; 95% CI: 0.46, 0.72; p&lt;0.0001). OS results were immature at the time of analysis with only 20% of deaths having occurred. Objective response rate (ORR) was 55.3% in the palbociclib plus letrozole arm compared with 44.4% in the placebo plus letrozole arm for patients with measurable disease at baseline.</li> </ul>	<p>The PFS benefit derived from palbociclib is statistically significant and clinically meaningful. It is unclear if there will be an OS benefit.</p>
<p><a href="#">Risk</a></p>	<ul style="list-style-type: none"> <li>Neutropenia was the most common adverse reaction in the palbociclib treatment arm, occurring in 80% of patients. Febrile neutropenia occurred in 2.5% of patients.</li> <li>Additional common adverse reactions (&gt;10%) with palbociclib include infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia. With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2. Permanent discontinuation associated with an adverse reaction occurred in 9.7% of patients receiving palbociclib plus letrozole.</li> <li>Neutropenia is the only adverse reactions being described in the warnings and precautions section of labeling.</li> </ul>	<ul style="list-style-type: none"> <li>The safety profile of palbociclib plus letrozole for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer is generally tolerable, with adverse reactions manageable through the use of palbociclib dose reduction, temporary treatment discontinuation, and/or standard medical care.</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Risk Management</a>	<ul style="list-style-type: none"> <li>• Palbociclib is intended to be prescribed by oncologists.</li> <li>• Oncologists are well versed in the identification and management of the toxicities associated with palbociclib.</li> <li>• Labeling details dose interruption, reduction, or discontinuation</li> <li>• Laboratory monitoring is recommended before and during treatment.</li> </ul>	<ul style="list-style-type: none"> <li>• The safe use of palbociclib can be managed through accurate labeling and routine oncology care.</li> <li>• No REMS is indicated.</li> </ul>

## 2 Therapeutic Context

### Analysis of Condition

The treatment of patients with advanced breast cancer is palliative in nature. Endocrine therapy is preferable to chemotherapy for patients with hormone receptor (HR)-positive metastatic breast cancer (MBC), provided there is no visceral crisis. First line endocrine based treatment options for postmenopausal women with HR-positive, human epidermal growth factor receptor 2 (HER2)-negative MBC include ribociclib + aromatase inhibitor, palbociclib + letrozole (accelerated approval), aromatase inhibitors (anastrozole, letrozole and exemestane) or tamoxifen. Patients whose tumors overexpress HER2 have separate prognoses and distinct treatment options.

#### 2.2. Analysis of Current Treatment Options

FDA-approved endocrine therapies for patients with HR-receptor positive locally advanced or metastatic breast cancer as first line therapy are shown in Table 1 .

**Table 1: Available Therapy for the Proposed Patient Population**

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Drug Class
<b>FDA Approved Treatments</b>						
Ribociclib	In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer	2017	600mg daily by mouth, 21 days on/7 days off	Ribociclib+letrozole vs placebo+letrozole PFS: NR vs 14.7 months, HR 0.556 (95% CI: 0.429, 0.720; p<0.0001)	Myelosuppression, abnormal liver function tests, vomiting. QT prolongation	CDK 4/6 inhibitor
Letrozole	First and second-line	1997	2.5mg daily by mouth	Vs tamoxifen TTP: 9.4 months vs	Bone mineral density	Aromatase inhibitor

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Statistical – Erik Bloomquist / Shenghui Tang

	treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer			6.4 months HR 0.72 (p<0.0001) OS: 35 months vs 32 months (p=0.5136)	decrease, hot flashes, and arthralgias	
Anastrozole	First-line treatment of postmenopausal women with HR-positive or unknown locally advanced or metastatic breast cancer	1995	1mg daily by mouth	Vs. tamoxifen TTP: 11.1 vs 5.6 months (p=0.006) and 8.2 vs 8.3 months (p=0.92)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor
Tamoxifen	In the treatment of metastatic breast cancer in women and men. Patients whose tumors are estrogen receptor positive are more likely to benefit.	1977	20mg daily by mouth	Response rate in 14 phase 2 studies and nine literature reports. The overall database included 1164 patients.	Uterine malignancies, stroke, pulmonary embolism and hot flashes	Selective estrogen receptor modulator
<b>Other Treatments</b>						
Exemestane	Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy	1999	25mg daily by mouth	Vs megestrol acetate TTP: 20.3 weeks vs 16.6 weeks (HR 0.84)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor

### 3 Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

Palbociclib was granted accelerated approval by the FDA on February 3, 2015 for use in combination with letrozole for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. This accelerated approval had a postmarketing requirement (PMR) to confirm the clinical benefit observed in Study 1003 (PALOMA-1). This PMR required PFS and OS data and results from the ongoing Study 1008 (PALOMA-2).

On February 19, 2016, the FDA approved palbociclib in combination with fulvestrant for the treatment of women with hormone receptor–positive, HER2–negative advanced or metastatic breast cancer with disease progression following endocrine therapy.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

**March 10, 2004:** IND 69324 for PD-0332991 (palbociclib) was submitted in the United States for the treatment of advanced cancers.

**November 27, 2012:** The protocol for Study 1008 was submitted to IND 69324 (SDN 171, eCTD 160). There was no special protocol assessment requested for Study 1008.

**April 9, 2013:** FDA granted Breakthrough Designation to palbociclib for the treatment of patients with breast cancer.

**February 3, 2015:** Palbociclib was granted accelerated approval in combination with letrozole for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

**February 19, 2016:** Palbociclib was approved in combination with fulvestrant for the treatment of women with HR–positive, HER2–negative advanced or metastatic breast cancer with disease progression following endocrine therapy.

**July 11, 2016:** Preliminary comments received for a Type B pre-sNDA meeting, scheduled for July 20, 2016, to discuss the top line summary of the final analysis for Study 1008. FDA agreed with the Sponsor’s format and content plans to submit a sNDA seeking full approval based on Study 1008, and the meeting was subsequently canceled.

(b) (4)



**October 27, 2016:** sNDA 207103/004 was submitted to FDA.

**December 12, 2016:** The sNDA was given priority review with PDUFA deadline of April 27, 2017.

### 3.3. Foreign Regulatory Actions and Marketing History

As of August 15, 2016, palbociclib has been approved in more than 15 countries globally, including the US and Canada. Applications for registration are currently under review in more than 70 countries, including the European Union, Australia, Switzerland, and South Korea.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

Three clinical sites for Study 1008 were chosen for Office of Scientific Investigations (OSI) inspections. These sites were selected based on the enrollment of a large number of patients. See Clinical Inspection Summary written by Lauren Iacono-Connors, Ph.D, Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, OSI. A summary of the site inspections are provided in Table 2.

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Clinical – Suparna Wedam / Laleh Amiri-Kordestani  
Statistical – Erik Bloomquist / Shenghui Tang

**Table 2: OSI Findings in Study 1008**

Inspection	Site #, and # of Subjects	Inspection Date	Interim Classification
Dr. Oleg Nikolaevich Lipatov State Budget Medical Institution Republican Ukraine	Site #: 1056 # of subjects: 34	February 6-15, 2017	NAI
Dr. Hope S. Rugo UCSF San Francisco, CA	Site #: 1078 # of subjects: 20	February 13-17, 2017	NAI
Dr. Samuel Finn UCLA School of Medicine Los Angeles, CA	Site #: 1009 # of subjects: 12	February 6-7, 2017	NAI

NAI = No deviation from regulations

***Reviewer Comment:*** According to the OSI review, the primary efficacy endpoint of PFS as determined by the clinical investigators was verified with the source records generated at the inspected clinical sites. There were no significant inspectional findings from any of three inspected sites and the data from all inspected sites associated with Study 1008 appear reliable.

#### 4.2. Product Quality

Not applicable. See Section 5.2

#### 4.3. Clinical Microbiology

Not applicable. See Section 5.2

#### 4.4. Nonclinical Pharmacology/Toxicology

For full details, please see Nonclinical pharmacology/Toxicology reviews by Dr. Wei Chen.

Altered glucose metabolism appears to be of no concern to adult patients; therefore these findings were (b) (4). However, these effects in immature rats may be relevant to pediatric patients, and therefore it was recommended to move this information to Section 8.4 of the label in the absence of any data in pediatric patients.

#### 4.5. Clinical Pharmacology

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Clinical – Suparna Wedam / Laleh Amiri-Kordestani

Statistical – Erik Bloomquist / Shenghui Tang

For full details, please see Clinical Pharmacology/ Pharmacometrics reviews by Drs. Wentao Fu.

ECG subgroup analysis: In an ECG subgroup analysis (N=77), no large QTc prolongation effect of palbociclib + letrozole was detected from the Phase 3 Study 1008. The conclusion from current QT-IRT review is the same as that from the previous QT-IRT review of palbociclib based on data collected from Studies 1001, 1002, and 1003. The review team concluded that QT interval prolongation is not likely to be clinically relevant.

E-R relationship: The exposure response (E-R) analysis using Study 1008 results concluded that investigator-assessed PFS was not significantly associated with palbociclib exposure at the fixed dose of 125 mg palbociclib.

Drug-drug interaction: For aromatase inhibitors anastrozole or exemestane, no clinical data are available to evaluate drug interactions between anastrozole or exemestane and palbociclib. A clinically significant drug interaction between anastrozole or exemestane and palbociclib is not expected based on mechanistic understandings of the potentials of palbociclib, anastrozole, and exemestane as a perpetrator or a victim.

#### **4.5.1. Mechanism of Action**

Palbociclib is a reversible inhibitor of CDK 4 and CDK6 and thus acts to prevent cellular proliferation by preventing G1 to S phase progression of the cell cycle. For further details see original NDA submission.

#### **4.5.2. Pharmacodynamics**

Not applicable.

#### **4.5.3. Pharmacokinetics**

Not applicable.

#### **4.6. Devices and Companion Diagnostic Issues**

No companion device or diagnostic is included in this application.

#### **4.7. Consumer Study Reviews**

Not applicable to this sNDA.

## **5 Sources of Clinical Data and Review Strategy**

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### **5.1. Table of Clinical Studies**

The primary evidence to support this supplement application is derived from Study 1008 as seen in Table 3.

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 Clinical – Suparna Wedam / Laleh Amiri-Kordestani  
 Statistical – Erik Bloomquist / Shenghui Tang

**Table 3: Listing of Clinical Trials Relevant to this sNDA**

<b>Trial Identity</b>	<b>Trial Design</b>	<b>Regimen/ schedule/ route</b>	<b>Study Endpoints</b>	<b>Treatment Duration/ Follow Up</b>	<b>No. of patients enrolled</b>	<b>Study Population</b>	<b>No. of Centers and Countries</b>
<b><i>Controlled Studies to Support Efficacy and Safety</i></b>							
A5481008	Randomized, double blind phase 3 study	Palbociclib 125mg daily for 3 weeks on 1 week off with letrozole vs. placebo plus letrozole	Investigator assessed PFS	Median days on treatment: palbociclib-603, letrozole-618 vs letrozole-413, placebo-420	666	Women with newly diagnosed ER+, HER2-negative advanced breast cancer	186 centers in 17 countries
<b><i>Studies to Support Efficacy</i></b>							
A5481023	Randomized, double-blind phase 3 study	Palbociclib 125mg daily for 3 weeks on 1 week off with fulvestrant 500mg days 1,15,29 and monthly thereafter vs fulvestrant alone (at same dose listed above)	Investigator assessed PFS	Median days on treatment: palbociclib-144, fulvestrant-148 vs fulvestrant-128, placebo-120	571	Women with HR+, HER2 negative advanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy	144 centers in 17 countries

## 5.2. Review Strategy

The clinical review was conducted by Dr. Suparna Wedam and the statistical review was conducted by Dr. Erik Bloomquist. The clinical review included the following:

1. Literature review of hormone receptor positive metastatic breast cancer, cyclin D1-CDK pathway and patient reported outcomes
2. Research of the FDA data base for regulatory history of the palbociclib IND 69,324 and review of meeting minutes conducted during drug development
3. Review of Applicant submitted CSR, protocol, protocol amendments, and selected datasets for Study 1008
4. Review of selected case report forms (CRFs) for Study 1008
5. Review of selected patient narratives for serious adverse events and deaths in Study 1008
6. Review of response to clinical and biostatistical queries sent to Applicant
7. Review of consultation reports from the Office of Scientific Investigations
8. Consultation with other disciplines, including Biostatistics, Clinical Pharmacology and Toxicology was undertaken

## 6 Review of Relevant Individual Trials Used to Support Efficacy

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### A5481008 (Study 1008 or PALOMA-2)

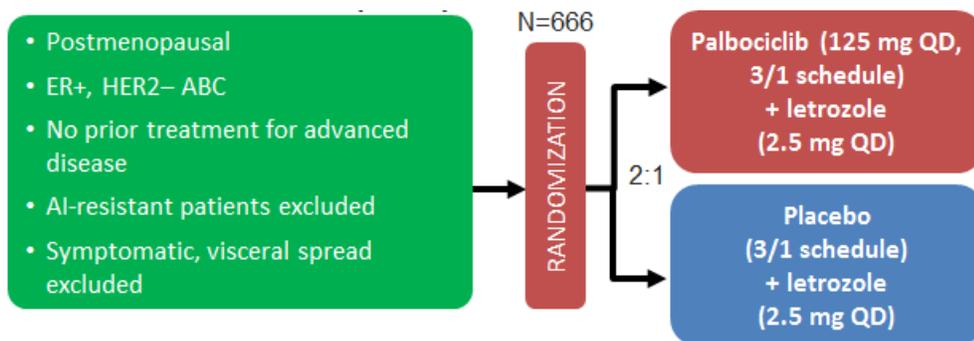
#### 6.1.1. Study Design

##### Overview and Objective

This sNDA contains data from Study 1008, entitled “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” ( Figure 1). Patients were treated with either palbociclib 125 mg/day or placebo orally for 3 of 4 weeks. Patients also received letrozole 2.5mg orally continuously. The primary objective was to demonstrate an improvement in investigator-assessed progression free survival with palbociclib plus letrozole over placebo plus letrozole. Key secondary objectives include overall survival, objective response rates, duration of response, and clinical benefit response (CR or PR or SD  $\geq$  24 weeks).

## Trial Design

**Figure 1: Study 1008 Trial Design**



Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. Patients were allowed to continue treatment as assigned at randomization beyond the time of RECIST-defined PD at the discretion of the investigator if that is considered to be in the best interest of the patient and as long as no new anti-cancer treatment is initiated.

***Reviewer's comment: Study 1008 was a phase 3 randomized study that was able to confirm the benefit previously seen in Study 1003 (PALOMA-1), which supported the accelerated approval of palbociclib in combination with letrozole.***

### Inclusion/Exclusion Criteria

#### **Inclusion Criteria:**

- Adult women ( $\geq 18$  years of age) with proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease not amenable to resection or radiation therapy with curative intent and for whom chemotherapy is not clinically indicated.
- Documentation of histologically or cytologically confirmed diagnosis of estrogen-receptor positive (ER+) breast cancer based on local laboratory results.
- Previously untreated with any systemic anti-cancer therapy for their locoregionally recurrent or metastatic ER+ disease.
- Postmenopausal women defined as women with:
  - Prior bilateral surgical oophorectomy, or
  - Medically confirmed post-menopausal status defined as spontaneous cessation of regular menses for at least 12 consecutive months or follicle-stimulating

hormone (FSH) and estradiol blood levels in their respective postmenopausal ranges with no alternative pathological or physiological cause.

- Measurable disease as defined per RECIST v.1.1 or bone-only disease (with bone lesions confirmed by CT, MRI or bone X-ray). Tumor lesions previously irradiated or subjected to other locoregional therapy will only be deemed measurable if disease progression at the treated site after completion of therapy is clearly documented.
- ECOG performance status (PS) 0-2
- Adequate organ and marrow function defined as follows:
  - $ANC \geq 1,500/mm^3$  ( $1.5 \times 10^9 /L$ )
  - Platelets  $\geq 100,000/mm^3$  ( $100 \times 10^9 /L$ );  $\geq$  Hemoglobin  $\geq 9$  g/dL (90 g/L)
  - Serum creatinine  $\geq 1.5 \times$  ULN or estimated creatinine clearance  $\geq 60$  mL/min as calculated using the method standard for the institution
  - Total serum bilirubin  $\geq 1.5 \times$  ULN ( $\geq 3.0 \times$  ULN if Gilbert's disease)
  - AST and/or ALT  $\geq 3 \times$  ULN ( $\geq 5.0 \times$  ULN if liver metastases present)
  - Alkaline phosphatase  $\geq 2.5 \times$  ULN ( $\geq 5.0 \times$  ULN if bone or liver metastases present).
- Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCI CTCAE version 4.0 Grade  $\leq 1$  (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).
- Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
- All patients must agree to provide tumor tissues for centralized retrospective confirmation of ER status and to evaluate correlation between genes, proteins, and RNAs relevant to the cell cycle pathways and sensitivity/resistance to the investigational agents. Freshly biopsied, recurrent/metastatic tumor samples must be provided whenever possible. If such a biopsy is not feasible or cannot be safely performed, then an archived tumor sample may be accepted. In either case a formalin fixed, paraffin embedded (FFPE) block or 12 unstained FFPE slides are required for patient participation.
- Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study before any study-specific activity is performed.

**Exclusion Criteria:**

- HER2-positive tumor
- Patients with advanced, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term
- Known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated with local therapy (eg, radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.

- Prior neoadjuvant or adjuvant treatment with a non-steroidal aromatase inhibitor (ie, anastrozole or letrozole) with disease recurrence while on or within 12 months of completing treatment.
- Prior treatment with any CDK4/6 inhibitor.
- Patients treated within the last 7 days prior to randomization with:
  - Food or drugs that are known to be CYP3A4 inhibitors (ie, amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit or grapefruit juice);
  - Drugs that are known to be CYP3A4 inducers (ie, carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort).
  - Drugs that are known to prolong the QT interval (see Appendix 3).
- Major surgery, chemotherapy, radiotherapy, any investigational agents, or other anti-cancer therapy within 2 weeks before randomization. Patients who received prior radiotherapy to  $\geq 25\%$  of bone marrow are not eligible independent of when it was received
- Diagnosis of any other malignancy within 3 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.
- QTc  $> 480$  msec (based on the mean value of the triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes (TdP).
- Uncontrolled electrolyte disorders that can compound the effects of a QTc-prolonging drug (eg, hypocalcemia, hypokalemia, hypomagnesemia). 11. Any of the following within 6 months of randomization: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE version 4.0 Grade  $\geq 2$ , atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.
- Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection.
- Known hypersensitivity to letrozole, or any of its excipients, or to any PD-0332991/placebo excipients.
- Known human immunodeficiency virus infection.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

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- Patients who are investigational site staff members or relatives of those site staff members or patients who are Pfizer employees directly involved in the conduct of the trial.
- Participation in other studies involving investigational drug (s) (Phases 1-4) within 2 weeks before randomization and/or during participation in the active treatment phase of the trial.
- Recent or active suicidal ideation or behavior

***Reviewer's comment: The eligibility criteria appear acceptable, although, it is not clear why male patients were not eligible for Study 1008.***

### **Allocation to Treatment**

Patients were randomized using a centralized internet/telephone registration system no more than 4 business days before administration of the first dose of investigational product.

Eligible patients were randomly assigned in a 2:1 ratio to either Arm A or Arm B stratified according to site of disease, disease-free interval since completion of prior (neo)adjuvant therapy, and nature of prior (neo)adjuvant anti-cancer treatment received.

The Interactive Randomization Technology (IRT) assigned a unique patient identification number. The IRT system was also used to assign study medication.

### **Study Treatments**

Arm A (experimental arm):

- Palbociclib 125 mg, orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment;  
in combination with
- Letrozole, 2.5 mg, orally once daily (continuously)

Arm B (control arm):

- Placebo orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment;  
in combination with
- Letrozole, 2.5 mg, orally once daily (continuously)

***Reviewer's comment: Palbociclib and letrozole were both administered at the approved dose and schedule for the combination.***

### Concomitant Radiotherapy or Surgery

Any concurrent radiotherapy (except palliative radiotherapy as specified below) or cancer-related surgery was prohibited throughout the duration of the active treatment phase of the study. Patients requiring any of these procedures were to be discontinued from the active treatment phase and will enter the follow-up phase.

Palliative radiotherapy is permitted for the treatment of painful bony lesions provided that the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression.

### Dose Modifications

No dose adjustment for letrozole was permitted but dosing interruptions were allowed. Treatment interruptions for letrozole-related toxicities were performed as per the investigator's best medical judgment.

Dose interruption, delay and/or reduction of palbociclib/placebo were allowed.

Dose interrupted for:

- Uncomplicated Grade 3 neutropenia ( $ANC < 1000/mm^3$ )
- Grade 3 neutropenia ( $ANC < 1000/mm^3$ ) associated with a documented infection or fever  $\geq 38.5^\circ C$
- Grade 4 neutropenia ( $ANC < 500/mm^3$ )
- Grade 4 thrombocytopenia (Platelet count  $< 25,000/mm^3$ )
- Grade  $\geq 3$  non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment)
- Grade 3 QTc prolongation (QTc  $\geq 501$  msec on at least two separate ECGs).

Dose delayed for:

- Platelet count  $\leq 50,000/mm^3$
- $ANC \leq 1000/mm^3$  and no fever
- Grade 3 or higher treatment-related non-hematologic AEs (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment), with the exception of alopecia, have recovered to Grade  $\leq 1$  or baseline (or, at the investigator's discretion, Grade  $\leq 2$  if not considered a safety risk for the patient).
- QTc  $< 501$  msec and potential reversible causes (eg, electrolyte imbalance, concomitant medications known to prolong QTc) corrected. If QTc remains above 480 msec, ECG should be monitored more frequently as per the investigator's best medical judgment until QTc  $\leq 480$  msec.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity.

Dose reduction of PD-0332991/placebo by 1 and, if needed, 2 dose levels as listed in Table 4 were allowed depending on the type and severity of toxicity encountered. Patients requiring more than 2 dose reductions will be discontinued from the study and entered into the follow-up phase.

**Table 4: Palbociclib dose levels**

Dose Level	PD-0332991/Placebo for 3 out of 4 weeks (3/1 schedule)	Letrozole on a continuous daily dosing regimen
Starting dose	125 mg/d	2.5 mg/d
-1	100 mg/d	2.5 mg/d
-2	75 mg/d*	2.5 mg/d
Discontinue Study Treatment		

\* PD-0332991/placebo dose de-escalation below 75 mg/d is not allowed.

Source: Study 1008 Protocol (Amendment 7), page 58

The pre-specified dose reductions for various treatment-related toxicities are shown in Table 5 below.

**Table 5: Palbociclib/Placebo Dose Modifications for Treatment-Related Toxicities**

Toxicity	Restart PD-0332991/Placebo Treatment at:
Uncomplicated Grade 3 neutropenia ( $ANC < 1000/mm^3$ )	Same dose level
Grade 3 neutropenia ( $ANC < 1000/mm^3$ ) associated with a documented infection or fever $\geq 38.5^\circ C$	↓ 1 Dose Level
Grade 4 neutropenia ( $ANC < 500/mm^3$ )	↓ 1 Dose Level
Grade 4 thrombocytopenia (Platelet count $< 25,000/mm^3$ )	↓ 1 Dose Level
Grade $\geq 3$ non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment)	↓ 1 Dose Level

Source: Study 1008 Protocol (Amendment 7), page 58

### **Procedures and Schedule**

A detailed schedule of activities is shown in Table 6.

**Table 6: Study 1008 Schedule of Activities**

Protocol Activity	Screening	Active Treatment Phase <sup>a</sup> - One Cycle = 28 days			End of Treatment / Withdrawal <sup>c</sup>	Post-Treatment Follow-Up <sup>d</sup>
		Cycles 1 and 2		Cycles ≥3		
		Day 1 <sup>b,v</sup>	Day 14	Day 1 <sup>v</sup>		
Study Day	Within 28 days prior to randomization unless specified otherwise	±2d	±2d	±2d		
Time Window						±7d
<b>Baseline Documentation</b>						
Informed Consent Process <sup>a</sup>	X					
Medical / Oncological History <sup>f</sup>	X					
Baseline Signs / Symptoms		X <sup>e</sup>				
Retained Pharmacogenomic Blood Sample <sup>h</sup>		X				
Tumor Tissue for Biomarker <sup>i</sup>	X				X <sup>l</sup>	
Physical Examination/Vital signs <sup>j</sup>	X	X <sup>b</sup>		X	X	
Ophthalmic Examination <sup>k</sup>	X			X	X	
ECOG Performance Status	X	X		X	X	
<b>Laboratory Studies</b>						
Hematology <sup>j</sup>	X	X <sup>b</sup>	X	X	X	
Blood Chemistry <sup>j</sup>	X	X <sup>b</sup>	X	X	X	
12-Lead ECG <sup>m</sup>	X <sup>m</sup>	X <sup>b</sup>	X <sup>m</sup>	X <sup>a</sup>	X	
<b>Disease Assessment</b>						
Computed Tomography (CT)/ Magnetic Resonance Imaging (MRI) Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; Clinical evaluation of superficial disease <sup>o</sup>	X	◀--▶ <sup>p,o</sup> Performed every 12 weeks (±7 days) from the date of randomization			X	X <sup>o</sup>

Protocol Activity	Screening	Active Treatment Phase <sup>a</sup> - One Cycle = 28 days			End of Treatment / Withdrawal <sup>c</sup>	Post-Treatment Follow-Up <sup>d</sup>
		Cycles 1 and 2		Cycles ≥3		
		Day 1 <sup>b,v</sup>	Day 14	Day 1 <sup>v</sup>		
Study Day	Within 28 days prior to randomization unless specified otherwise	±2d	±2d	±2d		
Time Window						±7d
Radionuclide Bone Scan, Whole Body <sup>o</sup>	X	◀--▶ <sup>q,o</sup> Performed every 24 weeks (±7 days) from the date of randomization			X	X <sup>o</sup>
<b>Other Clinical Assessments</b>						
Drug Compliance <sup>f</sup>		◀--▶				
Averse Event Reporting <sup>g</sup>	X	X	X	X	X	X
Review Concomitant Medications/Treatments <sup>g</sup>	X	X	X	X	X	X
EuroQol; EQ-5D <sup>h</sup>		X		X	X	
FACT - Breast Questionnaire <sup>u</sup>		X <sup>u</sup>		X	X	X <sup>v</sup>
Survival Follow-up						X
<b>Study Treatment</b>						
Randomization	X					
Letrozole (both treatment arms)		Once Daily ◀--▶ <sup>w</sup>				
PD-0332991 or Placebo		◀--▶ <sup>x</sup> Once Daily on Day 1 to Day 21 of each cycle followed by 7 days off				
<b>Special Laboratory Studies</b>						
Pharmacokinetics <sup>m</sup>			X			

- Active Treatment Phase:** All assessments should be performed prior to dosing with study medications on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. For the purposes of this trial 1 cycle is 28 days. A cycle could be longer than 28 days if persistent toxicity delays the initiation of the subsequent cycle.
- Cycle 1/Day 1:** Blood chemistry, hematology, 12-lead ECG and physical examination not required if acceptable screening assessment is performed within 7 days prior to randomization.
- End of Treatment/Withdrawal:** End of Treatment/Withdrawal evaluations will be performed as soon as possible but no later than 4 weeks (ie, 28 days) ±7days from last dose of study treatment and prior to the initiation of any new anti-cancer therapy. Obtain these assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks for disease assessments).

- d. **Post Treatment Follow-up:** After discontinuation of study treatment, post-treatment follow-up information (ie, survival status, and post-study anti-cancer therapy details [including regimen number, name of therapy, start/stop dates, and dates of disease progression on subsequent anti-cancer therapies]) will be collected every 6 months ( $\pm$  7 days) from the last dose of study treatment. Telephone contact is acceptable.
- e. **Informed Consent:** Informed consent may be obtained greater than 28 days from randomization; however, must be obtained prior to any protocol required assessments being performed (with the exception of certain imaging assessments if meeting the criteria defined in [Section 6.1](#)).
- f. **Medical/Oncological History:** To include information on prior anti-cancer treatments.
- g. **Baseline Signs/Symptoms:** Baseline tumor related signs and symptoms will be recorded at the Cycle 1 Day 1 visit prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency.
- h. **Retained Pharmacogenomic Blood Sample:** A single 4 mL blood sample (Prep D1; K2 EDTA whole blood collection optimized for DNA analysis) will be collected pre-dose at the Cycle 1 Day 1 visit from all patients, unless prohibited by local regulations, to be retained for possible analysis of genetic associations with pharmacokinetics, drug response or adverse drug reactions. Examples of genes that may affect pharmacokinetics or drug response include, but may not be limited to, genes encoding drug metabolizing enzymes and transporters, and genes thought to be related to the mechanism of drug action.
- i. **Mandatory Tumor Tissue For Confirmatory Testing and for Biomarker Assessments:** Tumor tissue is required for patient participation. Submission of formalin-fixed paraffin embedded (FFPE) tumor samples (blocks) of adequate size to allow for three 0.6 mm diameter x 5 mm deep core punches that will be used to generate a tissue microarray are needed. If FFPE tissue block cannot be submitted, at least 12 glass slides, each containing an unstained 5-micron FFPE tissue section, will be required for patient participation. Tissue sample from a metastatic or recurrent tumor lesion must be provided whenever possible. If such tissue sample is unavailable, a *de novo* fresh biopsy is recommended when, in the investigator's judgment, such biopsy is feasible and can be safely performed. A sample of the original diagnostic tissue (ie, archival) will also be collected when available and sent to the sponsor-designated central laboratories for assessment of biomarkers associated with sensitivity and/or resistance to PD-0332991 (eg, Ki67, CDKN2A (p16), pRb). Retrospective confirmation of ER status and prospective confirmation of HER2 status when required to be repeated for eligibility purpose will be performed using the most recent tumor sample. Original diagnostic tumor tissue will be used for confirmation of ER and HER2 status in the event that a recurrent/metastatic tissue sample is not available and a fresh biopsy of the recurrent/metastatic lesion is not feasible. An optional fresh tumor biopsy will be collected at the end of treatment visit, only for patients who discontinue treatment due to disease progression. The tumor tissue will be used to determine possible mechanisms of resistance. Tissue samples from all patients will be used for additional biomarker analyses. Details on preparation of these samples including processing, storage, and shipment will be provided in the Study Manual.
- j. **Physical Examination/Vital signs:** A full physical examination including an examination of all major body systems (including general appearance, head, ears, eyes, nose, mouth, throat, neck, thyroid, lungs, heart, breasts, abdomen, and musculoskeletal), height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider, will be required at screening and, Day 1 of Cycles 1 and 2. Symptom-directed physical examinations, blood pressure and pulse rate will be performed at subsequent visits.
- k. **Ophthalmic Examinations:** Once Amendment #3 is IRB approved, all newly enrolled patients will undergo an ophthalmic examination at baseline, and on study treatment after 3 months (Cycle 4 Day 1), 6 months (Cycle 7 Day 1), 12 months (Cycle 13 Day 1), every 12 months (Day 1 of Cycles 25, 37 etc...) thereafter, and at the End of Treatment visit. Additional ophthalmic examinations may be performed during the study as clinically indicated (including for patients randomized prior to Amendment 3 approval). The ophthalmic examinations will include: best corrected distant visual acuity (Snellen), refractive error associated with best corrected distant visual acuity, intraocular pressure (IOP – one reading), slit lamp biomicroscopy of the anterior segment including cell count and flare grading, crystalline lens grading using the Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading procedure, and funduscopy. All ophthalmic examinations will be performed by an ophthalmologist. Refer to [Section 7.2.3](#). Ocular Safety Assessments for further details on these procedures.
- l. **Hematology, and Blood Chemistry Panel:** Hematology includes hemoglobin, WBC, absolute neutrophils, platelet count. Blood chemistry includes AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, BUN (or urea), serum creatinine, and albumin. Additional hematology/chemistries panels may be performed as clinically indicated. Additionally, hemoglobin A1c will be measured during the active treatment phase in all patients every 3 months from the date of randomization (ie, C4D1, C7D1, C10D1, etc), and at the end of treatment visit.
- m. **12-Lead ECG/Pharmacokinetics:** Refer to [Pharmacokinetic and ECGs Schedule of Activities](#) table for details and timing of procedures.
- n. **12-Lead ECG:** To be performed on Day 1 of Cycles 4, 7, and 10. ECGs beyond Cycle 10 will be performed as clinically indicated. Refer to [Pharmacokinetic and ECGs Schedule of Activities](#) table for further details and timing of procedures.
- o. **Disease Assessments:** Please refer to the [tumor assessment requirement flowchart](#) for details and timing of procedures.
- p. **CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; clinical evaluation of superficial disease:** Please refer to the [tumor assessment requirement flowchart](#) for details and timing of procedures.
- q. **Radionuclide Bone Scan, Whole Body:** Please refer to the [tumor assessment requirement flowchart](#) for details and timing of procedures.
- r. **Drug Compliance:** PD-0332991, placebo and letrozole bottle(s)/blisters including any unused capsules/tablets will be returned to the clinic for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle.
- s. **Adverse Events:** For SAEs, the active reporting period begins from the time that the patient provides informed consent through and including 28 calendar days after the last administration of the investigational product. Following the active safety reporting period, other SAEs of which the investigator becomes aware should be reported to Pfizer, unless the SAE is attributed by the investigator to complications of either the underlying malignancy or any subsequent anti-cancer therapy or to the patient's participation in a subsequent clinical study. AEs (serious and non serious) should be recorded on the CRF from the time the patient has taken at least one dose of study treatment through last patient visit.
- t. **Concomitant Medications/Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days after the last dose of study treatment.
- u. **EQ-5D, FACT-B Assessments:** Patients will complete questionnaires prior to any study or medical procedure on Day 1 of Cycles 1, 2 and 3 and then Day 1 of every other cycle thereafter starting with Cycle 5 (ie, Cycle 5, 7, 9, etc), and at the end of treatment visit. All self-assessment questionnaires must be completed by the patients while in the clinic and cannot be taken home. Interviewer administration in clinic may be used under special circumstances.
- v. **Cycle X, Day 1:** In the event that the start of a new cycle is delayed due to treatment related toxicity, procedures required on Day 1 of the given cycle will be performed when PD-0332991/placebo is resumed. New cycle Day 1 procedures (ie, physical examination, ECOG performance status, ECG, Quality of Life questionnaires, blood chemistry, hematology) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated (1) if not required to determine whether study drug may be resumed and (2) if performed within 7 days prior to study drug resumption.
- w. **Letrozole (both treatment arms):** To be taken orally, daily, and continuously.
- x. **PD-0332991 or Placebo:** To be taken orally, daily from Day 1 to Day 21 (21 days) of every 28-day cycle followed by 7 days off treatment. In the event the Day 1 clinic visit of the subsequent cycle is scheduled during the -2 day allowable visit time window (ie, Day 27, Day 28), patients must be instructed to complete their 7-day off treatment period of the current cycle prior to resuming blinded therapy even if criteria for treatment resumption are met at the visit. Cycle off treatment periods of less than 7 days are considered protocol deviations.
- y. **FACT-B Assessments:** After patients discontinue from the active treatment phase, FACT-B questionnaire will continue to be collected during the follow-up period every 6 months ( $\pm$  7 days) from the last dose of investigational product until patient permanent discontinuation from study or end of follow-up period whichever occurs first. During the follow-up period, all self-assessment questionnaires should preferably be completed by the patients during a scheduled clinic visit. However, if no clinic visits are being scheduled during the follow-up period interviewer administration via phone call may be used instead and documented accordingly in the patient source notes.

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Source: Study 1008 Protocol (Amendment 7), pages 16-19

**Reviewer's comment: Dose modifications and safety monitoring appear acceptable in the study.**

### **Concomitant Medications**

Prohibited Medications included anti-cancer agents, strong/moderate CYP3A inhibitors/inducers, drugs known to cause QT interval prolongation, hormone replacement therapy and proton pump inhibitors

### **Subject completion, discontinuation, or withdrawal**

The term "discontinuation" refers to a patient's withdrawal from the active treatment phase, i.e., discontinues treatment of palbociclib/placebo AND letrozole. Patients may be withdrawn from the active treatment phase in case of disease progression, symptomatic deterioration, need for new or additional anticancer therapy not specified in the protocol, unacceptable toxicity, investigator's conclusion that discontinuing therapy is in the patient's best interest, lost to follow-up, patient choice to withdraw from treatment (follow-up permitted by patient), withdrawal of patient consent (cessation of follow-up), or death. Patients who discontinue from the active treatment phase must have end of treatment/withdrawal evaluations performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anticancer therapy. Data to be collected for the end of study treatment/withdrawal are described the schedule of activities in Table 3. Patients will be withdrawn from study in the case of withdrawal of patient consent (i.e. refuses tumor assessments or follow-up on survival status after the end of treatment), lost to follow-up, or death.

### **Study Endpoints**

The primary endpoint of Study 1008 was investigator-assessed PFS, defined as the time from the date of randomization to the date of the first documentation of objective progression of disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first. PFS data was planned to be censored on the date of the last tumor assessment on study for patients who do not have objective tumor progression and who do not die while on study. Patients lacking an evaluation of tumor response after randomization would have their PFS time censored on the date of randomization with a duration of 1 day. Additionally, patients who start a new anti-cancer therapy prior to documented PD would be censored at the date of the last tumor assessment prior to the start of the new therapy. Patients with documentation of PD or death after an unacceptably long interval (i.e., 2 or more incomplete or non-evaluable assessments) since the last tumor assessment were censored at the time of last objective assessment that did not show PD. The primary analysis was performed in the ITT population.

Secondary Endpoints include:

- Overall Survival (OS)
- 1-year, 2-year, and 3-year survival probabilities
- Objective Response (OR: Complete Response or Partial Response)
- Duration of Response (DR)
- Disease Control (DC: CR+PR+Stable disease  $\geq$ 24 weeks)
- Corrected QT interval (QTc)
- Tumor tissue biomarkers, including genes (eg, copy numbers of CCND1, CDKN2A), proteins (eg, Ki67, pRb), and RNA expression (eg, cdk4, cdk6)
- Trough plasma concentration of PD-0332991
- PRO endpoints including: EuroQol (EQ-5D) Score; Functional Assessment of Cancer Therapy - Breast (FACT-B)
- Type, incidence, severity (as graded by NCI CTCAE v4.0), seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities.

### **Tumor Assessments**

Disease assessments were to be performed every 12 weeks (+/-7 days) from the date of randomization by CT, MRI and/or X-rays (same imaging modality from baseline to be used). Patients with bone lesions identified at baseline also had repeat bone scans performed every 24 weeks (+/-7 days) from the date of randomization. Tumor assessments were performed until radiographically and/or clinically documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anti-cancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first.

***Reviewer's comment: The primary endpoint of PFS as assessed by the investigator is acceptable in this disease setting. A blinded independent review of the PFS data was conducted in order to assess possible bias of the endpoint.***

### **Statistical Analysis Plan**

The study was originally designed to enroll 450 patients with a primary endpoint of progression free survival determined through primary investigator assessment. The trial was to have a final PFS analysis at 267 events. The study had approximately 90% power to detect a hazard ratio of 0.64 which equates to an approximate 5 month difference in median PFS (9 vs 14 months).

In protocol amendment 2 (January 2014), the study changed the drug administration from fasting to with food. Because of this change, the Applicant decided to increase the sample size

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to 650 patients with a final PFS analysis to occur at 347 events. When determining the new sample size, the Applicant revised their intended hazard ratio target from 0.64 to 0.69.

The study originally included an interim analysis of PFS with an O'Brien-Fleming stopping boundary. In protocol amendment 3 (December 2014), however, the applicant changed their stopping rule to a Haybittle-Peto boundary where the minimum hazard ratio to declare efficacy at the interim boundary was approximately 0.56 (alpha allocation = 0.000013). The efficacy boundary was suggested by the agency in order to provide consistent advice across the CDK 4/6 drug class. The interim analysis was planned to occur when 226 PFS events had been observed (approximately 65% of the total PFS events). A final note, the applicant did conduct the interim analysis for PFS, but the boundary was not reached. The alpha allocation for the final PFS analysis was 0.024987.

For the primary PFS endpoint analysis patient observations were considered as censored under the following scenarios. One, if new anti-cancer therapy was started prior to progression, patients' observations were censored at last available follow-up. Two, if patients withdrew consent or were lost to follow-up, patients' observations were censored at last available follow-up. Finally, in patients with documented progression after 2 more missed visits, patients' observations were censored at the last available visit that documented no progression.

The Applicant included overall survival as a key secondary endpoint. An interim analysis of OS was to be conducted at the primary PFS analysis. Based upon a request by the agency, the sponsor also added a second interim analysis of OS with a cutoff date of November 24, 2016. The sponsor modified their SAP so that a nominal level of alpha was spent at the second interim analysis (0.0001). The final OS analysis is to occur when 347 deaths have happened.

***Reviewer's comment: The statistical analysis plan is acceptable and the protocol amendments do not affect the conclusions reached from the study.***

## **Protocol Amendments**

The applicant submitted 7 protocol amendments. Key changes are summarized here:

Amendment 1 (October 1, 2013): Protocol was amended to address a specific request from the French Regulatory Agency to emphasize the importance of obtaining tumor tissue from a recurrence/metastatic disease at the time of study entry. The protocol language was revised accordingly and implemented for France only.

Amendment 2 (January 3, 2014): Preliminary results from two clinical pharmacology studies A5481018 and A5481021 suggested that palbociclib exposure may be decreased when

administered in a minimally fasted state or concomitantly with proton-pump inhibitors. Therefore the protocol was amended to revise the study drug administration instructions from administration in a minimally fasted state to administration with food and also to prohibit the concomitant use of proton-pump inhibitors.

Amendment 3 (March 21, 2014): Taking into account the preliminary results from studies A5481018 and A5481021, it was assumed that drug exposures before and after implementation of Amendment 2 might be different in patients who took palbociclib in a minimally fasted state (ie, fast from 1 hour before to 2 hours after dosing) and/or concomitantly with proton-pump inhibitors compared to those patients who did not. This difference could potentially reduce the statistical power to detect the true treatment effect of palbociclib in the intent to treat (ITT) population under the current study design. As a result, the protocol is being amended prior to the interim analysis to increase the sample size from 450 patients to 650 patients to preserve the desired statistical power.

Additionally, based on the limited pre-clinical and clinical data currently available, it is not known whether true clinical risk exists for developing palbociclib-associated cataracts. The protocol was therefore amended to implement prospective ophthalmic assessments in all newly enrolled, lens grading patients at baseline and while on study treatment. The results of the ophthalmic assessments may provide a better understanding of the risk of ocular adverse events and will provide information to determine whether further actions are warranted.

Amendment 4 (September 18, 2014): Protocol amended to add prospective monitoring of hemoglobin A1c to characterize whether or not palbociclib affects glucose metabolism; report emergent data findings from the 27-week rat toxicity study suggesting that cataract pathogenesis in rats may be related to altered glucose metabolism; update to no longer require safety review by an internal oncology business unit safety data monitoring committee (IOBU-SDMC) for studies already monitored by an external data monitoring committee (E-DMC); provide results from study A5481038 designed to investigate the effect of H2-receptor antagonists, proton pump inhibitors and local antacids on the relative bioavailability of a single oral 125 mg of palbociclib commercial free base hard capsule formulation dose given under fed conditions in healthy volunteers.

Amendment 5 (December 2, 2014): Protocol amended to change the interim analysis efficacy boundary from O'Brien-Fleming to Haybittle-Peto boundary to ensure that the study would only be stopped at the interim analysis if the primary analysis (PFS) results are statistically significant, and clinically meaningful.

Amendment 6 (April 7, 2015): Protocol amended to reflect changes in the collection of Patient Reported Outcome data during the post-progression follow-up period to assess potential impact of post-progression status on patient's quality of life.

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Amendment 7 (October 15, 2015): Protocol amended to reflect changes in the collection of disease progression dates on subsequent anti-cancer therapies to better understand the potential influence of palbociclib on response to subsequent anticancer therapies.

***Reviewer’s comment: These amendments did not alter the study’s integrity.***

#### **Data Quality and Integrity: Sponsor’s Assurance**

The Sponsor stated that Compliance Oversight Leads (COLs) provided study and site level oversight to ensure that the study was delivered to high quality standards. COLs performed on-site and remote oversight to assess monitoring effectiveness and ensure compliance with the study protocol by investigational sites according to ICH/GCP, applicable Standard Operating Procedures and local regulation.

The External Data Monitoring Committee (E-DMC) is a single, external, independent, expert advisory group established to oversee this Pfizer-sponsored trial. The primary rationale for establishing this committee was to make certain that appropriate external safeguards were in place to help ensure the safety of subjects and to maintain scientific rigor and study integrity for these studies with planned interim analyses where treatment arms were to be compared with respect to the accumulating safety and efficacy data while the trial is on-going.

During study conduct, Pfizer or its agent conducted periodic monitoring visits to ensure that the protocol and GCPs were being followed. The monitors reviewed source documents to confirm that the data recorded on CRFs was accurate. The investigator and institution allowed Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

#### **Data Quality and Integrity – Reviewers’ Assessment**

The data submitted with this application were in AdAM and SDTM formats. The data were of good quality and the Applicant’s analyses were reproducible.

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### 6.1.2. Study Results

#### **Compliance with Good Clinical Practices**

The Applicant stated the study was conducted in accordance with the protocol, the International Conference on Harmonization (ICH) guideline Good Clinical Practice (GCP), and applicable local regulatory requirements and laws.

#### **Financial Disclosure**

All investigators were assessed for equity interest, significant payments of other sorts, other compensation by the sponsor and propriety interest. Financial disclosure information is provided for covered studies A5481003, A5481008, A5481010, A5481013, A5481019, A5481023, A5481027 and A5481034. Of the 4,021 investigators listed, certification was provided for 3,957. Due Diligence activities were required for 11 of the 4,021 clinical investigators. Fifty three of the 4,021 clinical investigators listed in the study report had financial information to disclose (1.3%).

Study A5481008 (PALOMA-2) included 1791 investigators. Twenty two had financial information to disclose and are summarized in Table 7.

**Table 7: Summary of Financial Disclosures for Study 1008**

Clinical Site Number	Investigator Name (PI or SI)	Study A5481008 Patient Enrollment at Site	Disclosure
(b) (4)	(b) (4)	1	Honorarium; Research and Development: \$387,888.62
		3	Honorarium and consulting fees: \$42,675.00
		3	Consultant expense: \$101,285.10
		2	Honorarium; Research and Development: \$98,608.00
		7	Honorarium and consulting fees: \$90,257.00
		3	Research and Development: \$81,123.05
		2	Research and Development: \$389,392.09
		20	Honorarium: \$75,750.00
		6	Honorarium and consulting fees: \$31,415.00
		2	Honorarium: \$31,000.00
		3	Honorarium and consulting fees: \$27,116.00
		7	Consulting; Research and Development: \$89,350.00
		3	Honorarium: \$43,801.99
		3	Honorarium; Research and Development: \$3,505,714.22
		2	Grants: \$403,034.00
		6	Honorarium; Research and Development: \$379,120.16
		2	Honorarium: \$45,000.00
		2	Honorarium: \$34,097.50
		12	Honorarium, consulting fees and external research: \$52,959.00
		6	Honorarium; Research and Development: \$1,293,471.41
2	(b) (6) \$100,000.00		
3	Honorarium: \$28,500.00		

PI: Principle Investigator; SI: Sub-Investigator. Source: sNDA 207103/004, Section 1.3.4 Financial Disclosures

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***Reviewer Comment:*** *Sites with investigators that had significant disclosable interests enrolled approximately 13.2% (N=88) of the total number of patients in Study 1008. Each individual site enrolled between 0.3-3.0% of the population which is small and unlikely to individually affect the results of the study. Results of a sensitivity analyses performed by the FDA statistician excluding these sites are consistent with the primary efficacy endpoint results (results shown under Sensitivity Analyses).*

### **Patient Disposition**

Between February 28, 2013 and July 29, 2014, 666 women were randomized at 186 sites in 17 countries. Four hundred and forty-four (444) patients were randomized to the palbociclib plus letrozole arm, and 222 patients were randomized to the placebo plus letrozole arm. All randomized patients were treated.

As of the data cutoff date, 26 February 2016, 53.8% of patients in the palbociclib plus letrozole arm and 72.5% of patients in the placebo plus letrozole arm had discontinued study treatment, while 46.2% of patients in the palbociclib plus letrozole arm and 27.5% of patients in the placebo plus letrozole arm were still on study treatment (Table 8). For the purpose of treatment, patients continuing on study with letrozole monotherapy following palbociclib/placebo discontinuation were still considered “on treatment”.

**Table 8: Study 1008 Patient Disposition**

	<b>Palbociclib plus Letrozole N=444 n (%)</b>	<b>Placebo plus Letrozole N=222 n (%)</b>	<b>Total N=666 n (%)</b>
<b>Randomized to study treatment</b>	444	222	666
Randomized and not treated	0	0	0
Randomized and treated	444 (100)	222 (100)	666 (100)
Discontinued	239 (53.8)	161 (72.5)	400 (60.1)
Ongoing at data cutoff date	205 (30.8)	61 (27.5)	266 (39.9)
<b>Reason for discontinuation</b>			
Adverse Event	20 (3.0)	9 (4.1)	29 (4.4)
Global deterioration of health status	16 (3.6)	9 (4.1)	25 (3.8)
Lost to Follow-Up	1 (0.2)	0	1 (0.2)
Medication error without associated AE	0	0	0
Objective progression or relapse plus progressive disease	172 (38.7)	125 (56.3)	297 (44.6)
Protocol violation	5 (1.1)	3 (1.4)	8 (1.2)
Study terminated by the sponsor	1 (0.2)	0	1 (0.2)
Patient died	6 (1.4)	2 (0.9)	8 (1.2)
Patient refused to continue treatment for reason other than AE	12 (2.7)	9 (4.1)	21 (3.2)

Source: Modified from Study 1008 CSR Table 12 and Table 13; *discon.xpt*

### Protocol Violations/Deviations

As seen in Table 9, informed consent deviations were the most common major protocol deviation reported for both treatment arms (58.8% and 58.1% in the palbociclib plus letrozole and placebo plus letrozole arms respectively). The most common significant informed consent deviations were “other” (eg, time ICD was signed is missing, dates inconsistencies, patient’s initials missing) and a delay in reconsenting patients on an updated version of the ICD.

**Table 9: Protocol Deviations in Study 1008**

Protocol Deviation Category	Palbociclib plus Letrozole N=444 N* (%)	Placebo plus Letrozole N=222 N* (%)
<b>Any protocol deviation</b>	428 (96.4)	212 (95.5)
Concomitant treatment	113 (25.5)	33 (14.9)
Discontinuation	3 (0.7)	1 (0.5)
Inclusion/exclusion criteria	22 (5.0)	17 (7.7)
Informed consent deviation	261 (58.8)	129 (58.1)
Investigational Product administration/Treatment	202 (45.5)	81 (36.5)
Laboratory	259 (58.3)	118 (53.2)
Other	37 (8.3)	26 (11.7)
Procedures/tests	341 (76.8)	162 (73.0)
Randomization	29 (6.5)	6 (2.7)
Safety Reporting	14 (3.2)	3 (1.4)
Visit schedule	216 (48.6)	104 (46.8)
<b>Any major protocol deviation</b>	324 (73)	143 (64.4)
Concomitant treatment	94 (21.2)	27 (12.2)
Discontinuation	1 (0.2)	0
Inclusion/exclusion criteria	22 (5.0)	17 (7.7)
Informed consent	261 (58.8)	129 (58.1)
Investigational Product administration/Treatment	54 (12.2)	12 (5.4)
Procedures/Tests	13 (2.9)	7 (3.2)
Randomization	21 (4.7)	3 (1.4)
Safety Reporting	14 (3.2)	3 (1.4)

Source: Modified from Study 1008 CSR Table 14; Table 16.2.2.2.1

\*Counts in row Any PD and Any Significant PD represent unique subjects. Counts below them represent unique subjects within each sub-category. Same subject can be counted in multiple sub-categories.

**Reviewer Comment:** The incidence of any protocol deviation was similar in the two treatment arms. The rate of major protocol deviations was higher in the palbociclib treated arm compared to placebo (73% vs 64.4%). The greatest imbalance regarding major protocol deviations between the two arms were due to concomitant treatment and investigational product administration/treatment. The most common concomitant therapy deviations included taking proton pump inhibitors (PPI), and certain antibiotics/antidepressants with the potential to prolong the QT interval. Deviations due to investigational product administration/treatment in the palbociclib arm were due to patient making up missed doses, overdose (i.e. > one dose of either study drugs on any given day and treatment for after dose interruption or start of new cycle did not meet protocol parameters. The nature of these deviations are unlikely to affect the efficacy results. In addition, results for Sensitivity Analysis

**#7 (influence of deviations in tumor lesion assessment) supports the primary efficacy endpoint results.**

**Enrollment by Country**

Breakdown of enrollment by country is shown in Table 10.

**Table 10: Study Enrollment by Country**

Country	Palbociclib plus Letrozole N=444 n (%)	Placebo plus Letrozole N=222 n (%)
United States	126 (28.4)	71 (32.0)
Canada	42 (9.5)	28 (12.6)
Spain	38 (8.6)	19 (8.6)
Russia	38 (8.6)	22 (9.9)
Japan	32 (7.2)	14 (6.3)
Ukraine	27 (6.1)	12 (5.4)
Belgium	22 (5.0)	6 (2.7)
Germany	20 (4.5)	7 (3.2)
France	19 (4.3)	14 (6.3)
Austria	15 (3.4)	5 (2.3)
Ireland	15 (3.4)	7 (3.2)
Korea	15 (3.4)	9 (4.1)
Great Britain	14 (3.2)	4 (1.8)
Italy	9 (2.0)	2 (0.9)
Hungary	5 (1.1)	2 (0.9)
Poland	5 (1.1)	0
Taiwan	2 (0.5)	0

Source: demog.xpt

***Reviewer Comment:*** This was an international study with patients enrolled from 17 countries. The top five countries for enrollment were the United States, Canada, Spain, Russia and Japan with a 30% of patients enrolled from the United States.

**Table 11: Demographic Characteristics for Study 1008**

Demographic Parameters	Palbociclib plus Letrozole N=444 N (%)	Placebo plus Letrozole N=222 N (%)	Total N=666 N (%)
<b>Sex</b>			
Female	444 (100)	222 (100)	666 (100)
<b>Age</b>			
Mean years (SD)	61.7	60.6	61.3
Median (years)	62	61	62
<b>Age Group</b>			
≥ 17 - < 65 years	263 (59.2)	141 (63.5)	404 (60.7)
≥ 65 - < 75 years	133 (30.0)	62 (27.9)	195 (29.3)
≥ 75 years	48 (10.8)	19 (8.6)	67 (10.1)
<b>Race</b>			
White	344 (77.5)	172 (77.5)	516 (77.5)
Black or African American	8 (1.8)	3 (1.4)	11 (1.7)
Asian	65 (14.6)	30 (13.5)	95 (14.3)
Other	27 (6.1)	17 (7.7)	44 (6.8)
<b>Ethnicity</b>			
Hispanic or Latino	39 (8.8)	15 (6.8)	54 (8.1)
Not Hispanic or Latino	386 (86.9)	193 (86.9)	576 (86.5)
Missing/Not reported	19 (4.3)	14 (6.3)	33 (5.0)

Source: Modified from Study 1008 CSR Table 17 and demog.xpt

**Reviewer Comment:** *Baseline patient demographics were well balanced between the two arms. All patients were female and a majority of patients were of White Race. Unfortunately, as with most clinical trials, there was an underrepresentation of Black patients and Hispanic/Latino patients.*

**Table 12: Baseline Disease Characteristics for Study 1008**

	<b>Palbociclib plus Letrozole N=444 N (%)</b>	<b>Placebo plus Letrozole N=222 N (%)</b>	<b>Total N=666 N (%)</b>
<b>Measurable disease</b>			
Yes	338 (76.1)	171 (77.0)	509 (76.4)
No	106 (23.9)	51 (23.0)	157 (23.6)
<b>Adequate baseline assessment</b>			
Yes	444 (100)	222 (100)	666 (100)
No	0	0	0
<b>Bone Only Disease</b>			
Yes	103 (23.2)	48 (21.6)	151 (22.7)
<b>ER Status</b>			
Positive	443 (99.8)	222 (100)	665 (99.8)
Negative	0	0	0
Missing	1 (0.2)	0	1 (0.2)
<b>HER2 status</b>			
Positive	0	0	0
Negative	444 (100)	222 (100)	666 (100)
Equivocal	0	0	0
<b>Histopathologic classification</b>			
Ductal	313 (70.5)	158 (71.2)	471 (70.7)
Lobular	68 (15.3)	30 (13.5)	98 (14.7)
Other	63 (14.2)	34 (15.3)	97 (14.6)
<b>Histologic Grade</b>			
1	52 (11.7)	18 (8.1)	70 (10.5)
2	205 (46.2)	108 (48.6)	313 (47.0)
3	100 (22.5)	49 (22.1)	149 (22.4)
<b>Stage at Initial Diagnosis</b>			
I	51 (11.5)	30 (13.5)	81 (12.2)
II	137 (30.9)	68 (30.6)	205 (30.8)
III	72 (16.2)	39 (17.6)	111 (16.7)
IV	138 (31.1)	72 (32.4)	210 (31.5)
Other/Unknown	46 (12.6)	13 (10.4)	59 (8.9)
<b>ECOG Performance Status</b>			
0	257 (57.8)	102 (45.9)	359 (53.9)
1	178 (40.1)	117 (52.7)	295 (44.3)
<b>Involved Disease Sites</b>			
Bone	325 (73.2)	162 (73.0)	487 (73.1)

Breast	137 (30.9)	74 (33.3)	211 (31.7)
Liver	75 (16.9)	46 (20.7)	121 (18.2)
Lung	150 (33.8)	71 (32.0)	221 (33.2)
Lymph Node	212 (47.7)	110 (49.5)	322 (48.3)
Other	115 (25.9)	64 (28.8)	179 (26.9)

Source: Modified from Study 1008 CSR Table 18, demog.xpt, and Table 14.1.2.5

***Reviewer Comment: There was a difference ( $\geq 5\%$ ) in baseline characteristics between treatment arms regarding ECOG performance status. This difference is unlikely to have affected the efficacy results.***

## Concomitant Medications and Subsequent Therapy

### Concomitant Medications

Most patients in both treatment arms received concomitant drug treatment during the study (429 [96.6%] of patients in the palbociclib plus letrozole arm vs 212 [95.5%] of patients in the placebo plus letrozole arm).

The following drug classes were reported in >10% higher percentages of patients in the palbociclib plus letrozole arm compared with the placebo plus letrozole arm: antibacterials for systemic use (47.5% vs 35.1%, respectively); otologicals (35.4% vs 23.0%, respectively); ophthalmologicals (65.1% vs 52.7%, respectively); immunostimulants (12.2% vs 0%, respectively); vasoprotectives (29.7% vs 17.6%, respectively); corticosteroids, dermatological preparations (29.5% vs 17.6%, respectively); ophthalmological and otological preparations (25.0% vs 14.0%, respectively); antibiotics and chemotherapeutics for dermatologic (26.8% vs 16.2%, respectively); nasal preparations (36.3% vs 25.7%, respectively); and gynecological anti-infectives and antiseptics (27.5% vs 17.1%, respectively).

Granulocyte colony stimulating factor was used only in patients on the palbociclib plus letrozole arm. The most common G-CSF agent used was filgrastim (8.6%). Other reported G-CSF agents included pegfilgrastim and lenograstim, used in 1.6% and 0.5% of patients, respectively.

### Subsequent Therapy

A total of 42.1% and 60.8% of patients in the palbociclib plus letrozole arm and placebo plus letrozole arm, respectively, had started a new anti-cancer therapy as follow-up systemic therapy. The anti-cancer therapies most commonly (>10% in at least 1 treatment arm) administered were fulvestrant (13.5% vs 21.6% of patients in the palbociclib plus letrozole and placebo plus letrozole arms, respectively), capecitabine (12.6% vs 17.6%, respectively), exemestane (10.1% vs 18.5%, respectively), everolimus (7.4% vs 13.5%, respectively), paclitaxel (8.8% vs 14.4%, respectively), and letrozole (7.4% vs 10.4%,

respectively). The most common reason for receiving follow-up systemic anti-cancer therapy was disease progression. There was only one reported instance where anti-cancer therapy was received prior to disease progression.

### Efficacy Results – Primary Endpoint

The primary analysis of PFS occurred when 331 progression events occurred in both arms. The results are displayed in Table 13 below. Figure 2 shows a Kaplan-Meier plot of PFS.

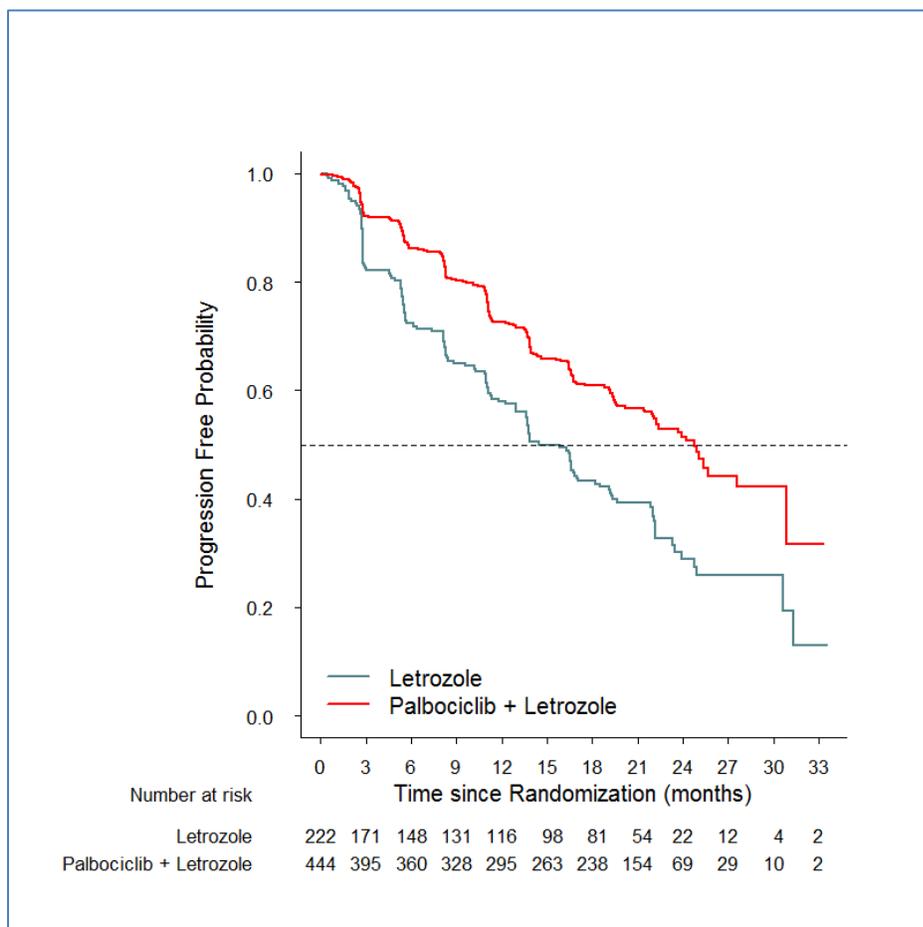
The results displayed in Table 13 correspond to the final PFS analysis. As described in the Statistical Analysis Plan section, the Applicant also conducted an interim analysis of PFS when 236 progression events had occurred. Based upon the results, however, the Data Monitoring Committee recommended that the study continue until the final PFS analysis since the results did not cross the pre-defined efficacy boundary

**Table 13: Primary Endpoint Results (PFS by investigator) for Study 1008**

	<b>Palbociclib plus Letrozole N=444</b>	<b>Placebo plus Letrozole N=222</b>
Events, n (%)	194 (43.7)	137 (61.7)
Censored, n (%)	250 (46.3)	85 (38.3)
Median, months (95% CI)	24.8 (22.1, NE)	14.5 (12.9, 17.1)
Hazard ratio, estimate (95% CI)	0.576 (0.463, 0.718)	
p-value	<0.0001	

*Source: Study 1008 CSR Table 20; NE = not estimable; The data cutoff for this analysis was February 26, 2016; The alpha allocation for the final analysis was 0.024987.*

**Figure 2: Kaplan-Meier Plot of Primary Analysis Results (PFS by investigator)**



Source: Reviewer's Analysis (dataset: eedrsp.xpt)

In addition to the PFS analysis conducted by the investigator, the sponsor subjected the PFS data to an independent review committee (BICR). The results of this analysis are shown in Table 14. A Kaplan-Meier plot of the BICR results is shown in Figure 3.

The BICR results showed good concordance with the primary PFS results. To examine this more rigorously, we estimated the early discrepancy rate (EDR) and late discrepancy rate (LDR) for each arm. The EDR and LDR are two ways to measure the differences between the primary investigator results and the secondary BICR results. By estimating the rates on each arm and then computing the difference, we can get a sense whether investigator bias exists in the primary results.

The EDR rate for the palbociclib + letrozole arm was 36.1% and the EDR rate on the letrozole arm was 40.1%. The LDR rate on the palbociclib + letrozole arm was 50.4% and the LDR rate on the letrozole arm was 45%. Since the EDR and LDR differences were approximately 5%, there

Clinical and Statistical Review NDA 207103/S-004 Ibrance (palbociclib)  
 Clinical – Suparna Wedam / Laleh Amiri-Kordestani  
 Statistical – Erik Bloomquist / Shenghui Tang

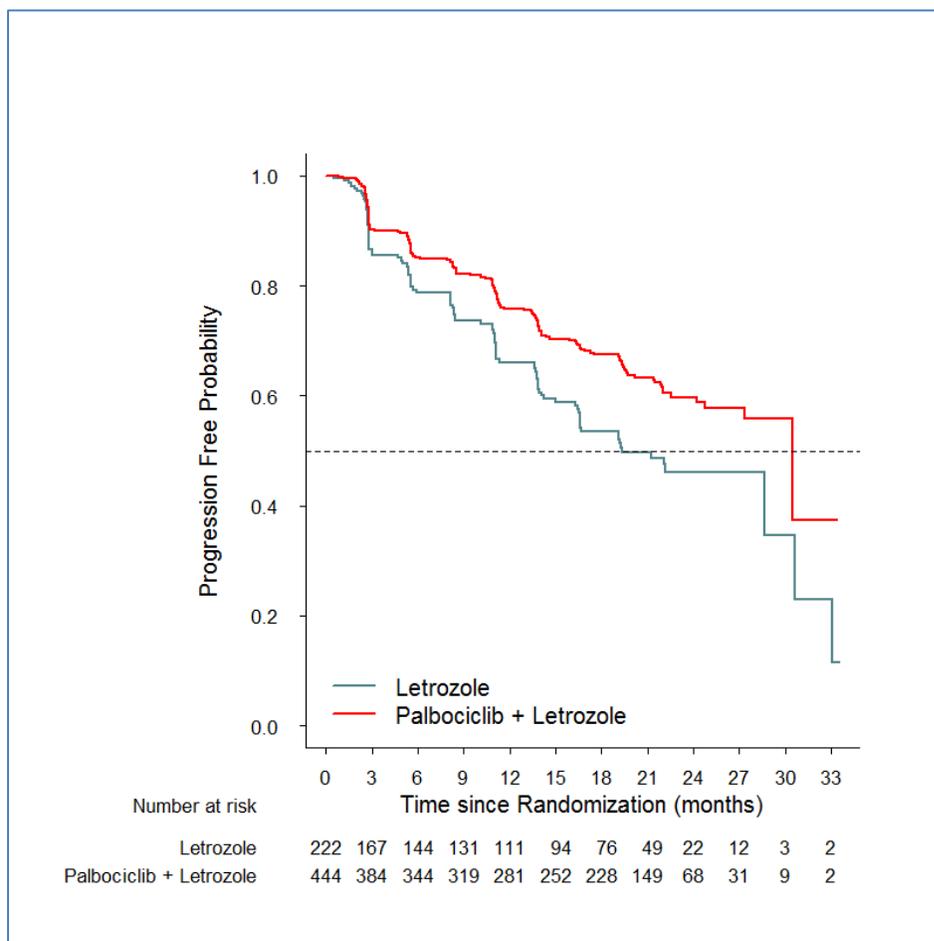
appears to be minimal bias in the primary PFS results.

**Table 14: Supportive PFS Results (PFS by BICR) for Study 1008**

	<b>Palbociclib plus Letrozole N=444</b>	<b>Placebo plus Letrozole N=222</b>
Events, n (%)	152 (34.2)	96 (43.2)
Censored, n (%)	292 (65.8)	126 (56.8)
Median, months (95% CI)	30.5 (27.4, NE)	19.3 (16.4, 30.6)
Hazard ratio, estimate (95% CI)	0.653 (0.505, 0.844)	
p-value	0.0005	

Source: Study 1008 CSR Table 23; NE = not estimable

**Figure 3: Kaplan-Meier Plot of Supportive PFS Results (PFS by BICR)**



Source: Reviewer's Analysis (dataset: eeiotb.xpt)

***Reviewer Comment: The final analysis for the primary endpoint of investigator assessed PFS demonstrated a statistically and clinically significant improvement in PFS with the addition of palbociclib to letrozole. In addition, the BICR results showed good concordance with the primary PFS results.***

Additional sensitivity analyses were done to assess the robustness of the PFS primary endpoint. An unstratified analysis of the primary endpoint gave a HR equal to 0.569 (95% CI: 0.457, 0.709). When patients were not censored for receiving new anti-cancer therapy, the HR equaled to 0.588 (95% CI: 0.473, 0.732). Finally, when excluding patients with any PPI (acid-reducing) or fasting conditions (see protocol amendment 2), the HR equaled 0.511 (0.380, 0.686).

Subgroup analysis results by age, race, and country for the primary PFS endpoint are shown in

Table 15. No outliers were observed across the three demographic categories.

**Table 15 Primary PFS Results by Subgroup (PFS by INV) for Study 1008**

	<u>N</u>	<u>HR</u>	<u>95% CI</u>
<b><u>AGE</u></b>			
< 65 Years Old	404	0.567	(0.434, 0.740)
>= 65 Years Old	262	0.571	(0.386, 0.843)
<b><u>RACE</u></b>			
White	516	0.576	(0.450, 0.739)
Asian	95	0.484	(0.269, 0.871)
<b><u>REGION</u></b>			
United States	197	0.759	(0.510, 1.131)
Elsewhere	469	0.502	(0.386, 0.652)

Source: Reviewer's Analysis (dataset: eedrsp.xpt, subvar.xpt)

### **Efficacy Results – Secondary and other relevant endpoints**

At the time of the primary PFS analysis, the Applicant also conducted an interim analysis of OS (data cutoff February 26, 2016). The results of this analysis demonstrated a hazard ratio equal to 1.22 (p-value = 0.22), with more deaths occurring on the palbociclib + letrozole arm (95 deaths, 21.4%) than the letrozole only arm (38 deaths, 17.1%). Based upon these results, the Agency asked for updated survival information to provide information that OS is not negatively impacted by the palbociclib.

Based upon the Agency's request, the sponsor submitted an additional 9 months of survival data (data cutoff November 24, 2016). The results are shown in Table 16 and the Kaplan-Meier plot of the results is shown in Figure 4. The results demonstrate no difference in overall survival between the two arms.

As illustrated in the Kaplan-Meier curve, there were more deaths in the control arm than the treatment arm prior to 24 months. To investigate reasons for this, the agency looked into

whether persons recruited prior to January 3, 2014 showed an imbalance in the OS results (as noted before, the study was amended in January 2014 to change the method of drug intake from fasting to with food). After analyzing the OS results, however, no meaningful differences were found between those enrolled prior to the amendment and after the amendment.

A final analysis was done to assess the posterior probability that the OS hazard ratio was less than 1. The analysis was done using a flat prior for the hazard ratio, and the likelihood was evaluated on the partial likelihood. At the time of the CSR report, the posterior probability that the OS HR was less than 1 was 13.5%. But with the additional information at the November 24, 2016 cutoff, the the posterior probability that the OS HR was less than 1 was 67.7%.

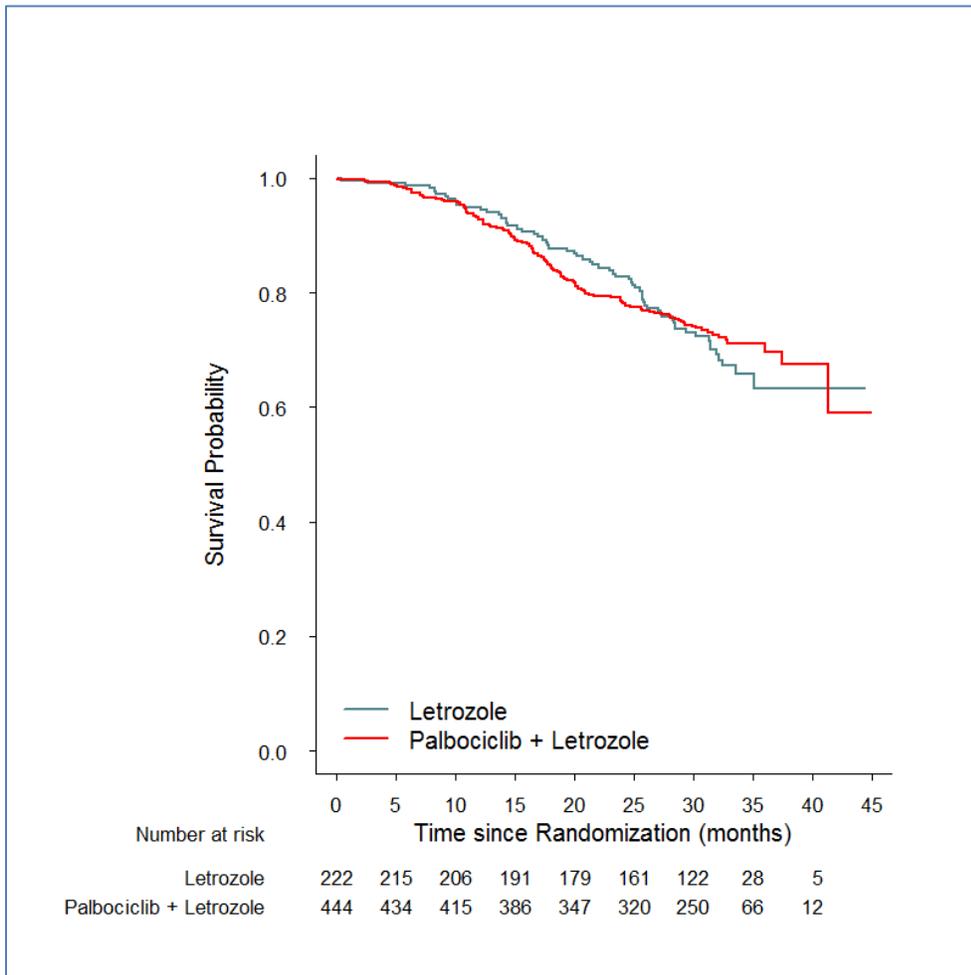
***Reviewer Comment: There was an imbalance in early deaths favoring the control arm based on the February 26, 2016 data cutoff. This result could be due to chance alone. The imbalance did not persist with the additional follow up (November 24, 2016 data cutoff). Overall survival will continue to be followed and the final OS results are being requested as a Postmarketing Commitment.***

**Table 16: OS Results for Study 1008**

	<b>Palbociclib plus Letrozole N=444</b>	<b>Placebo plus Letrozole N=222</b>
Deaths, n (%)	120 (27.0)	64 (28.8)
Censored, n (%)	324 (73.0)	158 (71.2)
Median, months (95% CI)	NE	NE
Hazard ratio, estimate (95% CI)	0.927 (0.684 – 1.256)	
p-value	0.31	

*Source: Sponsor IR response (February 16, 2017); The data cutoff for this analysis was November 24, 2016.*

**Figure 4: Kaplan-Meier Plot of OS Results (PFS by BICR)**



Source: Reviewer's Analysis (dataset: eesrv.xpt)

For patients with measurable disease, the palbociclib + letrozole arm had a confirmed ORR = 55.3% (95% CI = 49.9, 60.7). The letrozole only arm had a confirmed ORR = 44.4% (95% CI = 36.9, 52.2).

**Reviewer Comment: The ORR results further support the efficacy of palbociclib + letrozole over letrozole alone.**

**Dose/Dose Response**

Not Applicable.

### **Durability of Response**

These issues are addressed throughout the efficacy review given that the primary endpoint (PFS) of the trial is a time to event endpoint.

### **Persistence of Effect**

These issues are addressed throughout the efficacy review given that the primary endpoint of the trial is a time to event endpoint. The duration of response for the ORR also supports the primary endpoint results.

### **Additional Analyses Conducted on the Individual Trial**

#### **Biomarker Analysis**

Tissue samples from 568 of 666 randomized patients were suitable for biomarker testing and had results for analysis (Biomarker Analysis Population), including 379 samples from patients in the palbociclib plus letrozole arm and 189 samples from patients in the placebo plus letrozole arm. Expression of ER, Rb, CCND1, p16, and Ki67 (Table 17) were analyzed retrospectively at a Clinical Laboratory Improvement Amendments certified laboratory using validated IHC assays.

**Table 17: PFS by Biomarker Status in Study 1008**

		Median PFS (Months)		Hazard Ratio
		Palbociclib plus Letrozole	Placebo plus Letrozole	
ER	<b>Positive</b>			
	N	338	166	
	Estimate	24.9	16.3	0.571 (0.443, 0.737)
	95% CI	22.2, NR	12.9, 19.1	
	<b>Negative</b>			
	N	40	22	
Estimate	15.6	5.4	0.405 (0.218, 0.751)	
95% CI	8.3, 22.0	2.7, 11.1		
Rb	<b>Positive</b>			
	N	345	167	
	Estimate	24.2	13.7	0.531 (0.416, 0.680)
	95% CI	21.4, 25.7	11.0, 16.5	
	<b>Negative</b>			
	N	29	22	
Estimate	NR	18.5	0.675 (0.308, 1.481)	
95% CI	11.4, NR	2.9, NR		
CCND1	<b>Positive</b>			
	N	370	179	
	Estimate	24.8	13.8	0.555 (0.437, 0.705)
	95% CI	21.5, 27.6	11.3, 16.8	
	<b>Negative</b>			
	N	5	10	
Estimate	11.1	8.1	0.997 (0.287, 3.461)	
95% CI	2.2, 23.9	0.4, NR		
p16	<b>Positive</b>			
	N	305	161	
	Estimate	24.8	13.8	0.518 (0.400, 0.670)
	95% CI	21.5, NR	11.1, 16.8	
	<b>Negative</b>			
	N	59	25	
Estimate	16.8	13.8	0.731 (0.392, 1.364)	
95% CI	11.1, 24.9	8.1, NR		
p16	<b>H-Score&lt;175</b>			
	N	341	177	
	Estimate	23.7	13.8	0.581 (0.455, 0.742)
	95% CI	19.6, 25.7	11.2, 16.8	
	<b>H-Score≥175</b>			
	N	23	9	
Estimate	24.2	5.6	0.255 (0.100, 0.650)	
95% CI	11.1, NR	1.5, 19.1		
Ki67	<b>≤20%</b>			
	N	216	102	
	Estimate	27.6	16.8	0.530 (0.379, 0.742)
	95% CI	24.2, NR	13.7, 22.0	
	<b>&gt;20%</b>			
	N	152	83	
Estimate	17.5	8.4	0.569 (0.409, 0.791)	
95% CI	13.8, 22.0	5.6, 13.6		

---

Source: Tables 14.6.3.1.2, 14.6.4.1.2, 14.6.5.1.2, 14.6.6.1.2, 14.6.6.2.2, and 14.6.7.1.2  
Abbreviations: CCND1=Cyclin D1; CI=confidence interval; ER=estrogen receptor; N=number of patients;  
NR=not reached; Rb=retinoblastoma susceptibility gene product.  
a. Used a 2-sided unstratified log-rank test.  
b. Used unstratified Cox proportional hazards model.

Source: Study 1008 CSR pages 183-184

***Reviewer Comment: Biomarkers were listed as secondary endpoints in Study 1008; however, there was no alpha allocation for biomarker analyses in the statistical analysis plan. Palbociclib plus letrozole was favored regardless of biomarker status.***

### **Patient Reported Outcomes (PROs)**

PRO endpoints included: FACT-G total score, FACT-G subscales, BC subscale (BCS), FACT-B total score, trial outcome index (TOI), EQ-5D index score, EQ-VAS general health status score.

The FACT-B includes 5 subscale scores: physical well-being (PWB), social/family wellbeing (SWB), emotional well-being (EWB), functional well-being (FWB), and a breast cancer subscale (BCS). The EQ-5D index was derived by combining 1 level from each of the 5 dimensions and converting it to a single summary index or health utility value.

### **Patient Reported Outcomes Analyses**

The primary analysis set for the PRO endpoints was the ITT population. Some analyses were performed on the PRO evaluable population as appropriate.

The **FACT-B** produces 5 subscale scores: physical well-being (PWB), social/family wellbeing (SWB), emotional well-being (EWB), functional well-being (FWB), and a breast cancer subscale (BCS). These subscale scores are used to derive 3 assessment outcomes: FACT-B total score, FACT-G score, and TOI, which are calculated as follows:

- $\text{FACT-B total score} = \text{PWB} + \text{SWB} + \text{EWB} + \text{FWB} + \text{BCS}$ ;
- $\text{FACT-G total score} = \text{PWB} + \text{SWB} + \text{EWB} + \text{FWB}$ ;
- $\text{TOI score} = \text{PWB} + \text{FWB} + \text{BCS}$ .

The **EQ-5D index** was derived by combining 1 level from each of the 5 dimensions and converting it to a single summary index or health utility value.<sup>58</sup> Because the questions may be answered differently in different countries / regions due to different local customs and social perspectives, published weights from the EuroQol group were used in determining the country appropriate summary scores (EQ-5D User's Guide). The summary score was called the summary index or the health utility value. This study used the UK summary score which ranged from -

0.594 to 1 with lower scores corresponding to higher levels of dysfunction.

**FACT-G** is the sum of the scores from the 27 questions from the FACT-G domains. The FACT-G was summarized using means, medians, standard deviations, and 95% CIs at each assessment point, based on the observed values as well as changes from baseline both within group and between groups. Comparisons between treatment arms were based on a repeated measures analysis using a mixed effects model. The variables in the model were treatment, time, treatment-by-time, with baseline as covariate. The minimally important difference (MID) for FACT-G is 5-6 points. In fitting the mixed model, time was used as a continuous variable and the method of restricted maximum likelihood was used assuming an unstructured covariance matrix. No adjustments for multiple comparisons were made.

The 4 **FACT-G subscales**, called domains, are Physical, Social/Family, Emotional, and Functional well-being (PWB, SWB, EWB, FWB, respectively). Analysis of the FACT-G subscales followed the same methodology as for FACT-G total score except for the time to deterioration (TTD) analysis which was not carried out for the 4 individual domains. The MID for the FACT-G subscales is 2-3 points.

**FACT-G Subscales** consists of 10 items associated with BC. Analysis of BCS followed the same methodology as for FACT-G. The MID for BCS is 2-3 points.

**FACT-B** questionnaire consists 37 items (27 items from FACT-G and the 10 from BCS). Analysis of FACT-B followed the same methodology as for FACT-G. The MID for FACT-B is 7-8 points.

The **TOI** is defined as the sum of (PWB+FWB+BCS) making it 24 items altogether. Analysis of TOI followed the same methodology as for FACT-G. The MID for TOI is 5-6 points.

The **EQ-5D** index was derived by combining 1 level from each of the 5 dimensions and converting it to a single summary index or health utility value.

Descriptive statistics were calculated for the **EQ-5D VAS scores**. Comparisons between treatment arms were based on a repeated measures analysis using a mixed effects model. The variables in the model were treatment, time, treatment-by-time, with baseline as covariate.

**TTD** was carried out using survival analysis methods including Kaplan-Meier plots and log-rank tests to compare the 2 treatment arms. Deterioration was defined as a decrease of a prespecified number of points based on MID. This analysis was carried out for the variables BCS, FACT-B, FACT-G, and TOI, and the prespecified decreases from baseline were 2, 7, 5, and 5 points, respectively. The HR and its 95% CI, assuming proportional hazards, was calculated and the log-rank test was performed comparing the 2 treatment arms.

Table 18 displays completion rates for the FACT-B and EQ-5D instruments at each cycle.

***Reviewer Comment: Completion rates for the FACT-B and EQ-5D were good. In nearly all***

***cycles (except for one), 95-100% of patients remaining on the trial answered at least one question on both the FACT-B and EQ-5D instruments.***

Below is a listing of results from instruments as well as time-to-deterioration analysis.

**Table 18: Completion rates for the FACT-B and EQ-5D instruments at each cycle -Study 1008**

n (%)	Eligible Patients		FACT-B		EQ-5D	
	Palbo + Let	Let	Palbo + Let	Let	Palbo+ Let	Let
BASELINE	444 (100)	222 (100)	441 (99.3)	221 (99.5)	439 (98.9)	221 (99.5)
CYCLE2	436 (98.2)	218 (98.2)	426 (97.7)	214 (98.2)	422 (96.8)	215 (98.6)
CYCLE3	428 (96.4)	207 (93.2)	421 (98.4)	205 (99.0)	419 (97.9)	204 (98.6)
CYCLE5	397 (89.4)	175 (78.8)	393 (99.0)	172 (98.3)	392 (98.7)	172 (98.3)
CYCLE7	367 (82.7)	158 (71.2)	363 (98.9)	153 (96.8)	362 (98.6)	152 (96.2)
CYCLE9	359 (80.9)	149 (67.1)	352 (98.1)	146 (98.0)	353 (98.3)	147 (98.7)
CYCLE11	329 (74.1)	136 (61.3)	324 (98.5)	134 (98.5)	324 (98.5)	134 (98.5)
CYCLE13	291 (65.5)	124 (55.9)	284 (97.6)	120 (96.8)	284 (97.6)	120 (96.8)
CYCLE15	282 (63.5)	116 (52.3)	277 (98.2)	113 (97.4)	277 (98.2)	113 (97.4)
CYCLE17	261 (58.8)	102 (45.9)	253 (96.9)	100 (98.0)	253 (96.9)	100 (98.0)
CYCLE19	238 (53.6)	91 (41.0)	233 (97.9)	89 (97.8)	233 (97.9)	89 (97.8)
CYCLE21	221 (49.8)	85 (38.3)	216 (97.7)	84 (98.8)	216 (97.7)	83 (97.6)
CYCLE23	170 (38.3)	77 (34.7)	162 (95.3)	75 (97.4)	163 (95.9)	75 (97.4)
CYCLE25	113 (25.5)	46 (20.7)	111 (98.2)	46 (100)	110 (97.3)	46 (100)
CYCLE27	67 (15.1)	27 (12.2)	65 (97.0)	26 (96.3)	65 (97.0)	26 (96.3)
CYCLE29	33 (7.4)	17 (7.7)	33 (100)	17 (100)	33 (100)	17 (100)
CYCLE31	19 (4.3)	10 (4.5)	19 (100)	10 (100)	19 (100)	10 (100)
CYCLE33	9 (2.0)	5 (2.3)	9 (100)	4 (80.0)	9 (100)	4 (80.0)
CYCLE35	4 (0.9)	2 (0.9)	4 (100)	2 (100)	4 (100)	2 (100)
CYCLE37	3 (0.7)	2 (0.9)	3 (100)	2 (100)	3 (100)	2 (100)
<b>EOT</b>	<b>223 (50.2)</b>	<b>154 (69.4)</b>	<b>185 (83.0)</b>	<b>133 (86.4)</b>	<b>185(83.0)</b>	<b>132(85.7)</b>

Source: CSR section 11.4.10;

**FACT-G Total score:** No differences were observed between treatment arms (78.8 [95% CI 77.8, 79.9] vs. 78.7 [95% CI: 77.1, 80.3]) in overall FACT-G total score. The same analysis was also

carried out on change from baseline FACT-G scores, resulting in identical between-treatment differences, and showed the model estimated overall change from baseline FACT-G scores to be -0.39 (95% CI: -1.46, 0.68) for the palbociclib plus letrozole arm and -0.53 (95% CI: -2.08, 1.02) for the placebo plus letrozole arm.

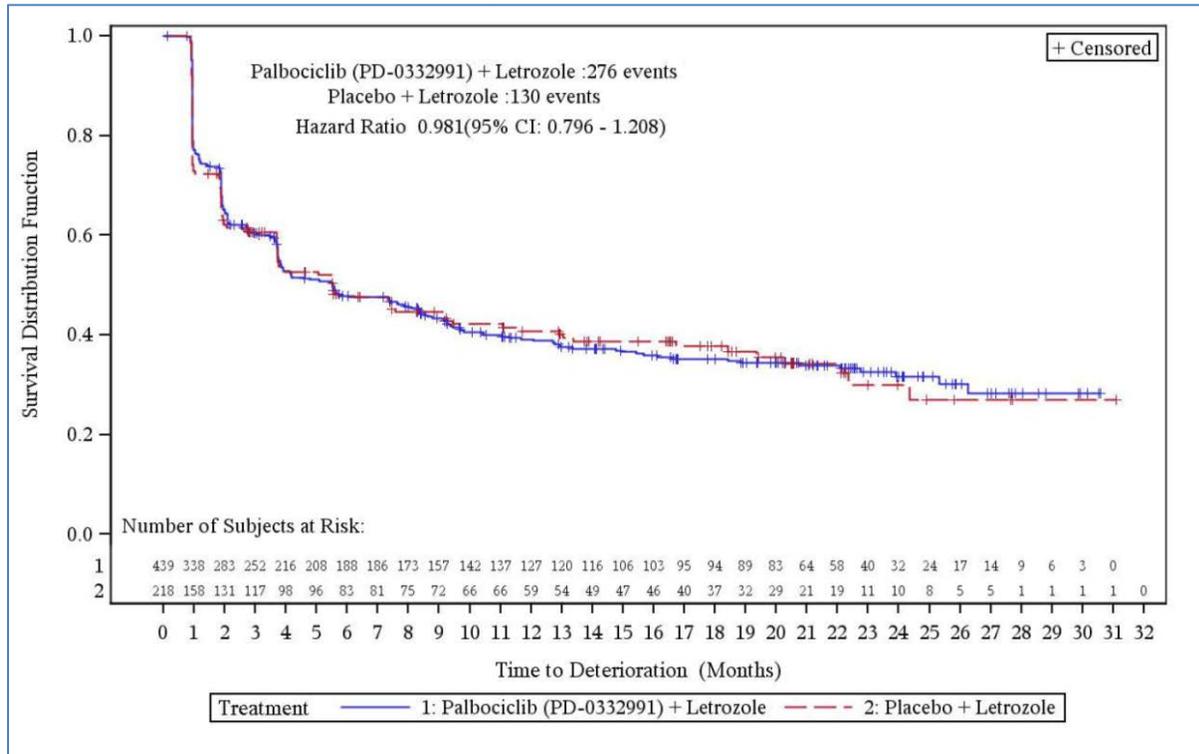
**FACT-B total:** No differences were observed between treatment arms (103.4 [95% CI 102.1, 104.7] vs. 103.7 [95% CI: 101.9, 105.6]) in overall FACT-B total score. The same analysis was also carried out on change from baseline FACT-B scores, resulting in identical between-treatment differences, and showed the model estimated overall change from baseline FACT-B scores to be -0.11 (95% CI: -1.42, 1.21) for the palbociclib plus letrozole arm and 0.22 (95% CI: -1.68, 2.12) for the placebo plus letrozole arm.

**EQ-5D:** No differences were observed in the overall EQ-5D index score on treatment between the palbociclib plus letrozole arm compared with the placebo plus letrozole arm (0.74 [95% CI: 0.72, 0.75] vs 0.71 [95% CI: 0.69, 0.73]).

**EQ-VAS:** No difference between treatment arms was found in overall VAS score and change from baseline in VAS scores.

**Time to Deterioration:** A time-to-deterioration analysis was done for the FACT-B and FACT-G scores. For the FACT-G score, deterioration was defined to be a drop of at least 5 points. For the FACT-B score, deterioration was defined to be a drop of at least 7 points in the total score. When analyzing this time-to-event data using a Cox Proportional hazards model, no difference was observed between the two treatment arms (FACT-G HR= 0.981 (95% CI: 0.796, 1.208); FACT-B HR = 1.042 (95% CI: 0.838, 1.295)). Figure 5 and Figure 6 display Kaplan-Meier results of the time-to deterioration analyses.

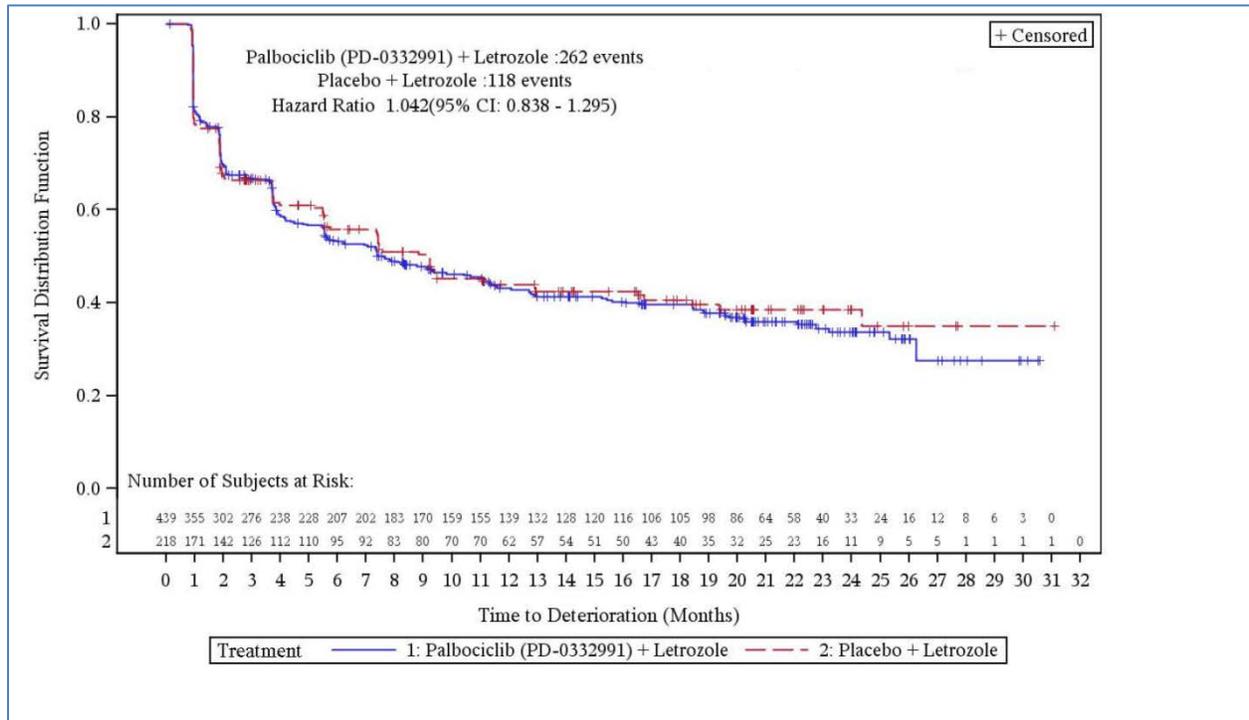
**Figure 5: Time To Deterioration Analysis of FACT-G**



Source: CSR Figure 14.5.5.1.

1. Time to deterioration was considered a drop of 5 points.

**Figure 6 : Time To Deterioration Analysis of FACT-B**



Source: CSR Figure 14.5.5.3.

1. Time to deterioration was considered a drop of 7 points.

**Reviewer Comment:** PROs were listed as secondary endpoints in Study 1008; however, there was no alpha allocation for PRO analyses in the statistical analysis plan, therefore any results should be considered exploratory. Baseline scores were similar between the 2 treatment arms for BC-specific health-related quality of life as measured by the FACT-B questionnaire. There was no difference in any of the PRO endpoints between treatment arms.

## **7 Integrated Review of Effectiveness**

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### **7.1. Assessment of Efficacy Across Trials**

#### **7.1.1. Primary Endpoints**

Not applicable since this sNDA is supported by a single study.

#### **7.1.2. Secondary and Other Endpoints**

Not applicable since this sNDA is supported by a single study.

#### **7.1.3. Subpopulations**

Not applicable since this sNDA is supported by a single study.

#### **7.1.4. Dose and Dose-Response**

Not applicable since this sNDA is supported by a single study.

#### **7.1.5. Onset, Duration, and Durability of Efficacy Effects**

Not applicable since this sNDA is supported by a single study.

### **7.2. Additional Efficacy Considerations**

#### **7.2.1. Considerations on Benefit in the Postmarket Setting**

Not applicable.

#### **7.2.2. Other Relevant Benefits**

##### **Palbociclib in combination with other aromatase inhibitors**

The Applicant provided an analysis of the DDI potential of combining palbociclib with the aromatase inhibitors (AIs), anastrozole and exemestane. A clinically significant drug interaction between anastrozole or exemestane and palbociclib is not expected based on analyses of the potentials of palbociclib, anastrozole, and exemestane as a perpetrator or a victim.

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The following information was provided from the Applicant in an Information Request dated 12/23/2016.

Palbociclib in combination with anastrozole:

A single-arm Phase 2 neoadjuvant study of palbociclib in combination with anastrozole has completed. Patients with estrogen receptor (ER)-positive, HER2-negative breast cancer were to be treated with anastrozole alone (1 mg orally once daily) for 28 days (Cycle 0). Palbociclib (125 mg once daily, Schedule 3/1; 3 weeks on treatment, 1 week off treatment) was then to be administered with anastrozole for 4 cycles (Cycles 1-4). The primary endpoint was complete cell cycle arrest (CCCA), defined as Ki67 <2.7% at Cycle 1 Day 15. Fifty patients were treated in this study with 45 patients evaluable for the primary endpoint. The most common all-causality AEs with the combination of palbociclib plus anastrozole was neutropenia (all grades: 56%; Grades 3 or 4: 26%), leukopenia (all grades; 46%; Grades 3 or 4: 0%), and fatigue (all grades: 40%; Grades 3 or 4: 0%). There were no reports of febrile neutropenia. Seven patients (14%) required 1 palbociclib dose reduction associated with AEs.

A second study evaluating the palbociclib plus anastrozole combination is the ongoing double-blind Phase 3 CRC study PENELOPE-B (GBG 078/NSABP B 54 1/BIG 1 13, NCT01864746), a study in patients with HR-positive, HER2 negative primary breast cancer with high relapse risk after neoadjuvant chemotherapy (N=366 as of February 2016). On January 25, 2016, the Applicant received confirmation that the external data monitoring committee (E-DMC) had evaluated the ongoing study and recommended it proceed as planned. A review of the Sponsor's safety database for this study has not identified any new safety signals. All other safety and efficacy data remain blinded for this ongoing study and are not anticipated to be available during the 1008 sNDA submission review cycle.

Palbociclib in combination with exemestane:

PEARL (Spanish Breast Cancer Research Group, NCT02028507), is an ongoing study evaluating the safety and efficacy of the combination of exemestane and palbociclib (N=229 as of February 2016). In December 2016, the Sponsor received confirmation that the E-DMC has recommended the study proceed as planned. A review of the Sponsor's safety database for this study has not identified any new safety signals. All other safety and efficacy data are not anticipated to be available during the 1008 sNDA submission review cycle.

***Reviewer Comments: Replacing “letrozole” with “aromatase inhibitor” in the indication appears acceptable based on the minimal potential for clinically significant DDI between aromatase inhibitors and palbociclib and results from the ongoing clinical studies (as outlined above). All three aromatase inhibitors (letrozole, anastrozole, exemestane) are used as first-line treatment of postmenopausal women with HR-positive advanced/metastatic breast cancer. Broadening the indication to use palbociclib in combination with any aromatase***

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***inhibitor provides flexibility to both patients and physicians to make therapeutic decisions based on the individual patient's prior adjuvant endocrine therapy, time to progression on prior therapy, and tolerance of the therapies' known potential side effects.***

### 7.3. **Integrated Assessment of Effectiveness**

Not applicable as the primary efficacy evaluation for palbociclib was based on one trial, PALOMA-2 as described in sections 7.1.

## **8 Review of Safety**

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### **8.1. Safety Review Approach**

In this sNDA, the Applicant submitted safety data from Study 1008, a Phase 3 trial of palbociclib plus letrozole versus placebo plus letrozole, with the original submission. A total of 444 patients were randomized and received palbociclib in Study 1008. Adverse events were assessed during the treatment period and for 28 days after the last dose of study drug. The incidence and severity of the adverse events were compared to prior and ongoing clinical trials with palbociclib.

Table 19 outlines the safety studies submitted with the sNDA, as well as the data cut-offs for Initial Submission and the 90-Day Safety Update. This studies listed in the table are Pfizer-sponsored studies.

**Table 19: Summary of Safety Populations Submitted with sNDA**

Study	Design	Population	N*	Status	SCS Cut-off	SU Cut-off
A5481008 <sup>1</sup>	Phase 3 R	Advanced Breast Cancer	444 <sup>2</sup> (444)	Completed	2/28/2016	8/31/2016
A5481010	Phase 1/2	Advanced solid tumors	48 (48)	Completed	2/28/2016	8/31/2016
A5481003	Phase 1/2	Advanced Breast Cancer	95 (95)	Completed	2/28/2016	8/31/2016
A5481034	Expanded Access	Advanced Breast Cancer	291 (334)	Ongoing	2/28/2016	8/31/2016
A5481053	Phase 3	Advanced solid tumors	86 (159)	Ongoing	2/28/2016	8/31/2016
A5481019	Phase 1	Advanced Breast Cancer	18 (26)	Ongoing	2/28/2016	8/31/2016
A5481023 <sup>1</sup>	Phase 3 R	Advanced Breast Cancer	345 <sup>2</sup> (345)	Completed	2/28/2016	8/31/2016
A5481013	Phase 1	Impaired Hepatic Function	18 (26)	Ongoing	2/28/2016	8/31/2016
A5481037	Expanded Access	Advanced Breast Cancer	66	Ongoing	Not included	8/31/2016
A5481053	Expanded Access	Advanced Breast Cancer	30	Ongoing	Not included	8/31/2016
A5481044	Phase 2 R	Head and Neck	20	Ongoing	Not included	8/31/2016
A5481059	Phase 1b	Pancreatic	19	Ongoing	Not included	8/31/2016

SCS=Summary of Clinical Safety submitted with sNDA; SU=90 day Safety Update

\*N=number of patients at SCS (number of patients with SU), R=randomized

<sup>1</sup>Blinded therapy<sup>2</sup> Number of patients randomized to palbociclib therapy at time of SCS (updated number from SU in parentheses)

Safety data from 8 Pfizer-sponsored Phase 1-3 clinical studies were included in the Summary of Clinical Safety submitted in the initial sNDA. This comprised of a total of 1902 patients/subjects

of whom 1884 patients were women with advanced breast cancer, and 18 subjects were those with hepatic impairment receiving single doses of palbociclib in Study 1013. Of the 1884 patients, approximately 1327 (70.4%) received at least 1 dose of palbociclib 125 mg QD on Schedule 3/1 in combination with endocrine therapy (either letrozole or fulvestrant with or without goserelin), comprising the target population receiving the recommended palbociclib dosing regimen.

The 90-Day Safety Update provided cumulative safety information as of August 31<sup>st</sup>, 2016 for those studies that were included in the original sNDA as well as four ongoing Pfizer-sponsored clinical studies of palbociclib (Study 1037, Study 1053, Study 1044, and Study 1059).

## **8.2. Review of the Safety Database**

### **8.2.1. Overall Exposure**

The duration of exposure to palbociclib or placebo plus letrozole in Study 1008 as of August 31, 2016 is summarized in Table 20 below.

**Table 20: Summary of Patient Exposure to Palbociclib and Letrozole in Study 1008**

	Palbociclib plus Letrozole (n= 444)		Placebo plus Letrozole (n=222)	
	Palbociclib	Letrozole	Placebo	Letrozole
Median number of cycles (range)	22 (1-44)	22 (1-45)	15 (1-45)	15 (1-45)
Median treatment duration in days (range)	610.5 (1-1218)	670 (1-1218)	413 (10-1262)	420 (10-1262)
Patients dose reduction (%)	167 (37.6)	N/A <sup>1</sup>	3 (1.4)	N/A <sup>1</sup>
Patients with temporary dose discontinuation	304 (68.5)	238 (53.6)	95 (42.8)	101 (45.5)
Patients with cycle delay (%) <sup>2</sup>	311 (70)	--	67 (30.2)	--
Mean total dose in mg (SD)	47106.6 (28165.5)	1476.8 (808.5)	43763 (30832.9)	1176.4 (826.8)
Median total dose in mg (range)	46762.5 (125-112875)	1643.8 (2.5-3035)	39187.5 (1250-115875)	1043.8 (25-3120)
Mean relative dose intensity (SD) <sup>3</sup>	86.5 (14.7)	99.1 (2.4)	98.2 (5.5)	99.2 (2.0)
Median relative dose intensity (range)	92.4 (40.3-109.5)	99.9 (73.4-100.2)	99.6 (56.1-102.9)	100 (79-100)

N/A=not applicable

<sup>1</sup> Protocol did not allow for letrozole dose adjustment, but temporary dosing discontinuation due to letrozole-related toxicity was allowed

<sup>2</sup> Cycle delay defined as any delay of the cycle start beyond 31 days for any given cycle

<sup>3</sup> Relative dose intensity = (actual dose intensity/intended dose intensity)\*100%

Source: 90-Day Safety Update, Tables 3-6, page 28-29

***Reviewer Comment: The median duration of therapy and median number of cycles administered was longer in the palbociclib plus letrozole arm vs. placebo plus letrozole arm highlighting the fact that patients were on treatment longer in the palbociclib plus letrozole arm due to a lower rate of disease progression.***

### 8.2.2. Relevant characteristics of the safety population:

Demographic information for the 666 patients in Study 1008 is included in Section 5.1.2.

### 8.2.3. Adequacy of the safety database:

The safety database from the 444 patients treated with palbociclib on Study 1008 is adequate.

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

Overall, data quality for this study was generally acceptable. Case report forms (CRFs) were reviewed and compared to the datasets and the patient narratives as needed.

### 8.3.2. Categorization of Adverse Events

An AE was any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event did not necessarily need to have a causal relationship with the treatment or usage. Worsening of signs and symptoms of the malignancy under study were to be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods was not to be reported as an AE.

An SAE was any untoward medical occurrence at any dose that resulted in death, was life-threatening (immediate risk of death), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions) or resulted in congenital anomaly/birth defect.

All AEs and SAEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 and AEs were graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 criteria. AEs were summarized by MedDRA primary system organ class (SOC), and by Preferred term (PT). Treatment emergent adverse events were defined as events reported up to 30 days after the last dose of study medication.

Because the frequency of certain medical events may be underestimated by reliance on a single MedDRA (PT), certain PTs representing a similar medical event were analyzed by the Applicant in aggregate using cluster terms (shown in uppercase letters). A list of these cluster terms along with PTs included in each cluster term is provided as follows:

ANEMIA: PTs of Anemia, Hematocrit decreased, and Hemoglobin decreased

HYPERGLYCEMIA: PTs of Blood glucose increased, Diabetes mellitus, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Diabetes mellitus inadequate control, Glycosylated hemoglobin increased, and Hyperglycemia

INFECTIONS: all PTs within the MedDRA SOC Infections and infestations

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LEUKOPENIA: PTs of Leukopenia and White blood cell count decreased

LYMPHOPENIA: PTs of Lymphopenia and Lymphocyte count decreased

NEUTROPENIA: PTs of Neutropenia and Neutrophil count decreased

PULMONARY EMBOLISM: PTs of Pulmonary artery thrombosis, Pulmonary embolism, and Pulmonary thrombosis

RASH: PTs of Dermatitis, Dermatitis acneiform, Rash, Rash erythematous, Rash maculo-papular, Rash papular, Rash pruritic, and Toxic skin eruption

STOMATITIS: PTs of Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, and Stomatitis

THROMBOCYTOPENIA: PTs of Platelet count decreased and Thrombocytopenia.

### 8.3.3. Routine Clinical Tests

In Study 1008, routine laboratory analyses included hemoglobin, WBC, neutrophils, lymphocytes, platelet count. BUN (or urea), creatinine, albumin, AST/ALT, total bilirubin, alkaline phosphatase, LDH, sodium, potassium, calcium, magnesium, albumin and hemoglobin A1c) were obtained at screening, Day 1 and 14 of cycles 1 and 2 and day 1 of cycles  $\geq 3$  and end of treatment visit.

Physical Examination included an examination of all major body systems, height (at screening only), weight, blood pressure and pulse rate at screening and, Day 1 of Cycles 1 and 2. Symptom-directed physical examinations, blood pressure and pulse rate were performed at subsequent visits.

After approval of Amendment #3, all newly enrolled patients underwent an ophthalmic examination at baseline, and on study treatment after 3 months (Cycle 4 Day 1), 6 months (Cycle 7 Day 1), 12 months (Cycle 13 Day 1), and every 12 months thereafter, and at the End of Treatment visit. The ophthalmic examinations included best corrected distant visual acuity (Snellen), refractive error associated with best corrected distant visual acuity, intraocular pressure (IOP – one reading), slit lamp biomicroscopy of the anterior segment including cell count and flare grading, crystalline lens grading using the Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading procedure, and fundoscopy.

Triplicate 12-Lead ECG performed on Day 1 of Cycles 4, 7, and 10. ECGs beyond Cycle 10 performed as clinically indicated.

Patients eligible for the ECG sub-study had ECGs on the day preceding treatment initiation (Day 0) at time 0 (time of first ECG also referred to as ECG1) and then 2, 4, 6, and 8 hrs after ECG1, and on Day 14 of Cycle 1 pre-dose (0 hrs) and 2, 4, 6, and 8 hrs following palbociclib administration. Additionally, triplicate ECGs for safety monitoring at 0 hour (pre-dose) on Day 1 of Cycle 1\*, Day 14 of Cycle 2, then on Day 1 of Cycles 4, 7, and 10 were also collected.

## Deaths

**Deaths on Study 1008:** As of February 26, 2016, 10 patients (2.3%) in the palbociclib plus letrozole arm and 4 patients (1.8%) on the placebo plus letrozole arm died during the study treatment period of Study 1008. A review of the narratives for the 14 patients was performed. The cause for death included disease progression, acute myocardial infarction, cardiogenic shock, cardiopulmonary failure, cardiovascular insufficiency, pulmonary embolism, respiratory failure, lower respiratory tract infection, bacterial peritonitis and pneumonia. Per investigator assessment, there was one treatment related death in both treatment arms. This included a death due to pneumonia in the palbociclib/letrozole treatment arm and a death due to pulmonary embolism in the placebo/letrozole treatment arm. The death events are summarized in Table 21.

An additional 19.1% of patients in the palbociclib plus letrozole arm and 15.3% of patients in the placebo plus letrozole arm died during the follow-up period (deaths that occurred more than 28 days after the last dose of study drug), as of the data cutoff date of February 26, 2016. The leading cause of death in both arms was disease progression (78 of 85 in the palbociclib/letrozole arm and 32 of 34 in the placebo/letrozole arm).

**Table 21: Deaths on Study 1008 (2/26/2016 Data Cut-off)**

	<b>Palbociclib+ Letrozole N=444 n (%)</b>	<b>Placebo + Letrozole N=222 n (%)</b>
<b>Patients who Died</b>	95	38
Disease Progression	81	34
Other	14	4
<b>Within 28 Days of Last Dose</b>		
Disease Progression	3	2
Study Drug Toxicity	1	1
Other	7	2
<b>After 28 days of Last Dose</b>		
Disease Progression	78	32
Other	7	2

The Applicant collected information concerning the cause of death in both a case report form (CRF) as well as detailed safety narrative summaries. Using the data from these sources, the causality for death appeared appropriate in all cases. There were two cases (death of Subjects (b) (6) and (b) (6)) in which IRs were sent to the Sponsor to further explain causality,

these cases are summarized below.

**Subject** (b) (6): This was a 58-year-old Caucasian who received palbociclib and letrozole from (b) (6). On (b) (6), the subject felt weakness and cold and experienced an acute respiratory viral infection. The subject died (b) (6). No autopsy or relevant labs/examinations were performed.

**Subject** (b) (6): This was a 74-year-old Caucasian woman who received palbociclib from (b) (6) to (b) (6) and letrozole from (b) (6) to (b) (6). It was reported that on (b) (6) the subject was going to visit the site for cycle 7, but she felt bad and died after several minutes. The diagnosis of thromboembolia of pulmonary artery was initially made basing on clinical findings at the time of death on (b) (6) and then confirmed by autopsy report results on (b) (6) (which was not available, autopsy results were provided to the site by phone). The investigator and Sponsor both felt there was not a reasonable possibility that the reported fatal thromboembolus of pulmonary artery was related to palbociclib, letrozole or any clinical trial procedure.

**Reviewer Comment:** *The Safety Report for Subject (b) (6) states that “Unless alternative information is provided, at present, the event death, cause unknown, is assessed as related to blinded study drug (unblinded=palbociclib) and letrozole...” However, this was not captured as a treatment related death as seen on Table 50 in the CSR. It is not clear why there was not a reasonable possibility the death due to fatal thromboembolus in Subject (b) (6) was related to palbociclib. An IR was sent to the Sponsor to provide clarification regarding the relatedness of death for these two cases.*

*For Subject (b) (6), the investigator was informed of the patient’s death by one of the patient’s relatives. The possibility of a preceding acute respiratory viral infection was raised by the patient’s relative but could not be confirmed. No autopsy or death certificate was provided to the site to shed any additional light on a possible cause of death. The patient’s death was not considered to be related to blinded study medication (palbociclib or placebo) by the investigator, nor to letrozole, concomitant drugs, or to a clinical trial procedure. Given the very limited, unconfirmed clinical information provided, the Sponsor is unable to provide a relatedness assessment in this case that is based on a medical rationale. In addition, the Sponsor noted that treatment relatedness in aggregate reports is based on the investigator’s causality assessment, not the Sponsor’s causality assessment.*

*For Subject (b) (6) the Sponsor states that while it is correct that pulmonary embolism is listed under the Warnings and Precautions section for the IBRANCE label, pulmonary embolism has never been considered by the Sponsor to be an adverse drug reaction of palbociclib. The Sponsor maintains that this patient’s multiple risk factors for pulmonary embolism significantly contributed to the reported event and its outcome, and that there is*

***currently insufficient evidence to consider palbociclib to be causally related to venous thromboembolic events, such as pulmonary embolism.***

The additional 5 patient deaths on study in the palbociclib plus letrozole arm not due to disease progression are summarized below:

**Subject** (b) (6): 70-year-old White woman with advanced breast cancer (bone metastases) died of Cardiovascular insufficiency on Day 435 (Cycle 16) with the event onset having occurred on the same day. Relevant medical history included arterial hypertension and atherosclerotic cardiovascular disease. The patient died in the clinic hallway while waiting to receive an intramuscular injection of meloxicam for her shoulder pain (metastases not confirmed). Autopsy was performed and based on the results the medico-legal diagnosis was atherosclerotic heart disease complicated by acute cardiovascular insufficiency. The investigator considered there was not a reasonable possibility that the reported cardiovascular insufficiency was related to study treatment.

**Subject** (b) (6): 78-year-old White woman with advanced breast cancer (lung metastases) died of Pneumonia and Respiratory failure on Day 424. The onset of events occurred 8 days before death and the patient received her last treatment 8 days before her death. The patient was hospitalized after she developed pneumonia, respiratory distress, and anemia. There was general deterioration of health since the beginning of hospitalization, with increased C-reactive protein, worsening neutropenia, and dyspnea. The patient died thereafter in the intensive care unit. The investigator considered there was a reasonable possibility that the reported Pneumonia was related to study treatment.

**Subject** (b) (6): 67-year-old White woman with advanced breast cancer (bone metastases) died of Cardiogenic shock (origin unknown) on Day 2 (Cycle 1); the event onset occurred the same day. Relevant medical history included hypothyroidism and hypertension. After taking antihypertensive medications, the patient experienced a malaise and fell down without loss of consciousness. She was immediately brought to the hospital. On the day of her death, she experienced a shock of an unknown origin accompanied by multiorgan failure. The patient's initial cardiac arrest, which was overcome by adrenaline administration and cardiac massage, was followed by a second cardiac arrest resulting in death. The autopsy results revealed cardiogenic shock of unknown origin, no profound infection, bilateral pleural metastases, and calcified amorphous tumor of the heart. The investigator considered there was not a reasonable possibility that the reported Cardiogenic shock of unknown origin was related to study treatment.

**Subject** (b) (6): 81-year-old White woman with advanced breast cancer died of cardiopulmonary failure on Day 214 with the event onset occurring the same day. She received her last dose of palbociclib on Day 161 and letrozole on Day 190. The patient was permanently discontinued from the study approximately 3 weeks before death and entered in-home hospice

care for declining status. The investigator considered there was not a reasonable possibility that the reported cardiopulmonary failure was related to study treatment. The event was likely a clinical consequence of end-stage disease.

**Subject** (b) (6): A 51-year-old White woman with advanced breast cancer died of Myocardial infarction on Day 317 and the event onset occurred on Day 289 (Cycle 11). The patient was permanently discontinued from treatment before death, although information on the exact timing of last dose was not provided. Relevant medical history included anemia, neutropenia leukopenia, coronary heart disease, arterial hypertension, exertional angina, and weight gain. The autopsy revealed acute transmural myocardial infarction of the left ventricle posterior wall and cardiogenic pulmonary edema. The investigator considered there was not a reasonable possibility that the reported Myocardial infarction was related to study treatment.

There was one additional death reported (Subject (b) (6)) with the 90 day Safety update (August 31, 2016) that occurred within 28 days of last study treatment. The patient was randomized to palbociclib+letrozole arm and died of disease progression. As of the 90 day Safety Update (August 31, 2016), 113 patients (26%) in the palbociclib plus letrozole arm and 53 patients (24%) in the placebo plus letrozole arm had died. On further follow up as of a November 24, 2016 data cut off, 116 patients (26%) in the palbociclib plus letrozole arm and 59 patients (27%) in the placebo plus letrozole arm had died.

***Reviewer Comment: At the time of initial sNDA submission, 21.4% of patients in the palbociclib plus letrozole arm and 17.1% of patients in the placebo plus letrozole arm died, as of the data cutoff date of February 26, 2016. It is not clear what led to a higher rate (%) of deaths in the palbociclib plus letrozole arm at the initial data cutoff as it does not appear there was increased death due to toxicity. However, with further follow up, the rates are starting to equalize, 26% in the palbociclib plus letrozole arm and 27% in the placebo plus letrozole arm had died as of the November 24, 2016 data cut off. Overall survival is further discussed in Section 5.1.2 under secondary endpoints.***

#### **Deaths in the Industry-Sponsored Clinical Studies**

A total of 55 (2.5%) of the 2235 patients with malignant solid tumors, including advanced breast cancer, died on study in Pfizer-sponsored clinical trials of palbociclib as of August 31, 2016. A fatal SAE of disease progression was reported most commonly (22/55 [40.0% patients]) in cases of death on study in Pfizer-sponsored clinical studies of palbociclib. No clear pattern in the type and frequency of remaining fatal SAEs reported in these studies was observed.

In addition, a total of 40 of the 2953 enrolled patients with malignant disease, including breast cancer, died on study in IIR/CRC clinical studies as of August 31, 2016. Consistent with Pfizer-sponsored clinical studies, the most frequently reported fatal SAE across these IIR/CRC studies was disease progression (25 of the 40 patients).

### 8.3.5. Serious Adverse Events

Information within the CSR, 90-Day Safety Update, Applicant’s narrative summaries (CIOMS narratives), and the CRFs were used to analyze Serious Adverse Events. SAEs of any grade up to 28-days after the last dose of study therapy occurred in 95 (21.4%) patients receiving palbociclib plus letrozole and 31 (14%) of patients receiving placebo plus letrozole as seen in Table 22.

**Table 22: SAEs Occurring in  $\geq 2$  Patients by Descending Frequency in the Palbociclib plus Letrozole Arm of Study 1008 as of 8/31/2016**

	Palbociclib plus Letrozole N=444 (%)	Placebo plus Letrozole N=222 (%)
Any <sup>1</sup>	95 (21.4)	31 (14)
Infections	22 (5)	9 (4.1)
Febrile neutropenia	6 (1.4)	0
Acute kidney injury	4 (0.9)	0
Pleural Effusion	4 (0.9)	1 (0.5)
Pulmonary embolism	4 (0.9)	3 (1.4)
Pyrexia	4 (0.9)	0
Disease progression	3 (0.7)	0
Malignant melanoma <sup>2</sup>	3 (0.7)	0
ALT increased	2 (0.5)	0
Anemia	2 (0.5)	0
AST increased	2 (0.5)	0
Atrial fibrillation	2 (0.5)	0
Constipation	2 (0.5)	0
Deep vein thrombosis	2 (0.5)	1 (0.5)
Neutropenia	2 (0.5)	0
Pain	2 (0.5)	1 (0.5)
Acute pancreatitis	2 (0.5)	0
Pathological fracture	2 (0.5)	0
Pericardial effusion	2 (0.5)	0
Rash	2 (0.5)	0
Syncope	2 (0.5)	0
Vomiting	2 (0.5)	2 (0.9)

Source: 90-Day Safety Update, Table 26, pages 76

<sup>1</sup>Any SAE without consideration for the minimum 2 patient cutoff used in this table

<sup>2</sup>New primary cancer

### 8.3.6. Dropouts and/or Discontinuations Due to Adverse Effects

Patients were allowed to be withdrawn from the active treatment phase in the case of disease progression as per RECIST v 1.1, symptomatic deterioration, need for new or additional anti-cancer therapy not specified in the protocol, unacceptable toxicity, investigator's conclusion that discontinuing therapy is in the patient's best interest, lost to follow-up, patient choice to withdraw from treatment, withdrawal of patient consent, and death. TEAEs leading to permanent discontinuation are summarized in Table 23.

**Table 23: TEAEs Associated with Permanent Discontinuation from Treatment in Study 1008 as of 8/31/2016**

	<b>Palbociclib plus Letrozole N=444 (%)</b>	<b>Placebo plus Letrozole N=222 (%)</b>
Any	29 (6.5)	3 (1.4)
Neutropenia	8 (1.8)	0
ALT increased	3 (0.7)	0
Acute kidney injury	2 (0.5)	0
AST increase	2 (0.5)	0
Diarrhea	2 (0.5)	0
Fatigue	2 (0.5)	2 (0.9)
Rash	2 (0.5)	0
Anemia	1 (0.2)	0
Dermatitis	1 (0.2)	0
Dysphonia	1 (0.2)	0
Female genital tract fistula	1 (0.2)	0
General health deterioration	1 (0.2)	0
Infections	1 (0.2)	1 (0.5)
Pneumonia	1 (0.2)	0
Pulmonary fibrosis	1 (0.2)	0
Respiratory failure	1 (0.2)	0
Lower respiratory tract infection	0	1 (0.5)
Pulmonary embolism	0	1 (0.5)

Source: 90 Day Safety Update Table 39, page 97

At least 1 dose reduction for palbociclib was reported for 160 (36.0%) patients in the palbociclib plus letrozole arm. The palbociclib dose was reduced from 125 to 100 mg for 160 (36.0%) patients, and for 63 of these patients the dose was further reduced to 75 mg. At least 1 placebo dose reduction was reported for 3 (1.4%) patients in the placebo plus letrozole arm. No all-causality AE were associated with a dose reduction for  $\geq 1\%$  of patients in the placebo plus letrozole arm as seen in Table 24. The AEs associated with dose reductions in the

placebo plus letrozole were Neutropenia, Diarrhea, and Electrocardiogram QT prolonged (0.4% each).

For 10 (2.3%) patients in the palbociclib plus letrozole arm, the AEs were considered to be treatment-related. In the placebo plus letrozole arm, no patient had a treatment-related AE that was associated with a dose reduction.

**Table 24: All-Causality AEs Associated With Dose Reduction for ≥1% of Patients in Either Treatment Arm of Study 1008**

	<b>Palbociclib plus Letrozole N=444 n (%)</b>	<b>Placebo plus Letrozole N=222 n (%)</b>
Any	160 (36)	3 (1.4)
Neutropenia	108 (24.3)	1 (0.5)
Neutrophil count decreased	23 (5.2)	0
Febrile neutropenia	6 (1.4)	0
Asthenia	7 (1.6)	0
Leukopenia	5 (1.1)	0
Fatigue	5 (1.1)	0

Source: Study 1008 CSR page 215

### 8.3.7. Significant Adverse Events

The overall Grade 3 or Grade 4 AE frequencies were higher in the palbociclib plus letrozole arm (64.0% and 14.4%, respectively) than in the placebo plus letrozole arm (23.9% and 2.3%, respectively) based on the August 31, 2016 Safety update cut-off . This observation was primarily due to the higher frequency of the myelosuppression-related Grade 3 or Grade 4 AEs of NEUTROPENIA and LEUKOPENIA reported in the palbociclib plus letrozole arm. The rate of Grade 3 neutropenia was 57 % and Grade 4 neutropenia was 11% in the palbociclib plus letrozole arm. The rate of Grade 3/4 neutropenia and leukopenia was 1% each in the placebo plus letrozole arm.

### 8.3.8. Treatment Emergent Adverse Events and Adverse Reactions

A summary of commonly reported treatment-related adverse reactions (ARs) regardless of severity grade experienced by at least 10% of patients in either treatment arm of Study 1008 as of February 26, 2016 are shown in Table 25.

**Table 25: Treatment Emergent ARs (>10%) in Study 1008**

Adverse Reaction	IBRANCE plus Letrozole (N=444)			Placebo plus Letrozole (N=222)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections <sup>a</sup>	60 <sup>b</sup>	6	1	42	3	0
Blood and lymphatic system disorders						
Neutropenia	80	56	10	6	1	1
Leukopenia	39	24	1	2	0	0
Anemia	24	5	<1	9	2	0
Thrombocytopenia	16	1	<1	1	0	0
Metabolism and nutrition disorders						
Decreased appetite	15	1	0	9	0	0
Nervous system disorders						
Dysgeusia	10	0	0	5	0	0
Gastrointestinal disorders						
Stomatitis <sup>c</sup>	30	1	0	14	0	0
Nausea	35	<1	0	26	2	0
Diarrhea	26	1	0	19	1	0
Vomiting	16	1	0	17	1	0
Skin and subcutaneous tissue disorders						
Alopecia	33 <sup>d</sup>	N/A	N/A	16 <sup>e</sup>	N/A	N/A
Rash <sup>f</sup>	18	1	0	12	1	0
Dry skin	12	0	0	6	0	0
General disorders and administration site conditions						
Fatigue	37	2	0	28	1	0
Asthenia	17	2	0	12	0	0
Pyrexia	12	0	0	9	0	0

Grading according to CTCAE 4.0.

CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable;

<sup>a</sup> Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.

<sup>b</sup> Most common infections ( $\geq 1\%$ ) include: nasopharyngitis, upper respiratory tract infection, urinary tract infection, oral herpes, sinusitis, rhinitis, bronchitis, influenza, pneumonia, gastroenteritis, conjunctivitis, herpes zoster, pharyngitis, cellulitis, cystitis, lower respiratory tract infection, tooth infection, gingivitis, skin infection, gastroenteritis viral, respiratory tract infection, respiratory tract infection viral, and folliculitis.

<sup>c</sup> Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oral discomfort, oropharyngeal pain, and stomatitis.

<sup>d</sup> Grade 1 events – 30%; Grade 2 events – 3%.

<sup>e</sup> Grade 1 events – 15%; Grade 2 events – 1%.

<sup>†</sup> Rash includes the following PTs: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption.

Source: Study 1008 adverse.xpt

The most common treatment emergent ARs (>20%) regardless of grade in the palbociclib plus letrozole treatment arm included neutropenia, infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea and anemia.

***Reviewer’s Comment: The treatment emergent ARs observed in Study 1008 are similar to the known toxicity profile for palbociclib.***

### 8.3.9. Laboratory Findings

**Table 26: Summary of Abnormal Clinical Hematology Laboratory Findings by Maximum Severity Grade in Study 1008**

	Palbociclib plus Letrozole (N=444)		Placebo plus Letrozole (N=222)	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
WBC decreased	429 (97)	158 (36)	56 (25)	1 (1)
Neutrophils decreased	423 (95)	298 (67)	45 (20)	4 (2)
Anemia	346 (78)	26 (6)	92 (41)	5 (2)
Platelets decreased	280 (63)	8 (2)	30 (14)	0
ALT increased	191 (43)	11 (3)	66 (30)	0
AST increased	229 (52)	15 (3)	76 (34)	2 (1)

Source: Study 1008 labs.xpt

***Reviewer Comment: Hematologic laboratory abnormalities in the palbociclib plus letrozole arm correspond to the reported TEAEs.***

**Table 27: Summary of Abnormal Clinical Chemistry Laboratory Findings by Maximum Severity Grade in Study 1008**

	Palbociclib plus Letrozole (N=444)		Placebo plus Letrozole (N=222)	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
ALT	191 (43)	11 (3)	66 (30)	0
Alkaline phosphatase	165 (37)	6 (1)	92 (41)	0
AST	229 (52)	15 (3)	76 (34)	2 (1)
Bilirubin	27 (6)	0	12 (5)	0
Creatinine	425 (96)	6 (1)	200 (90)	0
Hypercalcemia	88 (20)	0	52 (23)	2 (1)
Hyperkalemia	98 (22)	4 (1)	40 (18)	1 (1)
Hypermagnesemia	62 (14)	5 (1)	29 (13)	4 (2)
Hyponatremia	81 (18)	6 (1)	32 (14)	1 (1)
Hypoalbuminemia	95 (21)	1 (<1)	41 (19)	0
Hypocalcemia	147 (33)	9 (2)	46 (21)	1 (1)
Hypokalemia	96 (22)	9 (2)	34 (15)	2 (1)
Hypomagnesemia	111 (25)	2 (1)	36 (8)	0
Hyponatremia	91 (20)	9 (2)	35 (16)	4 (2)

Source: Study 1008 labs.xpt

***Reviewer Comment:*** Although all grade abnormalities in the chemistry laboratories were more common in the palbociclib plus letrozole treatment arm, grade 3/4 abnormalities were uncommon. It does not appear that any of these abnormalities had a significant impact on the clinical outcome of patients.

### 8.3.10. Vital Signs

The mean and median blood pressure, pulse rate, and weight were well balanced between the two treatment arms at baseline. No clinically relevant changes from baseline in any of the vital sign measurements were observed in either treatment arm as of 2/26/2016.

### 8.3.11. Electrocardiograms (ECGs)

ECGs were obtained from all patients during the study, including a total of 443 patients in the palbociclib plus letrozole arm, and 220 patients in the placebo plus letrozole arm who had both baseline and post baseline ECGs. Clinically relevant ECG findings observed in Study 1008 were reported as TEAEs.

The following AEs potentially relevant to QTc prolongation were reported in the palbociclib plus letrozole arm: Syncope (8 [1.8%] patients); Electrocardiogram repolarization abnormality (6 [1.4%]); Electrocardiogram QT prolonged (5 [1.1%]); and Electrocardiogram abnormal, Electrocardiogram QT interval, Electrocardiogram U-wave abnormality, and Seizure (1 [0.2%] each). None of these AEs were associated with QTcS or QTcF that were >500 msec. The AEs of Electrocardiogram QT prolonged (5 [1.1%] patients), Syncope (2 [0.5%]), and Electrocardiogram QT interval (1 [0.2%]) were considered to be related to treatment in the palbociclib plus letrozole arm. In addition, 2 Grade 3 AEs of Syncope and the Grade 3 AE of Seizure were assessed as serious.

The following AEs potentially relevant to QTc prolongation were reported in the placebo plus letrozole arm: Electrocardiogram QT prolonged (3 [1.4%] patients) Syncope (3 [1.4%]), and Electrocardiogram abnormal (1 [0.5%]). None of these AEs were associated with QTcS or QTcF that were >500 msec, and none were assessed as serious. The AEs of Electrocardiogram QT prolonged (2 [0.9%] patients) and Syncope (1 [0.5%]) were considered to be related to treatment.

The following AEs potentially relevant to QTc prolongation were not experienced by patients in either the palbociclib plus letrozole arm or the placebo plus letrozole arm: Sudden death, Torsade de pointes, Ventricular fibrillation, Ventricular flutter, and Ventricular tachycardia.

### 8.3.12. QT

For full details, see Clinical Pharmacology review and QT-IRC review.

In the QTc analysis population, no patients had a post baseline absolute mean maximum QTcF or QTcS of  $\geq 500$  msec or a maximum increase from QTcF or QTcS baseline of  $\geq 60$  msec during the intensive QTc assessment period. Palbociclib, when added to letrozole at the recommended dosing regimen, did not prolong QT interval to a clinically meaningful extent.

## 8.4. Analysis of Submission-Specific Safety Issues

Adverse events of special interest in this submission included: febrile neutropenia, lens disorders, interstitial lung disease, and torsade de pointes/QT prolongation.

### 8.4.1. Myelosuppression and Febrile Neutropenia

Neutropenia, thrombocytopenia and anemia were more frequent in the palbociclib treatment arm of Study 1008 as listed in Section 7.3.8. The febrile neutropenia rate was 2.5% in the palbociclib plus letrozole arm and there were no cases of febrile neutropenia in the placebo

plus letrozole arm. None of the patients in the palbociclib plus letrozole arm had febrile neutropenia associated with permanent discontinuation from treatment.

***Reviewer Comment: Myelosuppression was more common in the palbociclib treatment arm, consistent with the known mechanism of action and toxicity profile for palbociclib.***

#### 8.4.2. Lens Disorders

Eye disorders were more frequently reported in patients in the palbociclib plus letrozole arm (21.6%) than in the placebo plus letrozole arm (13.1%) as seen in Table 28. Treatment-related eye disorders occurred at a frequency of 12.4% in the palbociclib plus letrozole arm and 5.0% in the placebo plus letrozole arm.

**Table 28: Summary of MedDRA SOC Eye Disorders Experienced by ≥ 2 Patients in the Palbociclib plus Letrozole Arm**

	Palbociclib plus Letrozole N=444 n (%)			Placebo plus Letrozole N=222 n (%)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
Lacrimation increased	25 (6)	0	0	2 (1)	0	0
Dry eye	18 (4)	0	0	7 (3)	0	0
Vision blurred	16 (4)	1 (<1)	0	6 (3)	0	0
Cataract	14 (3)	4 (1)	0	1 (1)	0	0
Vitreous floaters	9 (2)	0	0	0	0	0
Visual impairment	8 (2)	0	0	2 (1)	0	0
Eye pruritus	5 (1)	0	0	1 (1)	0	0
Visual acuity reduced	5 (1)	0	0	0	0	0
Eye pain	3 (1)	0	0	2 (1)	0	0
Ocular hyperemia	3 (1)	0	0	3 (1)	0	0
Blepharitis	2 (1)	0	0	0	0	0
Conjunctival hemorrhage	2 (1)	0	0	1 (1)	0	0
Dacryostenosis acquired	2 (1)	0	0	0	0	0
Diplopia	2 (1)	0	0	1 (1)	0	0
Eye hemorrhage	2 (1)	0	0	0	0	0
Eye swelling	2 (1)	0	0	1 (1)	0	0
Ocular discomfort	2 (1)	0	0	0	0	0
Periorbital edema	2 (1)	0	0	0	0	0
Vitreous detachment	2 (1)	0	0	1 (1)	0	0

Source: Study 1008 advers.xpt

***Reviewer Comment: Although eye disorders were more common in the palbociclib treatment arm, the majority of these were grade 1 or 2. There were no grade 4 events in either treatment arm and six grade 3 events in the palbociclib arm (one patient with vision blurred, one patient with posterior capsule opacification, and 4 patients with cataracts). Special attention was paid to HYPERGLYCEMIA in relationship to lens disorders based on nonclinical findings of the appearance of cataracts/lens degeneration in association with altered glucose metabolism (glycosuria and/or hyperglycemia) in rats and dogs administered repeat doses of palbociclib. None of the 15 patients with Cataract or Cataract nuclear in the palbociclib plus letrozole arm had AE reports of HYPERGLYCEMIA; however, 3 of these patients were diabetic.***

### 8.4.3. Respiratory Disorders

Respiratory disorders were more common in the palbociclib plus letrozole arm compared to placebo plus letrozole. The most frequent all-causality AEs in both treatment arms were Cough (25.0% in the palbociclib and letrozole arm and 18.9% in the placebo plus letrozole arm) and Dyspnea (14.9% and 13.5%, respectively). In the palbociclib plus letrozole arm, pneumonitis and interstitial lung disease were reported in 1 (0.2%) patient each.

**Table 29: TEAEs within the MedDRA SOC Respiratory, thoracic and mediastinal disorders in ≥ 1% Patients by Descending Frequency in the Palbociclib plus Letrozole Arm**

	Palbociclib plus Letrozole N=444 n (%)			Placebo plus Letrozole N=222 n (%)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
Cough	111 (25)	0	0	42 (19)	0	0
Dyspnea	66 (15)	5 (1)	0	30 (14)	3 (1)	0
Epistaxis	41 (9)	0	0	14 (6)	0	0
Oropharyngeal pain	41 (9)	0	0	7 (3)	0	0
Rhinorrhea	20 (5)	0	0	4 (2)	0	0
Nasal congestion	16 (4)	0	0	7 (3)	0	0
Dyspnea exertional	14 (3)	0	0	7 (3)	0	0
Pleural effusion	12 (3)	2 (1)	0	3 (1)	1 (1)	0
Productive cough	12 (3)	0	0	1 (1)	0	0
Nasal dryness	9 (2)	0	0	1 (1)	0	0
Upper-airway cough syndrome	9 (2)	0	0	1 (1)	0	0
Dysphonia	8 (2)	0	0	1 (1)	0	0
Rhinitis allergic	8 (2)	0	0	1 (1)	0	0
Pulmonary embolism	7 (2)	4 (1)	1 (<1)	5 (2)	3 (1)	1 (1)
Pleurisy	5 (1)	0	0	0	0	0
Sinus congestion	5 (1)	0	0	0	0	0
Wheezing	5 (1)	0	0	1 (1)	0	0
Throat irritation	2 (1)	0	0	1 (1)	0	0
Interstitial lung disease	1 (<1)	0	0	0	0	0
Pneumonitis	1 (<1)	1 (<1)	0	1 (1)	0	0

Source: Study 1008 advers.xpt

***Reviewer Comment: Respiratory disorders were more common in the palbociclib plus letrozole treatment arm and most of these were of grade 1 or 2 severity.***

#### 8.4.4. Venous Thromboembolism

Thrombotic events seen in Study 1008 are summarized in Table 30. Of these, deep vein thrombosis (0.7%), pulmonary embolism (0.2%), and Peripheral embolism (0.2%) were considered to be treatment-related in the palbociclib plus letrozole arm, and pulmonary embolism (0.5%) in the placebo plus letrozole arm.

**Table 30: Summary of thrombotic events reported in Study 1008**

	Palbociclib plus Letrozole N=444 n (%)			Placebo plus Letrozole N=222 n (%)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
Pulmonary embolism	7 (1.6)	4 (1)	1 (<1)	5 (2.3)	3 (1)	1 (1)
Deep vein thrombosis	4 (1)	1 (<1)	0	1 (1)	0	0
Thrombophlebitis	2 (1)	0	0	0	0	0
Embolism	1 (<1)	0	0	1 (1)	0	0
Peripheral embolism	1 (<1)	0	0	0	0	0
Post thrombotic syndrome	1 (<1)	0	0	0	0	0
Thrombophlebitis superficial	1 (<1)	0	0	0	0	0
Pelvic venous thrombosis	0	0	0	1 (1)	0	0

Source: Study 1008 advers.xpt

***Reviewer Comment:*** *Thromboembolism rates are similar in both treatment arms for Study 1008. Pulmonary embolism had a higher rate in the placebo arm compared to the palbociclib treatment arm despite patients being on treatment longer in the palbociclib treatment arm. There was one treatment related SAE of pulmonary embolism (in Study 1003) in the palbociclib treatment arms of Study 1003, Study 1034, Study 1027 and Study 1023.*

***The findings above support removal of “pulmonary embolism” from the Warnings and Precautions section in the label as it is not clear that pulmonary embolism is a clear adverse reaction of palbociclib. In addition, thrombotic events (including pulmonary embolism) are complications often observed in patients with metastatic disease.***

#### 8.4.5. Torsade de pointes/QT prolongation

In the QTc analysis population, no patients had a post baseline absolute mean maximum QTcF or QTcS of  $\geq 500$  msec or a maximum increase from QTcF or QTcS baseline of  $\geq 60$  msec during the intensive QTc assessment period. A random effect analysis of the QTc data in the QTc analysis population demonstrated that the upper bounds of the 1- sided 95% CI for the mean change time-matched from baseline for QTcF, QTcS and QTcB were  $< 8$  msec at all-time points in the QTc assessment period, indicating that palbociclib, when added to letrozole at the recommended dosing regimen, did not prolong QT interval to a clinically meaningful extent.

The following AEs potentially relevant to QTc prolongation were not experienced by patients in either the palbociclib plus letrozole arm or the placebo plus letrozole arm: Sudden death, Torsade de pointes, Ventricular fibrillation, Ventricular flutter, and Ventricular tachycardia.

## 8.5. Safety Analyses by Demographic Subgroups

### Age

Safety data reported in Study 1008 were analyzed by age (<65 years of age and ≥65 years of age). The overall frequencies of AEs and treatment-related AEs were similar between the 2 age groups within either treatment arm. Whereas, the overall frequencies of SAEs, treatment-related SAEs, grade 5 AEs, permanent discontinuation from treatment associated with either AEs or treatment-related AEs were higher among patients ≥65 years of age than among those <65 years of age as seen in Table 31.

**Table 31: Summary of AEs by Age in Study 1008**

	Palbociclib plus Letrozole (N=444)		Placebo plus Letrozole (N=222)	
	<65 yrs N=263	≥ 65 yrs N=181	<65 yrs N=141	≥ 65 yrs N=181
Any AE	259 (98.5)	180 (99.4)	134 (95)	78 (96.3)
Grade 3/4 AEs	198 (75.3)	146 (80.7)	38 (27)	18 (22.2)
Grade 5 AEs	2 (0.3)	8 (4.4)	3 (2.1)	1 (1.2)
Any SAE	38 (14.4)	49 (27.1)	15 (10.6)	13 (16)
TEAE	253 (96.2)	175 (96.7)	119 (84.4)	60 (74.1)
Grade 3/4 treated related AEs	184 (70)	135 (74.6)	11 (7.8)	3 (3.7)
Grade 5 treatment related AEs	0	0	0	1 (1.2)
Treatment-related SAE	9 (3.4)	15 (8.3)	0	2 (2.5)
Discon palbo/placebo due to TEAE	8 (3)	17 (9.4)	1 (0.7)	2 (2.5)
Discon letrozole due to TEAE	3 (1.1)	8 (4.4)	1 (0.7)	2 (2.5)

Source: Study 1008 Summary of Clinical Efficacy, page 183 (modified Table 81)

In the palbociclib plus letrozole arm in Study 1008, infections, anemia and decreased appetite were observed substantially more frequently (>10%) by patients >65 years of age compared to those <65 years of age. Neutropenia, infections, leukopenia, alopecia and stomatitis were reported more frequently (>10% absolute difference in AE frequency) in both age groups in the palbociclib plus letrozole arm than in the respective age groups in the placebo plus letrozole arm.

### Sex

No analysis of palbociclib safety data with regard to patients' were performed on the data from Study 1008 since all patients in this study were women.

## Race

Safety data from Study 1008 were analyzed by race (White, Black, Asian, and Other). Most patients participating in this study were White (77.5% in each treatment arm). The second largest race group in both treatment arms was Asian (14.6% in the palbociclib plus letrozole arm and 13.5% in the placebo plus letrozole arm). The number of patients whose race was Black was less than 10 patients in either treatment arm, and the number of patients denoted as “Other” in each treatment arm was small, the race group analysis was confined to comparisons between White and Asian patients as seen Table 32. In the palbociclib plus letrozole arm, the overall AE and treatment-related AE frequencies were comparable between White and Asian patients. A comparison of AE and treatment-related AE data between White and Asian patients showed a higher overall Grade 3 or Grade 4 AE and treatment-related AE frequency in Asian patients than in White patients. An opposite trend was observed for the overall frequencies of SAEs, with that frequency being lower in Asian patients than in White patients. However, the overall treatment-related SAE frequencies were comparable between White and Asian patients. The difference mentioned above between White and Asian patients observed in the palbociclib plus letrozole arm were not observed in the placebo plus letrozole arm, although the number of Asian patients was small (n=30) in the placebo plus letrozole arm.

**Table 32: Summary of AEs by Race in Study 1008**

Patient category	Palbociclib plus Letrozole (N=444 Number (%) of Patients	
	White (N=344)	Asian (N=65)
Any AE	339 (98.5)	65 (100)
Grade 3/4 AE	257 (74.7)	60 (92.3)
Grade 5 AE	10 (2.9)	0
Any SAE	71 (20.6)	9 (13.8)
Any TEAE	329 (95.6)	65 (100)
Grade 3/4 TEAE	234 (68)	59 (90.8)
Grade 5 TEAE	0	0
Any treatment related SAE	19 (5.5)	3 (4.6)
Discontinued palbociclib due to TEAEs	17 (4.9)	5 (7.7)
Discontinued letrozole due to TEAEs	8 (2.3)	1 (1.5)

Source: Study 1008 Summary of Clinical Efficacy, page 190 (modified Table 85)

## 8.6. Specific Safety Studies/Clinical Trials

There is an ongoing double-blind, placebo-controlled, Phase 3 Study 1027 in Asian postmenopausal women with ER-positive, HER2-negative advanced breast cancer receiving blinded treatment (palbociclib/placebo) in combination with letrozole as first-line treatment of

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Clinical – Suparna Wedam / Laleh Amiri-Kordestani

Statistical – Erik Bloomquist / Shenghui Tang

their disease. In addition, there is an ongoing phase 1 Study 1019 PK study in postmenopausal Chinese women. These two studies will provide more information regarding safety/efficacy specific to Asian women.

There is also an ongoing Phase 1 Study 1013 of palbociclib in subjects with hepatic impairment but are otherwise healthy, which will provide additional safety data specific to patients with underlying hepatic impairment.

## **8.7. Additional Safety Explorations**

### **8.7.1. Human Carcinogenicity or Tumor Development**

See Pharmacology/Toxicology Review.

### **8.7.2. Human Reproduction and Pregnancy**

See Pharmacology/Toxicology Review.

### **8.7.3. Pediatrics and Assessment of Effects on Growth**

Not applicable.

### **8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

#### **Overdose**

A study drug overdose was defined as an increase in a daily dose; in addition any intake of palbociclib or placebo exceeding 21 doses in any given treatment cycle was considered to be the overdose. A total of 5 patients experienced AEs associated with palbociclib overdose; all related to myelosuppression. No AEs of overdose were reported in the placebo plus letrozole arm.

#### **Drug Abuse Potential**

There are no data available on the potential for abuse or dependence with palbociclib.

#### **Withdrawal and Rebound**

A formal study has not been conducted by the applicant to investigate withdrawal and/or rebound.

## 8.8. Safety in the Postmarket Setting

### 8.8.1. Safety Concerns Identified Through Postmarket Experience

Overall, it is estimated that approximately (b) (4) patients were exposed to palbociclib worldwide in the postmarketing setting from February 3, 2015 (day of the US approval) through August 2, 2016 (Palbociclib Periodic Safety Update Report 2). The cumulative postmarketing safety data of palbociclib provided by the Applicant were generally consistent with the known safety profile of palbociclib and did not raise any new safety concerns.

### 8.8.2. Expectations on Safety in the Postmarket Setting

Not applicable.

## 8.9. Additional Safety Issues From Other Disciplines

Not applicable.

## 8.10. Integrated Assessment of Safety

The safety profile of palbociclib plus letrozole or fulvestrant for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer is generally tolerable, with adverse reactions manageable through the use of palbociclib dose reduction, temporary treatment discontinuation, and/or standard medical care. No new safety concerns have been identified based on the cumulative safety data submitted in this sNDA.

## 9 Advisory Committee Meeting and Other External Consultations

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No advisory committee meeting was held for this sNDA.

## 10 Labeling Recommendations

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### 10.1. Prescribing Information

There were several internal labeling discussions. Key clinical labeling recommendations include:

1. Update indication:  
*IBRANCE is a (b) (4) kinase (b) (4) inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)*

*negative advanced or metastatic breast cancer in combination with:*

- *an aromatase inhibitor as initial endocrine based therapy in postmenopausal women or*
- *fulvestrant in women with disease progression following endocrine therapy.*

2. Remove pulmonary embolism from Warnings and Precautions.
3. In Section 6.1 and Section 14, update Study 1 to refer to results from PALOMA-2 (Study 1008) and remove PALOMA-1 (Study 1003) results.
4.  (b) (4)

## 10.2. Patient Labeling

Please see final patient labeling.

## 10.3. Nonprescription Labeling

This is not applicable for this sNDA.

# **11 Risk Evaluation and Mitigation Strategies (REMS)**

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## 11.1. Safety Issue(s) that Warrant Consideration of a REMS

None

## 11.2. Conditions of Use to Address Safety Issue(s)

None

## 11.3. Recommendations on REMS

None

## **12 Postmarketing Requirements and Commitments**

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No PMRs were requested. The clinical team recommends the following Postmarketing Commitment (PMC):

- Submit the overall survival (OS) data and results from 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”

Rationale: The original postmarketing requirement (2860-1) from the accelerated approval of palbociclib in combination of letrozole has been fulfilled with the final PFS analysis submitted in this supplement. However, the OS data was not available and is expected 11/2020. This is important information to include in Section 14 of the package insert.

## 13 Appendices

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### 13.1. References

1. Siegel R., Miller K., Jemal A. Cancer Statistics, 2017. *Cancer J Clin* ; 67 7-30. (2017)
2. American Cancer Society Facts and Figures. <https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html>
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8. Ma CX, Gao F, Northfelt D, et al. A phase II trial of neoadjuvant palbociclib, a cyclin dependent kinase (CDK) 4/6 inhibitor, in combination with anastrozole for clinical stage 2 and 3 estrogen receptor positive HER2 negative (ER+HER2-) breast cancer (BC). Abstract S6-05, San Antonio Breast Cancer Symposium. (2015)

### 13.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number): Study A5481008 (PALOMA-2)**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 1791		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 22		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none</p> <p>Significant payments of other sorts: 22</p> <p>Proprietary interest in the product tested held by investigator: none</p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: none</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>10</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Clinical and Statistical Review NDA 207103/S-004 Ibrance (palbociclib)  
Clinical – Suparna Wedam / Laleh Amiri-Kordestani  
Statistical – Erik Bloomquist / Shenghui Tang

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03/30/2017

LALEH AMIRI KORDESTANI  
03/30/2017

RAJESHWARI SRIDHARA  
03/30/2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207103Orig1s004**

**CHEMISTRY REVIEW(S)**

**Office of New Drug Products  
Division of New Drug Products I  
Review of Chemistry, Manufacturing, and Controls**

**1. NDA Supplement Number: NDA 207103 / ES-004**

**2. Submission(s) Being Reviewed:**

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Supplement	Efficacy Supplement	26-Oct-2016	27-Oct-2016	31-Oct-2016	29-Apr-2016	30-Nov-2016

**3. Proposed Changes:** It is an efficacy supplement. It seeks Full Approval for palbociclib in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

**4. Review #:1**

**5. Clinical Review Division: DOP1**

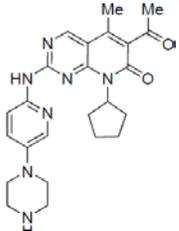
**6. Name and Address of Applicant:**

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

**7. Drug Product:**

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Ibrance (palbociclib)	Capsules	75, 100, 125 mg	Oral	Rx	No

**8. Chemical Name and Structure of Drug Substance:**

	<p><b>USAN:</b> palbociclib <b>Chemical name:</b> pyrido[2,3-<i>d</i>]pyrimidin-7(8<i>H</i>)-one, 6-acetyl-8-cyclopentyl-5-methyl-2-[[5-(1-piperazinyl)-2-pyridinyl]amino]- <b>Molecular formula:</b> C<sub>24</sub>H<sub>29</sub>N<sub>7</sub>O<sub>2</sub> <b>MW:</b> 447.54 g/mole</p>
---	---

**9. Indication:** Advanced breast cancer

**10. Supporting/Relating Documents:** N/A

**11. Consults:** N/A

**12. Executive Summary:**

It is an efficacy supplement. It seeks Full Approval for palbociclib in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

No CMC changes have been proposed in the supplement. Pfizer Inc. claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR Part 25.31 (a) applicable for action on a supplemental NDA when the action does not increase the use of the active moiety. Pfizer Inc. claims that to their knowledge, no extraordinary circumstances exist. The claim for a categorical exclusion to the environmental assessment is deemed acceptable.

**13. Conclusions & Recommendations:**

This supplement is recommended for approval.

**14. Comments/Deficiencies to be Conveyed to Applicant:**

**15. Reviewer:**

Xiao Hong Chen, Acting QAL,  
Branch 2, Division of New Drug Products I, Office of New Drug Products, Office of  
Pharmaceutical Quality (OPQ)





Xiao  
Chen

Digitally signed by Xiao Chen  
Date: 12/01/2016 09:59:18AM  
GUID: 508da7220002a138fcc70fbccbfd08bf



**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207103Orig1s004**

**PHARMACOLOGY REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY SUPPLEMENTAL NDA REVIEW AND  
EVALUATION**

Application number: 207103/S-04  
Supporting document/s: 1  
Applicant's letter date: October 27, 2016  
CDER stamp date: October 27, 2016  
Product: Ibrance (palbociclib)  
Indication: women with hormone receptor (HR)-positive,  
human epidermal growth factor receptor 2 (HER2)-  
negative advanced or metastatic breast cancer  
Applicant: Pfizer Inc.  
Review Division: Division of Hematology Oncology Toxicology  
(for Division of Oncology Products 1)  
Reviewer: Wei Chen, PhD  
Supervisor/Team Leader: Todd Palmby, PhD  
Division Director: John Leighton, PhD  
(Geoffrey Kim, MD)  
Project Manager: Amy Tilley

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of [REDACTED] (b) (4) are owned by Pfizer Inc. or are data for which Pfizer Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 207103/S-04 that Pfizer Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 207103/S-04.

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# 1 Executive Summary

## 1.1 Introduction

Ibrance (palbociclib) is an oral, small molecule kinase inhibitor with activity against cyclin-dependent kinase (CDK) 4 and 6 that was approved in combination with letrozole in February, 2015 in the United States (US) for the treatment of postmenopausal women with hormone estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer as initial endocrine based therapy. The Applicant submitted this prior approval supplement to seek the approval for an indication of palbociclib in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

## 1.2 Brief Discussion of Nonclinical Findings

The original NDA submission for palbociclib included a 27-week rat study with a dosing regimen of 3 weeks of consecutive daily dosing followed by a 1-week non-dosing period for 27 weeks (a total of 7 cycles). Beside the adverse effects in the bone marrow, lymphoid tissues, and male reproductive organs (also shown in dogs), the study showed that administration of palbociclib to rats resulted in increased serum glucose levels, glucosuria and other adverse effects possibly associated with increased glucose, including pancreatic islet cell vacuolation, eye lens degeneration, degeneration of tooth ameloblasts, and renal tubuloepithelial cell vacuolation. Mortality observed at 100 mg/kg resulted from degeneration and/or inflammation of the feet and other adverse effects, which are considered to be associated with treatment induced hyperglycemia. The lens degeneration and chronic progressive nephropathy remained at the recovery euthanasia, suggesting a permanent and/or progressive nature of these effects. The rats used in this 27-week study were approximately 7 weeks old at the beginning of the studies.

To further investigate the altered glucose metabolism in rats, a GLP 27-week repeat-dose toxicology study in male aged rats (12 months old at initiation of dosing) was conducted in which palbociclib was administered orally following the recommended clinical dosing regimen of daily for 3 weeks followed by a 1-week period without dosing. The male aged rats were administered palbociclib at 30 mg/kg/day for 7 cycles or at 100 mg/kg/day for 4 or 7 cycles. The administration of palbociclib to male aged rats did not result in mortality or severe toxicities at doses up to 100 mg/kg (HD). Males administered 100 mg/kg/day (4 or 7 cycles) demonstrated a treatment-related overall body weight loss during the dosing phase. In general, rats lost weight during the dosing period (weeks 1-3 of each dosing cycle) and gained body weight back during the week without dosing (week 4 of each dosing cycle). The only other palbociclib-related clinical observation was discolored white incisor teeth of males administered 100 mg/kg/day for 4 or 7 cycles, with correlating macroscopic discoloration at euthanasia and the microscopic correlate of ameloblast degeneration/necrosis. Palbociclib-related microscopic findings were noted at the interim (4-cycles) and terminal (7 cycles)

ethanasia in the liver of males administered >30 mg/kg/day, including increased incidence and severity of hepatocyte vacuolation compared with control.

Administration of palbociclib to aged male rats did not affect serum glucose levels assessed in Oral Glucose Tolerance Test (OGTT) and did not affect the levels of C-peptide, corticosterone or HbA1c in at doses up to 100 mg/kg/day for 27 weeks. The observed adverse effects in young rats associated with increase of glucose were not observed in aged rats. Odontopathy in the incisor teeth was observed in both young rats and aged rat, suggesting independent of the endocrine/metabolic changes. TK studies showed that the systemic exposures ( $C_{max}$  and AUC) were similar in young and aged rats. The absence of dysregulated glucose and pancreatic or renal effects in aged rats suggest that young rats maybe susceptible to the development of dysregulated glucose in response to palbociclib administration, potentially related to differences in beta cell proliferation capacity or beta cell biology. Note that no changes in glucose levels and other related toxicities (e.g. eyes) were observed in adult patients treated with palbociclib.

### **1.3 Recommendations**

#### **1.3.1 Approvability**

Recommending approval. The nonclinical studies adequately support the safety of oral palbociclib for the proposed indication.

#### **1.3.2 Additional Non Clinical Recommendations**

Additional nonclinical studies are not needed at this time.

#### **1.3.3 Labeling**

Information needed for nonclinical sections of the label are provided in this review or the pharmacology/toxicology reviews for NDA 207103 (1/17/2015) and NDA 207103/S-02 (2/8/2016).

Section (b) (4) was updated based on the re-evaluation of altered glucose metabolism in a 27-week study using aged rats. The absence of effects on glucose metabolism, the pancreas, eyes, and kidney in aged rats at the systemic exposures at which effects were observed in young rats, together with the absence of similar clinical signals in patients suggested that these risks may not be relevant to adult patients. However, these potential risks still remain for a younger patient population. Therefore, the results from the repeat-dose toxicity study in young rats were moved to section 8.4 Pediatric Use, consistent with FDA guidance documents recommending of pediatric information into labeling of human pharmaceuticals.

Section 12.1 was updated based on the in vitro pharmacology study results (NDA 207103/S-02, 2/8/2016). The in vitro pharmacology studies suggested that the mechanism of palbociclib-induced bone marrow suppression was different from that induced by cytotoxic chemotherapeutic agents, and the mechanisms of palbociclib-induced cell growth inhibition are different in human bone marrow mononuclear cells and human breast cancer cells.

For final agreed upon changes, refer to the approved package insert.

## 2 Drug Information

### 2.1 Drug

CAS Registry Number: 571190-30-2

Trade name: Ibrance

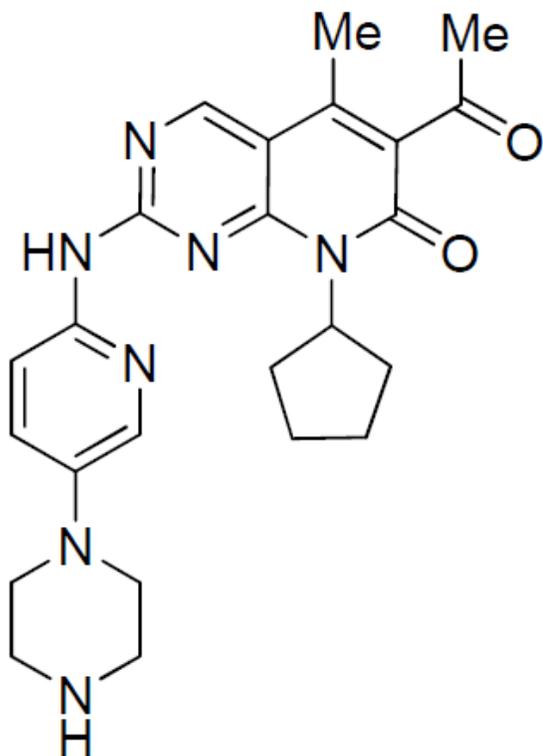
Generic Name: Palbociclib

Code Name: PD-0332991

Chemical Name: 6-Acetyl-8-cyclopentyl-5-methyl-2-[[5-(piperazin-1-yl)pyridin-2-yl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one

Molecular Formula/Molecular Weight:  $C_{24}H_{29}N_7O_2$ / 447.54 g/mole

Structure or Biochemical Description:



Pharmacologic Class: kinase inhibitor

Mechanism of action: an inhibitor of CDK 4/6

**Relevant INDs, NDAs, BLAs and DMFs:** IND 69,324

**2.2 Drug Formulation: capsule, 75 mg, 100 mg or 125 mg**

**2.4 Comments on Novel Excipients: N/A**

**2.5 Comments on Impurities/Degradants of Concern: none**

**2.6 Proposed Clinical Population and Dosing Regimen**

Proposed clinical population:

Women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

Proposed dose and dose regimen:

125 mg, once daily for 21 consecutive days followed by 7 days off treatment with food, and in combination with endocrine therapy.

Route of administration: oral

### 3 Studies Submitted

#### Studies Reviewed

Toxicology

Repeat dose

	Title	Study no.	Folder/file
1	27-Week Investigational Oral Gavage Toxicity and Toxicokinetic Study with PD-0332991 in Aged Rats	8313012	M4.2.3.2

#### Studies submitted, but not reviewed

Pharmacokinetics

	Title	Study no.	Folder/fil name
Absorption			
1	In vitro transporter OATP1B1 and OATP1B3 uptake of PD-0332991	PD-332991_28Jan16_042704	M4.2.2.2
Distribution			
1	In Vitro Protein Binding of PD 0332991 to Plasma Proteins of Mouse, Rat, Dog, and Human	RR 764-04174	M4.2.2.3
Metabolism			
1	Metabolism of PD-0332991 in mouse hepatocytes	PD-0332991_01Sep15_150813	M4.2.2.4
Pharmacokinetic Drug Interaction			
1	In vitro evaluation of PD-0332991 as an inhibitor of OCT1 transporter	PD-332991_19Jan16_043304	M4.2.2.6
2	In vitro evaluation of PD-0332991 as an inhibitor of OAT1, OAT3 and OCT2 transporters	PD-0332991_09Oct15_161616	M4.2.2.6
3	Effect of PD-0332991 on human drug metabolizing enzymes in vitro	PD-0332991_27MAY10_181141	M4.2.2.6
4	In vitro Interaction Studies of Selected Test Articles with Human Renal Uptake Transporters	12_03729	M4.2.2.6

Toxicology studies

## Repeat dose

	Title	Study no.	Folder/file
1	15-week oral dose exploratory toxicity study of PD-0332991 in rats	14LJ122	M4.2.3.2

## Genotoxicity

	Title	Study no.	Folder/file
1	Exploratory bacterial mutagenicity assay of <span style="background-color: #cccccc;">(b) (4)</span> , an impurity of PD-0332991	15GR456	M4.2.3.3

**Previous Reviews Referenced**

	Type of Review	Submission type	Author	Submitted Date
1	Pharmacology/toxicology NDA review and evaluation	Original-1	Wei Chen	01/17/2015
2	Pharmacology/toxicology NDA review and evaluation	Supplement-2 (Efficacy)	Wei Chen	11/10/2015

## 4 Pharmacology

No new data submitted

## 6 General Toxicology

**Study title:** 27-Week Investigational Oral Gavage Toxicity and Toxicokinetic Study with PD-0332991 in Aged Rats

Study no.: 8313012  
Study report location: Electronic submission, M4. pages 1-987  
Conducting laboratory and location:  (b) (4)  
Date of study initiation: December 10, 2014  
GLP compliance: yes  
QA statement: yes ( X ) no ( )  
Drug, lot #, and % purity:  
PD-0332991  
Batch No: E010014769, E010014768  
% purity: 98.9%

### Key Study Findings

- No deaths or severe toxicities occurred in aged male rats at doses up to 100 mg/kg
- Decreased body weights were observed at 100 mg/kg during the dosing phase
- Discolored white incisor teeth was observed in rats at 100 mg/kg/day, correlating to the microscopic findings of ameloblast degeneration /necrosis
- Administration of palbociclib did not affect serum glucose levels, and no changes associated with altered glucose metabolism were detected

## Methods

Doses: 30, 100 mg/kg/day

\* Doses were selected based on 15-week oral dose study in Sprague Dawley rats (6-8 weeks of age at initiation of dosing).

Frequency of dosing: Daily x 21, 28 days/cycle for 15 weeks (group 4-5) or 27 weeks (Group 1 -3).

Group <sup>b,c</sup>	No. of Animals		Dose <sup>a</sup> (mg/kg/day)	Dose Concentration (mg/mL)
	Male	Female		
1 (Control)	16	16	0	0
2 (Low)	16	16	30	3
3 (High)	16	16	100	10
4 (Control)	10	10	0	0
5 (High)	10	10	100	10

Route of administration: Oral gavage

Dose volume: 10 mL/kg

Formulation 0.5% (w/v) methylcellulose (4000 cps) in reverse osmosis water

/Vehicle:

Species/Strain: Male Sprague Dawley rats

Number/Sex 16/group for Dose group 1-3, 10 /group for dose group 4-5

/Group:

Age: 12 months old

Weight: 442-688 g

Satellite groups: Yes, 4/sex/group (3/sex for the control group) for TK study

Unique study design: glucose metabolism assessment

Deviation from study protocol: Yes, but no major impact on the study results

## Observations and Results

**OBSERVATIONS AND TIMES:**

<u>Mortality</u>	twice daily (AM and PM)												
<u>Cageside observations</u>	once daily												
<u>Detailed physical examinations</u>	prior to dosing on Day 1, weekly (based on Day 1) throughout the dosing phase to Week 27, and on Day 189 of the dosing phase in Groups 1-3												
<u>Body weights</u>	before dosing on Day 1, weekly (based on Day 1) throughout the dosing phase to Week 27, and on Day 189 of the dosing phase in Groups 1-3												
<u>Food consumption</u>	Weekly in Groups 1-3												
<u>Ophthalmoscopy</u>	once during the acclimation phase and during Week 27 of the dosing phase												
<u>Oral Glucose Tolerance Test (OGTT)</u>	on Days 18, 46, 74, 130 and 186 of the dosing phase												
<u>Glucose and Insulin Analysis</u>	on Days 18, 46, 74, 130 and 186 of the dosing phase												
<u>Hematology</u>	predose on Days 18 and 186 of the dosing phase. For Groups 4-5, hematology samples were collected predose on Days 18 and 102 of the dosing phase.												
<u>Urinalysis and Urine Chemistry</u>	For Groups 1-3, urine samples were collected on Days 18, 46, 74, 130, and 186 of the dosing phase (coinciding with the predose OGTT blood collection) and on the day of scheduled euthanasia.												
<u>Gross pathology:</u>	On Day 106 (Interim euthanasia), all surviving rats in Groups 4-5; On Day 190 (Terminal Euthanasia), all surviving rats in Groups 1-3. All animals unscheduled euthanasia and Deaths												
<u>Organ weights:</u>	On Day 106 (Interim Euthanasia), all surviving rats in Groups 4-5; on Day 190 (Terminal Euthanasia), all surviving rats in Groups 1-3. All animals unscheduled euthanasia and Deaths												
<u>Histopathology:</u>	On Day 106 (Interim Euthanasia), all surviving rats in Groups 4-5; on Day 190 (Terminal Euthanasia), all surviving rats in Groups 1-3. All animals unscheduled euthanasia and Deaths Note: only the adrenal, eye, liver, kidney, pancreas, and teeth were examined.												
<u>Toxicokinetics:</u>	on Days 8 and 49 <table border="1"> <thead> <tr> <th>Group</th> <th>Set</th> <th>Dosing Phase</th> <th>Time Points<sup>a</sup></th> </tr> </thead> <tbody> <tr> <td>1 (Control)</td> <td>First 3 rats</td> <td>Days 8 and 49</td> <td>1, 2, and 4 h postdose</td> </tr> <tr> <td>2 and 3</td> <td>First 4 rats/group</td> <td>Days 8 and 49</td> <td>1, 2, 4, 7, 12 and 24 h postdose</td> </tr> </tbody> </table> <p><sup>a</sup> Blood collection times were approximate.</p>	Group	Set	Dosing Phase	Time Points <sup>a</sup>	1 (Control)	First 3 rats	Days 8 and 49	1, 2, and 4 h postdose	2 and 3	First 4 rats/group	Days 8 and 49	1, 2, 4, 7, 12 and 24 h postdose
Group	Set	Dosing Phase	Time Points <sup>a</sup>										
1 (Control)	First 3 rats	Days 8 and 49	1, 2, and 4 h postdose										
2 and 3	First 4 rats/group	Days 8 and 49	1, 2, 4, 7, 12 and 24 h postdose										
<u>Gene Expression</u>	Liver and right kidney, all animals euthanized at a scheduled or												

<u>Analysis</u>	unscheduled Euthanasia. Four genes associated with gluconeogenesis (PGC1a, PEPCK, G6PC, and FOXO1) and four housekeeping genes (ACTB, GAPDH, B2M, and HPRT1) were evaluated by quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) using standard methods.
<u>Transmission Electron Microscopy (TEM)</u>	Pancreas and right adrenal (cortex) tissues All animals euthanized at a scheduled or unscheduled interval,
<u>Immunohistochemistry</u>	Pancreas and right eye tissues all rats euthanized at a scheduled or unscheduled interval

**RESULTS:**

Mortality: No palbociclib-related mortality occurred.

Seven rats died or were euthanized at an unscheduled interval during the dosing phase.

Group 1 (control):

2 males (B20915 and B20918), on Day 15 and 46-

Cause of death: gavage-related

2 males (B20920 and B20922), on Day 57 or 67

Cause of death: not evident based on results of the anatomic pathology

Group 4 (100 mg/kg):

1 male (B20944), on Day 15

Cause of death: not evident based on results of the anatomic pathology

Note: The body weight loss was approximately 24% from Day 1,

roughly 2x higher than any other rat administered 100 mg/kg/day during the same interval.

Group 5 (control):

1 male (Animal B26216): found dead, day 9

Cause of death: had minimal clinical observations that were consistent with findings seen in other study rats, and a cause of death could not be determined from the anatomic pathology data

Group 6 (100 mg/kg):

1 male (B26226): found dead, day 9

Cause of death: cause of death could not be determined from the anatomic pathology data; no abnormal clinical observations prior to its death and body weight loss (-14 g) was minimal

Although 2 males administered 100 mg/kg/day died or were euthanized during the first cycle of their dosing phase without an obvious cause, neither animal presented with palbociclib-related clinical observations and one demonstrated minimal body weight loss while the other lost a notable amount of body weight. Based on the data for these males and all other males administered 100 mg/kg/day (4 or 7 cycles), and considering the deaths of 3 control animals, also without obvious cause, the moribund condition/euthanasia and death of the 2 males administered 100 mg/kg/day were not considered palbociclib-related.

Clinical Signs

Table 1 Summary of Clinical Observations

Duration of study	27 week			15 week	
Group	1	2	3	4	5
Dose (mg/kg)	0	30	100	0	100
Number of animals	16	16	16	10	10
Appearance					
hunched			1		
raised area umbilical, midline abdomen swollen, left hind digits	3	7	7	2	3
swollen, right hind digits		1	1		
teeth, bottom, left incisor, white			3		2
teeth, bottom, right incisor, white			4		2
teeth, top, left incisor, white			14		7
teeth, top, right incisor, white			13		7

Body Weights

Figure 1 Changes of body weights (27-week)

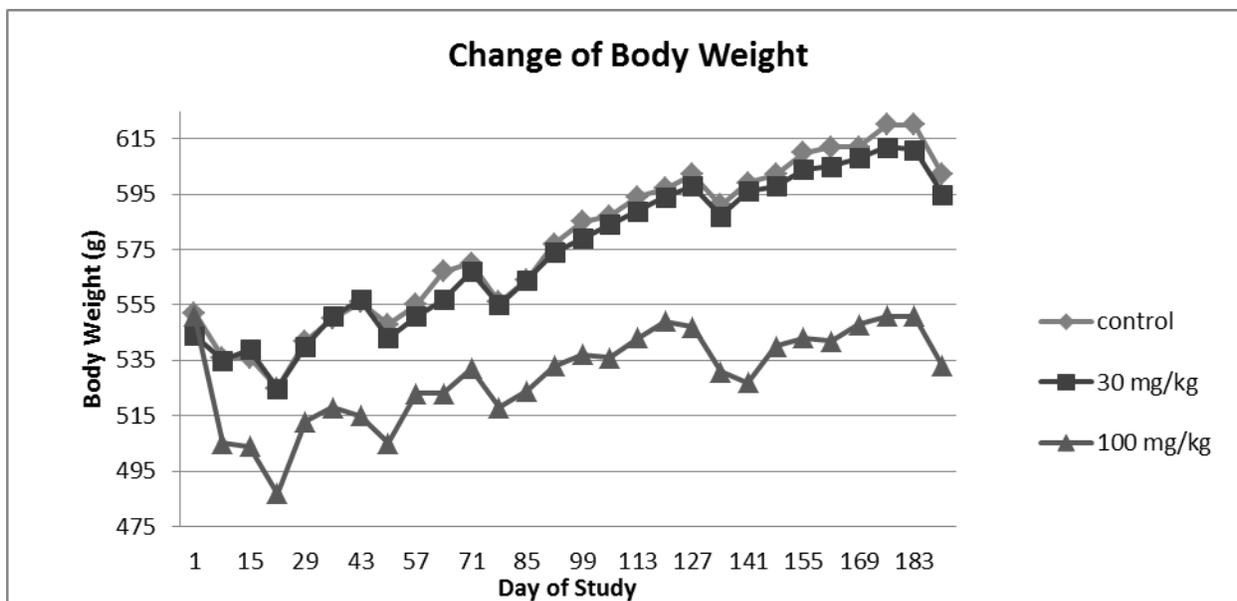
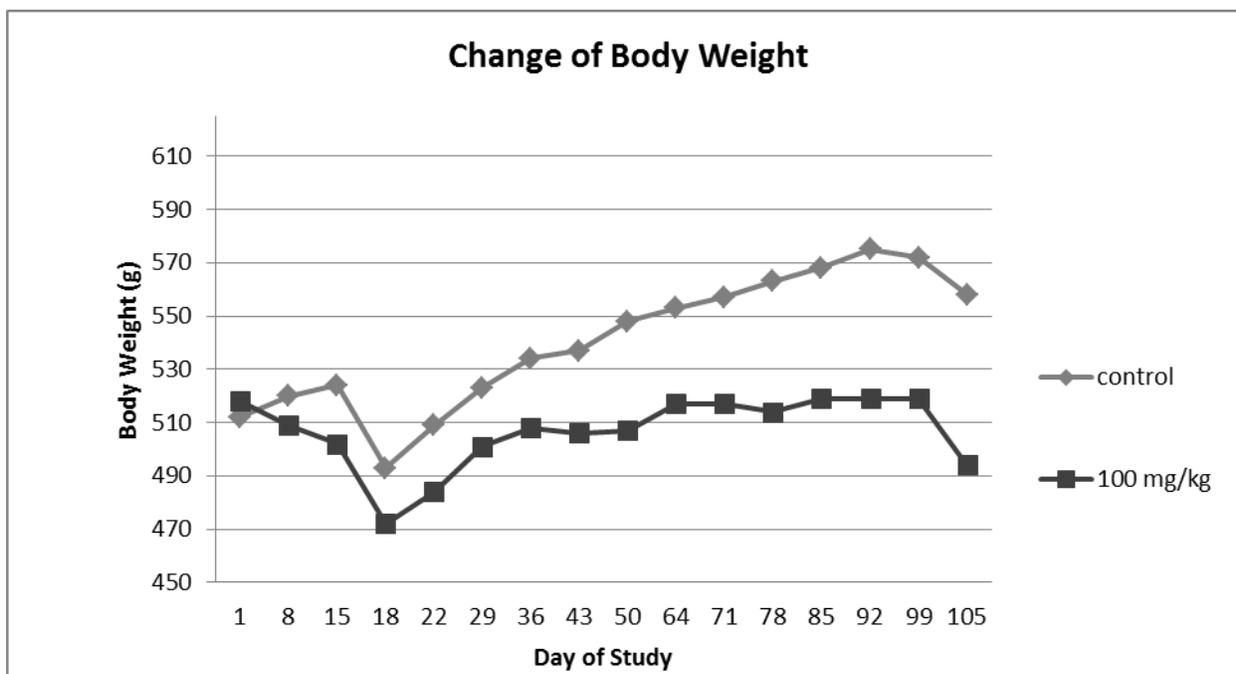


Figure 2 Changes of body weights (15-week)



**Summary:** Dose dependent decreased body weights were observed. At the end of the respective dosing phases (Day 105 or 189), the mean body weight of males administered 100 mg/kg/day was approximately 11% lower compared with the concurrent control (statistically significant).

Food Consumption: unremarkable

Ophthalmoscopy: unremarkable

Hematology (including HbA1c): unremarkable

Clinical Chemistry (including Insulin, C-Peptide, and Corticosterone Analyses): unremarkable

Oral Glucose Tolerance Test (OGTT) with Glucose and Insulin Analyses: unremarkable

Urinalysis: unremarkable.

Gross Pathology

Table 2 Incidence of Palbociclib-Related Macroscopic Findings

Duration of study	27 week (terminal)			15 week (interim)	
	1	2	3	4	5
Group	0	30	100	0	100
Dose (mg/kg)	12	16	15	9	9
Number of animals					
Tooth, Right Lower Incisor Discolored Present			2		2
Tooth, Right Upper Incisor Discolored Present			6		7

## Organ Weights:

Table 3 Summary of organ weight (27-week rat Study)

	Percentage deviation from control (n=12)			
	Absolute Organ Weight		Organ Weight/body Weight	
Dose Group (mg/kg)	30	100	30	100
Number animals./group	16	15	16	15
Spleen	-5	-28*	-4	-19*
Testis		-25*		-15*

Blank cells: unremarkable

\*: P&lt; 0.05

Note: Histopathological correlates were not determined because no microscopic examinations were performed on the spleen and testis according to the protocol. Decreased cellularity (lymphoid and red cells) in the spleen and seminiferous degeneration in the testis with lower organ weights in the spleen and testis were observed in the repeated dose toxicology studies in young rats.

## Histopathology

Table 4 Incidence and Severity of Palbociclib-Related Microscopic Findings

Duration of study	27 week (terminal)			15 week (interim)	
	1	2	3	4	5
Group	1	2	3	4	5
Dose (mg/kg)	0	30	100	0	100
Number of animals	12	16	15	9	9
Tooth, Right Lower Incisor					
Degeneration/necrosis, ameloblasts					
			6		6
			4		2
Infiltrate, mononuclear cell, pigmented					
			4		5
			5		1
Infiltrate, neutrophil					
			1		
			1		
Tooth, Right Upper Incisor					
Degeneration/necrosis, ameloblasts					
			3		3
			10		3
			1		2
Infiltrate, mononuclear cell, pigmented					
			3		3
			10		2
			1		1
Infiltrate, neutrophils					
			1		

Liver					
Vacuolation, hepatocyte	-Minimal	6		5	8
	-Mild			1	
	-Moderate				2

Others:

## Gene Expression Analysis:

Note: Four genes associated with gluconeogenesis (PGC1a, PEPCK, G6PC, and FOXO1) and four housekeeping genes (ACTB, GAPDH, B2M, and HPRT1) were evaluated by quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) using standard methods.

There was a statistic decrease in the expression of phosphoenolpyruvate carboxykinase (PEPCK) for rat administered 100 mg/kg/day for 7 cycles.

Transmission Electron Microscopy (TEM): unremarkable

Immunohistochemistry: The Ki-67 immunoreactivity of insulin-staining islet cells was generally very low ( $\leq 12$  cells) in controls. For animals that received palbociclib, there was consistently no Ki-67 positivity in insulin-staining islet cells. No palbociclib-related change was evident in Ki-67 immunoreactivity of ocular lens capsular cells.

Note: 1) Pancreas tissue was immunolabeled for detection of insulin, glucagon, Ki-67, and cleaved caspase-3 (singly or in multiplex detection). Eye tissue was immunolabeled for detection of Ki-67 and cleaved caspase-3 (singly or in multiplex detection).

2) The absence of Ki-67 immunoreactivity in animals administered palbociclib suggested that no beta cells were active in the cell cycle. The absence of caspase-3 immunoreactivity suggested this pathway of cell death was not triggered in the cells.

Toxicokinetics:

Table 5 Summary of Toxicokinetic Parameters in rats (palbociclib) (27-week rat study)

Study day	Dose level (mg/kg/dose)	C <sub>max</sub> (ng/mL)	Dose Normalized C <sub>max</sub>	AUC <sub>0-24</sub> (ng.h/mL)	Dose Normalized AUC <sub>0-24</sub>	t <sub>max</sub> (h)
8	30	806	27	13300	443	7
	100	1990	20	36700	367	3
49	30	755	25	12700	423	6
	100	2270	23	36400	364	2

## Conclusion:

- On Days 8, 49 plasma exposures (C<sub>max</sub> and mean AUC<sub>0-24</sub>) were increased in proportion to the dose increases from 30 mg/kg to 100 mg/kg.
- No apparent accumulation was observed following repeated dosing;
- T<sub>max</sub> ranged from 2 to 7 hours in male rats.

Note: Plasma exposures (C<sub>max</sub> and mean AUC<sub>0-24</sub>) were increased in proportion to the dose increases from 10 mg/kg to 30 mg/kg, but increased less than proportionally to the dose increases from 30 mg/kg to 100 mg/kg in the 27-week study with male young rats. The plasma exposures at 100 mg/kg in aged rats on Day 49 were similar to that in young rats on Day 103.

## 11 Integrated Summary and Safety Evaluation

Table 6 Toxicology tabulated summary

Repeat Dose Toxicity Studies			
Duration	27-week		
GLP compliance	yes		yes
Species	Young rats (6-7 weeks)*		Aged rats (12 months)
Test System	Oral gavage		Oral gavage
Schedule	Daily x 21, 28 days/cycle		Daily x 21, 28 days/cycle
Dose (mg/kg/day)	Male: 10, 30, 100 Female: 50, 100, 300		Male: 30, 100 mg/kg
Mortality	100 mg/kg: 7/20 males, 1/20 female The cause of death (5/8 males): Degeneration and/or inflammation in one or more of the feet		None of any treatment-related
Clinical sign	rigid stance; swollen feet, legs, abdomen, penis, or perioral area; white incisor teeth; thin appearance; hypoactivity; lateral recumbence; nonformed feces; clear or red oral discharge; pale eyes, feet, ears, tail, or oral mucosa; audible or irregular respiration; cold to touch (entire body or hind feet); discolored (yellow) skin on the ears, entire body, feet, nose, or tail; discolored (red) skin on the feet, nose, penis, or tail; discolored (red) haircoat on the entire head, nose, perioral; and rough haircoat. reversible		Male: 100 mg/kg discolored white incisor teeth
Body weight	Male: ↓ up to 38% dose dependent	Female: ↓ up to 14% dose dependent	Male: ↓ up to 11% dose dependent
Food consumption	Male: ↓ at 100 mg/kg (↓ up to 28% at week1) Dose dependent	Female: at 300 mg/kg ( ↓ up to 17% at week5) Dose dependent	-
Ophthalmoscopy	Male: Lens cataract at 100 mg/kg	Females: -	Male: -

Hematology	Male: ↓ WBC (↓up to 59%) ↓RBC (↓up to 37%) ↑RETIC(↑up to 94%) Dose dependent reversible	Female: ↓ WBC (↓up to 17%) ↓RBC (↓up to 18%) ↑RETIC(↑up to 34%) Dose dependent reversible	Male: -
Clinical chemistry	Male: 100 mg/kg ↑GLU, UN, ↑AST, ALT, ALP Not recovery after 12 weeks		-
Urinalysis	-		-
Organ weight	Male: ↓ spleen(↓44%), , testes (↓40%), thymus, epididymis ↑ adrenal reversible		Male: ↓ spleen(↓28%), testes (↓25%)  Reversibility: unknown
Gross Pathology	100 mg/kg: foot, tooth, adrenal, lung, GI, spleen, kidney, male reproductive system. reversible		Male: 100 mg/kg/day Discoloration of incisor teeth Reversibility: unknown
Histopathology	Male: -Hypocellularity in bone marrow, spleen, lymph nodes, thymus; -Degeneration in kidney and chronic progressive nephropathy; -Degeneration in tooth; -Islets cells vacuolar change in pancreas; -Vacuolation in liver; -Lens degeneration in eyes -Degeneration in testes, Epididymides; -Adipose atrophy in skin.	Female: -Hypocellularity in bone marrow, lymph nodes; -Islets cells vacuolar change in pancreas; -lens degeneration in eyes. Reversible	Male: 100 mg/kg/day -ameloblast degeneration/ necrosis and neutrophilic inflammation and macrophage infiltrate in the incisor teeth; -vacuolation in liver Reversibility: unknown Note: compared to the adverse effects observed in young rats 1. There were no changes in <u>kidney, pancreas, eyes</u> ; 2. No evaluation were performed in bone marrow, spleen, lymph nodes, thymus; testes, skin.

	Changes in eye and kidney did not recover, others reversible		
HbA1c	n/a, not measured		-
Oral Glucose Tolerance Test (OGTT)	n/a, not performed		-
Insulin and C-Peptide Analysis	<p>≥ 30 mg/kg ↓ up to 60%, dose dependent Note: changes of insulin values correlated with microscopic findings of lens degeneration, pancreatic islet cell vacuolation, ameloblast degeneration and/or renal tubuloepithelial cell vacuolation.</p>	<p>≥100 mg/kg ↓ up to 20%,</p>	-
Immuno-histochemistry	<p>Immunoreactivity to insulin in the Pancreas 100 mg/kg</p> <ul style="list-style-type: none"> <li>•Reduction in the relative percentage of beta cell area;</li> <li>•Reduction in the percentage and total number of beta cells;</li> <li>•Higher average alpha cell size.</li> </ul>		-
Transmission Electron Microscopy	<p>Pancreatic islet vacuoles</p> <ul style="list-style-type: none"> <li>• Unscheduled necropsy (1 male at 100 mg/kg): Beta cell granules larger than those present in controls. Note: Because only one was submitted for examination, the relationship of this finding to PD-0332991 was not clear.</li> <li>• Terminal necropsy (3 males at 100 mg/kg/day): 2 animals had vacuoles in their Beta cells that were correlate of the light microscopic finding.</li> <li>• Recovery animals (3 males at 100 mg/kg/day):</li> </ul>		<p>n/a Note: Pancreases and right adrenal (cortex) tissue were collected; however analysis/Evaluation of embedded tissue was not conducted.</p>

	unremarkable.			
Gene Expression	Liver Applicant stated that study results could not be interpreted.			Liver and right kidney A statistical decrease in the expression of PEPCK at 100 mg/kg/day
TK	Male: Day 103			Male: on Day 49
	Dose (mg/kg)	C <sub>max</sub> (ng/mL)	AUC (ng.h/mL)	Dose (mg/kg)
	30	1490	21700	30
	100	2060	35000	100
				C <sub>max</sub> (ng/mL)
				755
				2270
				AUC (ng.h/mL)
				12700
				36400

\*Reviewed under NDA 207103 (the nonclinical review 1/17/2015)

“-“ unremarkable, n/a: not applicable

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/s/  
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WEI CHEN  
03/24/2017

TODD R PALMBY  
03/27/2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207103Orig1s004**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## Clinical Pharmacology NDA Review

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<b>NDA</b>	207103/SDN 426
<b>Brand Name</b>	Ibrance™
<b>Generic Name</b>	Palbociclib
<b>Submission Date</b>	10/27/2016
<b>Submission Type; Code</b>	Prior Approval Labeling Supplement 004
<b>Review Classification</b>	Priority
<b>PDUFA Due Date</b>	April 27, 2017
<b>Proposed Dosage Form / Strength</b>	125 mg, 100 mg, and 75 mg capsules
<b>Proposed Dosing Regimen</b>	125 mg once daily taken with food for 21 days followed by 7 days off treatment.
<b>Proposed Indication</b>	Indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with: <ul style="list-style-type: none"><li>• an aromatase inhibitor as initial endocrine based therapy in postmenopausal women;</li></ul>
<b>Related IND</b>	69324
<b>Applicant</b>	Pfizer Inc.
<b>OCP Reviewer</b>	Wentao Fu, Ph.D.
<b>Pharmacometrics Reviewer</b>	Jingyu (Jerry)Yu, Ph.D.
<b>OCP Team Leader</b>	Qi Liu, Ph.D.
<b>Pharmacometrics Team Leader</b>	Jingyu (Jerry)Yu, Ph.D.
<b>OCP Division</b>	Division of Clinical Pharmacology V (DCP V)
<b>Clinical Division</b>	Division of Oncology Products 1 (DOP1)

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## EXECUTIVE SUMMARY

Palbociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Palbociclib was granted accelerated approval on February 3, 2015 for use in combination with *letrozole* (*an aromatase inhibitor*) for the treatment of postmenopausal women with estrogen receptor –positive (ER+), human epidermal growth factor receptor 2 –negative (HER2-) advanced breast cancer as initial endocrine-based therapy for their metastatic disease. The approval was based on the efficacy and safety data from a Phase 2 Study 1003 (PALOMA-1). Under Efficacy Supplement-2 (SDN 193, 194, 221), palbociclib was approved on February 19, 2016 for use in combination with fulvestrant for the treatment of women with hormone receptor–positive (HR+), HER2- advanced or metastatic breast cancer with disease progression following endocrine therapy based on results from a Phase 3 Study 1023 (PALOMA-3).

Under current submission of Efficacy Supplement-4 (SDN 426), the applicant seeks the full approval for the use of palbociclib in combination with *an aromatase inhibitor* as initial endocrine based therapy for the treatment of women with HR+, HER2- advanced or metastatic breast cancer. The recommended palbociclib starting dose, which is the same as the previous approvals, is 125 mg once daily taken with food for 21 days followed by 7 days off treatment.

In support of full approval, results from a confirmatory, randomized, double-blind, placebo-controlled, parallel-group Phase 3 Study 1008 (PALOMA-2), comparing the efficacy and safety of palbociclib + letrozole (N=444) versus placebo + letrozole (N=222) in postmenopausal women with ER-positive/HER2-negative advanced breast cancer who had not received any prior systemic anticancer therapies for their advanced disease. In the Phase 3 Study, 125 mg palbociclib or placebo was administered orally once daily on Days 1 to 21 of each 28-day cycle and 2.5 mg letrozole was administered orally once daily. The addition of palbociclib to letrozole resulted in a statistically significant improvement in the primary endpoint, investigator-assessed progression free survival (PFS). The median PFS was 24.8 months (95% CI: 22.1, not estimable) in the palbociclib + letrozole arm and 14.5 months (95% CI: 12.9, 17.1) in the placebo + letrozole arm. The hazard ratio was 0.576 (95% CI: 0.463, 0.718). In a ECG subgroup analysis (N=77), no large QTc prolongation effect of palbociclib + letrozole was detected on from the Phase 3 Study 1008. The largest upper bound of the 2-sided 90% CI for the mean difference between palbociclib + letrozole and placebo + letrozole was below 10 ms. In an exposure response (E-R) analysis using Study 1008 results, investigator-assessed PFS prolongation was not significantly associated with palbociclib exposure at the fixed dose of 125 mg palbociclib. Palbociclib is proposed in combination with an aromatase inhibitor (letrozole, anastrozole or exemestane). However, the Phase 3 Study 1008 only evaluated letrozole in combination with palbociclib. For aromatase inhibitors anastrozole or exemestane, no clinical data are available to evaluate drug interactions between anastrozole or exemestane and palbociclib. A clinically significant drug interaction between anastrozole or exemestane and palbociclib is not expected based on mechanistic understandings of the potentials of palbociclib, anastrozole, and exemestane as a perpetrator or a victim.

## 1.1 RECOMMENDATIONS

The NDA labeling supplement is acceptable from a clinical pharmacology perspective, provided that the applicant and the agency come to a mutually satisfactory agreement regarding the labeling language.

## 1.2 POST-MARKETING REQUIREMENTS (PMRS) AND COMMITMENTS (PMCS)

There are no clinical pharmacology requested PMRs or PMCs.

Signatures:

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Wentao Fu, Ph.D.

Clinical Pharmacology Reviewer

Division of Clinical Pharmacology V

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Qi Liu, Ph.D.

Team Leader

Division of Clinical Pharmacology V

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Cc: DDOP1: MO –Suparna Wedam; MTL – Laleh Amiri Kordestani; RPM – Amy Tilley

DCP V: DDD –Brian Booth; DD – Atiqur Nam Rahman

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## 2 CLINICAL PHARMACOLOGY REVIEW

*(Reviewer's Note: For brevity, updates related to the current labeling supplement submissions are addressed below. For additional information, please refer to the clinical pharmacology reviews dated January 15, 2015 for original NDA 207103 submission and dated February 10, 2016 for Supplement-2 submission in DARRTS.)*

### 2.1 INTRODUCTION

Palbociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Palbociclib was granted accelerated approval on February 3, 2015 for use in combination with *letrozole (an aromatase inhibitor)* for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. The approval was based on the efficacy and safety data from a Phase 2 Study 1003 (PALOMA-1). Under Efficacy Supplement-2 (SDN 193, 194, 221), palbociclib was approved on February 19, 2016 for use in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy based on results from a Phase 3 Study 1023 (PALOMA-3). Under current submission of Efficacy Supplement-4 (SDN 426), the applicant seeks the full approval for the use of IBRANCE in combination with *an aromatase inhibitor* as initial endocrine based therapy for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer.

The proposed palbociclib starting dose, which is the same as the previous approvals, is 125 mg once daily taken orally with food in combination with an aromatase inhibitor (letrozole, anastrozole or exemestane) for 21 days followed by 7 days off treatment.

### 2.2 GENERAL CLINICAL PHARMACOLOGY

#### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Study 1008 (PALOMA-2) was an international, randomized, double-blind, parallel-group, multicenter study of palbociclib plus letrozole versus placebo plus letrozole conducted in postmenopausal women with ER+, HER2- advanced breast cancer who had not received previous systemic treatment for their advanced disease. A total of 666 patients were randomized 2:1 to palbociclib plus letrozole (Arm A; N=444) or placebo plus letrozole (Arm B; N=222). Patients in Arm A received palbociclib (125 mg orally QD on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment) in combination with letrozole (2.5 mg orally QD) and patients in Arm B (control arm) received placebo (orally QD on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment) in combination with letrozole (2.5 mg orally QD). The study also included:

- QTc monitoring to evaluate the effect of palbociclib on QT interval via triplicate ECGs time-matched with select serial PK draws (subset study in 77 patients enrolled at selected sites, Group 1);

- Quantification of trough palbociclib plasma concentration;

The QTc and Pharmacokinetic schedule for Group 1 (77 patients in QTc subgroup) and Group 2 (all other patients) of activities are list in Table 1.

Table 1. Pharmacokinetic and Electrocardiograms, Schedule of Activities

Protocol Activity	Screening							Active Treatment Phase							End of Treatment
	Within 28 days prior to randomization unless specified otherwise							Cycle 1				Cycle 2	Cycle ≥4		
	Day -27 to Day 0	Day 0 (day prior to Day 1)						Day 1	Day 14				Day 14	Day 1	
	ECG <sub>E</sub> <sup>a</sup>	ECG1 <sup>b</sup>	2 Hrs Post-ECG1	4 Hrs Post-ECG1	6 Hrs Post-ECG1	8 Hrs Post-ECG1	0 Hrs Predose	0 Hrs Postdose	2 Hrs Postdose	4 Hrs Postdose	6 Hrs Postdose	8 Hrs Postdose	0 Hrs Predose	0 Hrs Postdose	
<b>Group 1 (approx. 60 Patients) at selected sites</b>															
12 Lead ECG <sup>2</sup>	X	X	X	X	X	X	X <sup>a</sup>	X	X	X	X	X	X	X	X
Pharmacokinetics <sup>3</sup>								X	X	X	X	X	X		
<b>Group 2 (All other patients)</b>															
12 Lead ECG <sup>2</sup>	X						X <sup>a</sup>	X					X	X	X
Pharmacokinetics <sup>3</sup>								X					X		

\*ECG<sub>E</sub>=TriPLICATE ECGs performed to determine patient's eligibility.  
<sup>b</sup>ECG1=First triplicate ECGs performed for patients in Group 1.  
a. **12-lead ECG:** A 12-lead (with a 10-second rhythm strip) tracing was to be used for all ECGs. ECGs were performed in triplicate approximately 2 minutes apart but within 10 minutes for all 3 ECGs. It was preferable that the machine used had the capacity to calculate the standard intervals automatically. ECG interval readings by the ECG recorder's algorithm were read and interpreted at the investigational site for eligibility determination and patient safety monitoring and documentation stored in the source documents. Blinded manual interval measurements at a core ECG laboratory were used for primary statistical analysis of ECG data in group 1 patients (as described below). ECG measurements included PR interval, QT interval, RR interval and QRS complex. Additional ECGs could be performed as clinically indicated.  
TriPLICATE ECGs were performed during the screening period for all patients to determine the mean QTc for eligibility purpose.  
Patients found to be eligible were part of one of the 2 groups highlighted below, depending on which site screened the patient. ECG frequency for each group is described below:  
  
Group 1 (approximately 60 patients) at selected sites:

- On the day preceding treatment initiation (Day 0), triplicate ECGs were obtained at time 0 (first ECG also referred to as ECG1), and then 2, 4, 6, and 8 hours after ECG1.
- At Cycle 1 Day 14, triplicate ECGs were obtained at 0 hour (predose) and then, 2, 4, 6, and 8 hours following palbociclib/placebo dosing. Timing of ECGs performed on Day 14 had to be time-matched (clock time +/- 35 minutes) with ECG assessments performed on Day 0 (eg, if ECG1 on Day 0 was performed at 10:00 AM then the 0 hour triplicate ECGs on Day 14 had to be performed within the 9:25AM-10:35AM timeframe but as close as possible to 10:00AM whenever feasible). On Day 14 of Cycle 1, study treatment was to be administered immediately after the predose PK draw was collected.

b. **Pharmacokinetics (collected right after ECG assessment):** For patients in the ECG Group 1, plasma PK samples for palbociclib (including its active metabolites, if appropriate) determination were obtained at the times indicated for ECGs. One additional plasma PK sample was collected predose on Day 14 of Cycle 2.  
For all other patients (ECG Group 2), plasma PK samples for palbociclib (including its active metabolites, if appropriate) determination were collected prior to dosing (predose) on Day 14 of Cycle 1 and Cycle 2.  
Additional blood samples could be requested from patients experiencing unexpected or SAEs, or AEs that led to discontinuation.

Source Table 2 of Full Clinical Study Report Protocol A5481008 (Report Date 04 October 2016; Date of Data Cutoff 26 February 2016)

The primary efficacy endpoint is investigator-assessed PFS. The addition of palbociclib to letrozole resulted in a statistically significant improvement in the primary endpoint. The median PFS was 24.8 months (95% CI: 22.1, not estimable) in the palbociclib + letrozole arm and 14.5 months (95% CI: 12.9, 17.1) in the placebo + letrozole arm. The hazard ratio was 0.576 (95% CI: 0.463, 0.718). In a ECG subgroup analysis (N=77), no large QTc prolongation effect of palbociclib + letrozole was detected on from the Phase 3 Study 1008. The largest upper bound of the 2-sided 90% CI for the mean difference between palbociclib + letrozole and placebo + letrozole was below 10 ms. In an E-R analysis using Study 1008 results, investigator-assessed PFS prolongation was not significantly associated with palbociclib exposure at the fixed dose of 125 mg palbociclib.

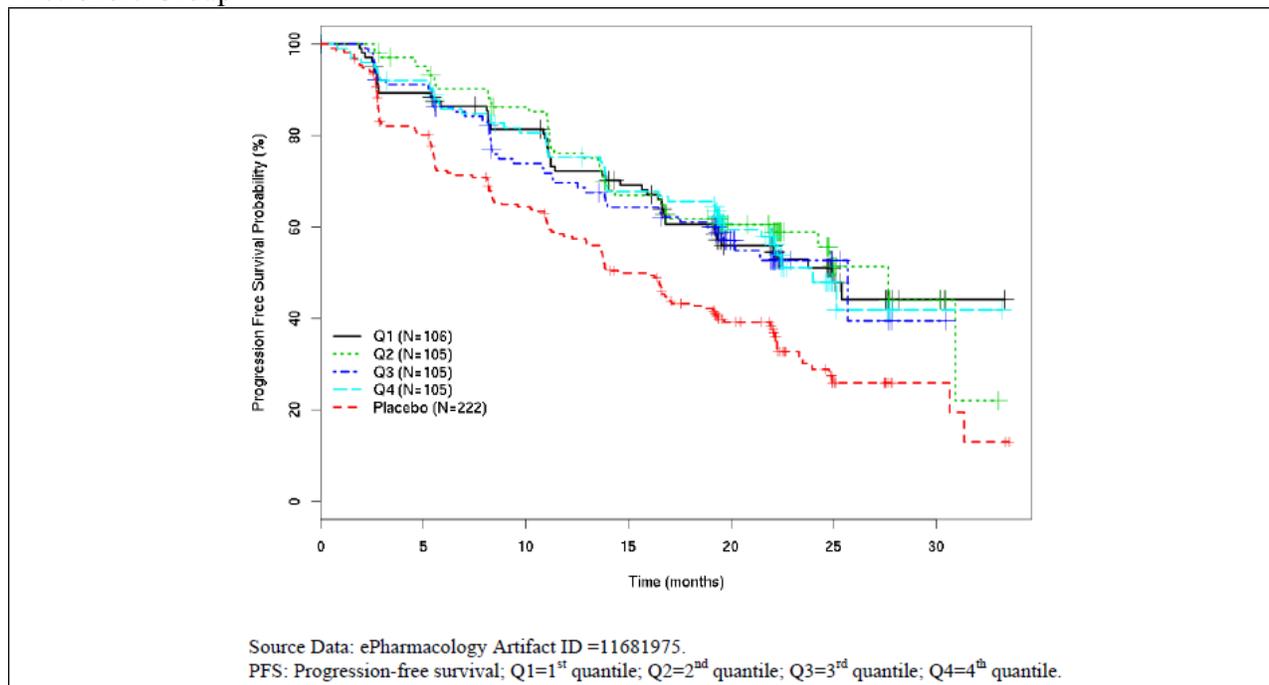
## 2.2.2 What are the update on clinical pharmacology study results

ECG subgroup analysis for QTc prolongation: No large QTc prolongation effect of palbociclib + letrozole was detected on from the Phase 3 Study 1008 (N=77). The largest upper bound of the 2-sided 90% CI for the mean difference between palbociclib + letrozole and placebo + letrozole was 5.1 ms, which is below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. Palbociclib had no large effect on QTc (i.e. > 20 ms) at 125 mg once daily. The assay sensitivity was not accessed because there was no positive control in this study (See QT Study Review in DARRTs dated 01/24/2017 for detail).

The conclusion from current QT-IRT review is the same as that form the previous QT-IRT review of palbociclib based on data collected from Studies 1001, 1002, and 1003 (See QT Study Review in DARRTs dated 10/22/2014 for detail). The review team concluded that QT interval prolongation is not likely to be clinically relevant.

E-R relationship: The exposure response (E-R) analysis using Study 1008 results concluded that investigator-assessed PFS was not significantly associated with palbociclib exposure at the fixed dose of 125 mg palbociclib. The Kaplan-Meier plot of the quantile palbociclib exposure and placebo plus letrozole groups using Study 1008 is presented in **Figure 1**. In addition, the PFS did not appear to be associated with palbociclib exposure after Cox univariate and multivariate analysis with and without consideration about the dose modifications.

Figure 1: Kaplan-Meier Plot of Palbociclib Exposure Quantile Groups and Placebo Plus Letrozole Group



Sources Sponsor's report "Exposure Response Analysis of Palbociclib Exposure and the Progression-Free Survival (PFS) in Patients with Advanced Breast Cancer, Page 18"

### **2.2.3 Does the exposure-response analysis for efficacy and safety support the proposed dose?**

Yes. The proposed dose regimen was supported by the flat E-R relationship for PFS in Study 1008 and positive E-R relationship for lower neutrophil counts in other studies (see Pharmacometrics Review section in clinical pharmacology review in DARRTs dated 02/05/2016 and 01/25/2015 for detail).

### **2.2.4 What are the drug-drug interaction potentials between palbociclib and anastrozole or exemestane?**

No clinical data are available to evaluate drug interactions between anastrozole or exemestane and palbociclib. A clinically significant drug interaction between anastrozole or exemestane and palbociclib is not expected based on analyses of the potentials of palbociclib, anastrozole, and exemestane as a perpetrator or a victim.

#### Palbociclib (recommended dose 125 mg once daily (QD)):

As a perpetrator: A weak CYP3A time dependent inhibitor (TDI). Palbociclib 125 mg QD increased midazolam (a sensitive CYP3A substrate) AUC by 61% and Cmax by 37%.

As a victim: Mainly metabolized by CYP3A and SULT2A1

Anastrozole (recommended dose 1 mg QD): Anastrozole has a wide therapeutic window. Recommended dose is 1 mg QD for postmenopausal women with advanced breast cancer. Up to 10 mg QD dose of anastrozole given to postmenopausal women with advanced breast cancer were well tolerated

As a perpetrator: Anastrozole (1mg QD) is unlikely affect other drugs by inhibition of cytochrome P450. In vitro anastrozole inhibits CYP1A2, 2C8, 2C9, and 3A4 with Ki values ~30 fold higher than the steady-state Cmax values observed at 1mg QD.

As a victim: It is not a sensitive CYP3A substrate and is cleared by CYP3A and other pathways.

#### Exemestane (recommended dose 25 mg QD)

As a perpetrator: In vitro does not inhibit any of the major isoenzymes, including CYP1A2, 2C9, 2D6, 2E1, and 3A4.

As a victim: It is primarily metabolized by CYP3A4 and aldoketoreductases. However, in vivo concomitant use of ketoconazole, a strong inhibitor of CYP3A4, had no significant effect on exemestane pharmacokinetics

### 3 DETAILED LABELING RECOMMENDATIONS

The applicant proposed labeling changes are in the left column. FDA proposed labeling changes are in the right column. The changes of **red fonts** proposed by the applicant to black ones with underscore indicate the content is acceptable. **Green fonts** indicate the content that is added by the agency, and a ~~strike through~~ indicates the content that is taken out from the proposed label by the agency. FDA proposed labeling changes were conveyed to the applicant on March 10, 2017. The applicant agreed with all the changes.

The Applicant's Proposed Labeling Changes	FDA Proposed Labeling Changes
<p>----- <b>DOSAGE AND ADMINISTRATION</b> -----            IBRANCE capsules are taken orally with food in combination with <b>an aromatase</b> inhibitor or fulvestrant. (2)</p>	<p>----- <b>DOSAGE AND ADMINISTRATION</b> -----            IBRANCE capsules are taken orally with food in combination with <u>an aromatase</u> inhibitor or fulvestrant. (2)</p>
<p><b>7.3 Drugs That May Have Their Plasma Concentrations Altered by Palbociclib</b></p> <p>Coadministration of midazolam with multiple doses of IBRANCE increased the midazolam plasma exposure by 61%, in healthy subjects, compared <b>to</b> administration of midazolam alone. The dose of the sensitive CYP3A substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimoziide, quinidine, sirolimus, and tacrolimus) may need to be reduced, as IBRANCE may increase <b>its</b> exposure [see Clinical Pharmacology (12.3)].</p>	<p><b>7.3 Drugs That May Have Their Plasma Concentrations Altered by Palbociclib</b></p> <p>Coadministration of midazolam with multiple doses of IBRANCE increased the midazolam plasma exposure by 61%, in healthy subjects, compared <u>to</u> administration of midazolam alone. The dose of the sensitive CYP3A substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimoziide, quinidine, sirolimus, and tacrolimus) may need to be reduced, as IBRANCE may increase <u>its</u> exposure [see Clinical Pharmacology (12.3)].</p>
<p><b>12.2 Pharmacodynamics</b></p> <p><b>Cardiac Electrophysiology</b></p> <p>The effect of palbociclib on the QT interval <b>corrected for heart rate (QTc)</b> was evaluated <b>using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with breast cancer.</b> (b) (4)</p>	<p><b>12.2 Pharmacodynamics</b></p> <p><b>Cardiac Electrophysiology</b></p> <p>The effect of palbociclib on the QT interval <u>corrected for heart rate (QTc)</u> was evaluated <u>using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with breast cancer.</u> (b) (4)</p> <p><b>albociclib had no large effect on QTc (i.e. &gt; 20 ms) at 125 mg once daily (Schedule 3/1).</b></p>
<p><b>12.3 Pharmacokinetics</b></p> <p>.....</p> <p><b>Drug Interactions</b></p> <p>.....</p>	<p><b>12.3 Pharmacokinetics</b></p> <p>.....</p> <p><b>Drug Interactions</b></p> <p>.....</p> <p><b>Anastrozole or exemestane: No clinical data are available to evaluate drug interactions between anastrozole or exemestane and palbociclib. A clinically significant drug interaction between anastrozole or exemestane and palbociclib is not expected based on analyses of the effects of anastrozole, exemestane and palbociclib on or by metabolic pathways or transporter systems.</b></p>

## 4 APPENDIX

### Clinical Pharmacology Information Request related to drug-drug interaction between palbociclib and anastrozole or exemestane.

1. Clinical Pharmacology December 16, 2016 (information request and response to information request in DARRTs dated 12/23/2016 (SDN 473))  
Reference is made to your “2.7.2 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES”. There are completed and ongoing clinical studies to evaluate DDI potentials between palbociclib and aromatase inhibitors (anastrozole and exemestane). Provide your available analysis results for the completed studies and provide a timeline on the ongoing studies results submissions. All related datasets and/or code/control streams should also be submitted along with your analysis results.

Applicant’s response related to it studies:

Two studies evaluating the safety and efficacy of the combination of palbociclib and anastrozole are ongoing or have completed. A single-arm neoadjuvant Investigator Initiative Research (IIR) study (Phase 2 study at Washington U, St Louis, Missouri, NCT01723774)<sup>3</sup> in patients with early breast cancer has completed, and safety and efficacy results from this study are included in the response to [Section 2.1](#) below and in [Appendix 1](#). In this study, sparse PK sampling of anastrozole and palbociclib were incorporated in the study protocol in a late protocol amendment. However, it has since been determined that very few PK samples were actually collected in this study and the PK samples were not sent by the study Sponsor for analyte concentration determination within the timeframe of established stability for the respective bioanalytical methods. Supportive PK data from this study is no longer expected.

The second study evaluating the palbociclib plus anastrozole combination is the ongoing double-blind Phase 3 CRC study PENELOPE-B (GBG 078/NSABP B-54-1/BIG 1-13, NCT01864746), a study in patients with HR-positive, HER2-negative primary breast cancer with high relapse risk after neoadjuvant chemotherapy. In this study, patients enrolled in the PK/safety assessment group receiving palbociclib/placebo plus anastrozole will have intensive PK samples drawn at steady state until data from approximately 24 PK-evaluable patients are available. The PK data will be used to conduct a 2-way DDI assessment where anastrozole steady-state PK parameters will be compared between the palbociclib and placebo treatment arms, and the palbociclib steady-state PK parameters will be compared with historical controls. The unblinded PK DDI data and general safety data will be reviewed and evaluated by the external data monitoring committee (E-DMC). On 08 December 2016, the Sponsor received confirmation that sufficient PK samples for palbociclib/placebo and anastrozole had been collected to complete the planned PK DDI analysis, and enrollment to the PK/safety assessment group is being closed. The timelines for receipt of the collected PK samples by the study central lab, the analysis of the samples at the bioanalytical labs, and the generation of the unblinded PK analysis sets are currently under discussion with the Sponsor (GBG: German Breast Group), however the results of this unblinded PK analysis are not anticipated to be available during the 1008 sNDA submission review cycle.

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/s/  
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WENTAO FU  
03/27/2017

JINGYU YU  
03/27/2017

QI LIU  
03/27/2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207103Orig1s004**

**OTHER REVIEW(S)**

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

<b>NDA</b>	207103
<b>Brand Name</b>	Ibrance
<b>Generic Name</b>	palbociclib
<b>Sponsor</b>	Pfizer, Inc.
<b>Indication</b>	Advanced Breast Cancer (ABC)
<b>Dosage Form</b>	Capsules
<b>Drug Class</b>	Cyclin-dependent kinase (CDK) 4/6 inhibitor
<b>Therapeutic Dosing Regimen</b>	125 mg once daily taken with food for 21 days followed by 7 days off treatment
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	225 mg
<b>Submission Number and Date</b>	207103
<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**

No large QTc prolongation effect of Palbociclib + Letrozole was detected based on ECG subgroup analysis from the phase 3 study A5481008. The largest upper bound of the 2-sided 90% CI for the mean difference between Palbociclib + Letrozole and Placebo + Letrozole was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The assay sensitivity was not accessed because there was no positive control in this study.

Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Palbociclib + Letrozole (FDA Analysis)**

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Palbociclib + Letrozole	6	0.6	(-3.9, 5.1)

Based on the information collected from ECG subgroup in the Study A5481008. The geometric mean Cmax, 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

110 ng/mL. Based on the population PK analysis, mild hepatic impairment has no impact on the exposure of palbociclib. Coadministration of a strong CYP3A inhibitor (itraconazole) increased the plasma exposure of palbociclib in healthy subjects by 87% and such supra-therapeutic exposure is avoided through recommended labeling. The pharmacokinetics of palbociclib has not been studied in patients with moderate or severe hepatic impairment.

## 1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

In the previous QT-IRT review of palbociclib based on data collected from Studies 1001, 1002, and 1003, a positive but relatively flat exposure-response relationship was identified. The FDA review team concluded that palbociclib did not prolong the QT interval to any clinically relevant extent. The current review is based on the data collected from Study 1008. No evident relationship between palbociclib concentration and baseline adjusted QTc prolongation was identified. The QT-IRT review team agrees with the previous conclusion that palbociclib does not prolong the QT interval to any clinically relevant extent.

## 2 PROPOSED LABEL

The following proposed labeling information is provided by the sponsor related to cardiac electrophysiology:

### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

The effect of palbociclib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with breast cancer. (b) (4)

*We have the following edits to the suggested labeling language. We defer final labeling decisions to the Division.*

### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

The effect of palbociclib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with breast cancer. (b) (4)

—Palbociclib had no large effect on QTc interval (i.e., > 20 ms) and there was no relationship between palbociclib exposure and change in QTc interval.

*Reviewer's Comment: Based on the data collected from study A5481008, sponsor proposed labeling language is generally acceptable, however the labeling language should reflect that the results are not from a TQT study, i.e. we can only rule large effects.*

### 3 BACKGROUND

#### 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 days followed by 7 days off treatment.

#### 3.2 MARKET APPROVAL STATUS

In 2015, palbociclib was approved for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in combination with letrozole as initial endocrine-based therapy for their metastatic disease.

In 2016, palbociclib was approved for the treatment of hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer in combination with fulvestrant in women with disease progression following endocrine therapy.

#### 3.3 PRECLINICAL INFORMATION

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  $\mu$ M (4475 ng/mL) in the dog Purkinje fiber assay, and had an IC50 of 3.2  $\mu$ M (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 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.

Previous PK/PD modeling (QTc-C) was conducted using the data from A5481001, hereafter referred to as Study 1001 (PMAR-00152). This prior analysis was based on a linear mixed effects model and results suggested that at the proposed therapeutic dose of 125 mg QD, no clinically significant QT prolongation would be expected. Further,

pooled data from 3 studies (Study 1001, A5481002, and A5481003) were utilized to evaluate the concentration-dependent effect on QTc or RR interval for palbociclib, which includes a range of doses and regimens (PMAR-EQDD-A548b-DP4-287 QTc). The analysis, using linear mixed effects model, indicated that palbociclib does not appear to have a concentration-dependent effect on heart rate and QT prolongation was not a major safety concern at the recommended therapeutic dose of palbociclib.

### **3.5 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of palbociclib clinical pharmacology.

## **4 SPONSOR'S SUBMISSION**

### **4.1 OVERVIEW**

The QT-IRT team provided consult regarding the A5481008 electrocardiogram (ECG) sub-study under IND 69324. The sponsor submitted the study report A5481008 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

### **4.2 TQT STUDY**

#### **4.2.1 Title**

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

#### **4.2.2 Protocol Number**

A5481008 (PALOMA-2)

#### **4.2.3 Study Dates**

First Patient First Visit: 22 February 2013

Study completion: Ongoing, date of data cutoff 26 February 2016

#### **4.2.4 Objectives**

Primary Objective:

- To demonstrate that the combination of palbociclib with letrozole is superior to placebo plus letrozole in prolonging PFS in postmenopausal women with ER-positive/HER2- negative ABC who have not received any prior systemic anti-cancer therapies for their advanced/metastatic disease.

Secondary Objectives:

- To compare measures of tumor control duration and overall survival between the treatment arms;
- To compare safety and tolerability between the treatment arms;
- To compare health related quality of life between the treatment arms;

- To characterize the effects of palbociclib at therapeutic doses in combination with letrozole on QTc in this patient population;
- To determine trough palbociclib plasma concentration in this patient population and explore correlations between exposure and response and/or safety findings;
- To characterize alterations in genes, proteins, and RNAs relevant to the cell cycle (eg, cyclin D1 (CCND1) amplification, cyclin-dependent kinase inhibitor 2A, also known as ‘p16INK4A’, the product of the CDKN2A gene [CDKN2A] deletion), drug targets (eg, CDK4/6), and tumor sensitivity and/or resistance (eg, Ki67, pRb) in tumor tissues.

## 4.2.5 Study Description

### 4.2.5.1 Design

This was an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 clinical study comparing the efficacy and safety of palbociclib in combination with letrozole versus placebo in combination with letrozole in postmenopausal women with ER-positive/HER2-negative ABC.

### 4.2.5.2 Controls

The control arm consisted of letrozole 2.5 mg orally QD.

### 4.2.5.3 Blinding

Treatment arms were blinded.

## 4.2.6 Treatment Regimen

### 4.2.6.1 Treatment Arms

Patients randomized to Arm A (experimental arm) received:

- Palbociclib, 125 mg, orally QD on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment;
- in combination with
- Letrozole, 2.5 mg, orally QD (continuously).

Patients randomized to Arm B (control arm) received:

- Placebo orally QD on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment;
- in combination with
- Letrozole, 2.5 mg, orally QD (continuously).

### 4.2.6.2 Sponsor’s Justification for Doses

Schedule 2/1 and Schedule 3/1 were evaluated at each palbociclib dose-escalating level during Cycle 1 of the first-in-human study in patients with advanced solid tumors (Study 1001). The 200-mg QD dose on Schedule 2/1 and the 125-mg QD dose on Schedule 3/1 were identified as the RP2Ds (and MTDs). That a greater proportion of patients on

Schedule 2/1 (97.0%) experienced TEAEs, in addition to the greater long-term antitumor activity observed with Schedule 3/1 relative to that with Schedule 2/1, led to the selection of dosing regimen 125 mg QD on Schedule 3/1.

*Reviewer's Comment: The proposed therapeutic schedule (125 mg daily for 21 consecutive days followed by 7 days off to comprise a complete cycle of 28 days) is reasonable.*

#### **4.2.6.3 Instructions with Regard to Meals**

In Study A5481008, Patients were to take palbociclib/placebo with food. Patients enrolled in ECG group were to fast from 1 hour before to 2 hours after dosing, during Cycle 1. In Cycle 2 and beyond, patients were to take palbociclib/placebo with food.

*Reviewer's Comment: It is acceptable to administer the drug with food to increase the bioavailability.*

#### **4.2.6.4 ECG and PK Assessments**

As described in Table S1, PK and ECG samples were to be collected at the same time for some of the prespecified sampling times. However, due to operational feasibility, ECG and PK samples could not be obtained at the same time; therefore ECG and PK samples collected within 1 hour apart were considered time-matched ECG-PK pairs for this analysis. Only those time-matched palbociclib concentrations and ECG data were planned to be used in this primary analysis. In this study, 12-lead ECGs were scheduled to be performed in triplicate approximately 2 minutes apart but within 10 minutes for all 3 ECGs. All ECGs had to be obtained after a fast of at least 1 hour. ECGs were expected to be performed immediately before PK blood draws at the respective time points. In practice, ECG and PK samples collected within 1 hour apart were considered time-matched ECG-PK pairs for this analysis. Patients who could not complete ECG measurements on Day 0 and/or PK-matched ECG measurements (ie, both ECG and PK collected) on Day 14 were to be replaced. All triplicate ECG tracings were sent electronically to a core ECG laboratory for blinded manual interval measurements.

#### **Table 2: ECG and Pharmacokinetic Sampling Schedule**

Protocol Activity	Screening								Active Treatment Phase								End of Treatment <sup>1</sup>			
	Within 28 Days Prior to Randomization Unless Specified Otherwise																			
	Day 0 (day prior to Day 1)								Day 1				Day 14					Cycle 2 Day 14		Cycle 24 Day 1
	ECG <sub>r</sub>	ECG <sub>1</sub>	2 h Post-ECG <sub>1</sub>	4 h Post-ECG <sub>1</sub>	6 h Post-ECG <sub>1</sub>	8 h Post-ECG <sub>1</sub>	0 h Predose	0 h Predose	2 h Postdose	4 h Postdose	6 h Postdose	8 h Postdose	0 h Predose	0 h Predose	Anytime					
<b>Group 1 (approximately 60 Patients) at selected sites</b>																				
12 lead ECG <sup>a</sup>	X	X	X	X	X	X	X <sup>a</sup>	X	X	X	X	X	X	X	X					
Pharmacokinetic <sup>b</sup>								X	X	X	X	X	X							
<b>Group 2 (All other patients)</b>																				
12 lead ECG <sup>a</sup>	X						X <sup>a</sup>	X					X	X	X					
Pharmacokinetic <sup>b</sup>								X					X							

Source: Study A5481008 Clinical Study Report.

ECG<sub>r</sub>=TriPLICATE ECGs performed to determine patient's eligibility; ECG<sub>1</sub>=First triplicate ECGs performed for patient in Group 1.

a. Group 1 at selected sites:

On the day preceding treatment initiation (Day 0), triplicate ECGs were to be obtained at time 0 (first ECG also referred to as ECG<sub>1</sub>), and then 2, 4, 6, and 8 hours after ECG<sub>1</sub>.

At Cycle 1 Day 14, triplicate ECGs were to be obtained at 0 hour (predose) and then, 2, 4, 6, and 8 hours following PD-0332991/placebo dosing. Timing of ECGs performed on Day 14 MUST be time-matched (clock time +/- 35 minutes) with ECG assessments performed on Day 0.

Additionally, triplicate ECGs were to be obtained for safety monitoring at 0 hour (predose) on Day 1 of Cycle 1<sup>3</sup>, Day 14 of Cycle 2, then on Day 1 of Cycles 4, 7, and 10. ECGs beyond Cycle 10 were to be performed as clinically indicated.

Group 2 (all other patients):

Triplicate ECGs were to be obtained for safety monitoring at 0 hour (predose) on Day 1 of Cycle 1<sup>3</sup>, Day 14 of Cycle 1 and Cycle 2, then on Day 1 of Cycles 4, 7, and 10. ECGs beyond Cycle 10 were to be performed as clinically indicated.

<sup>3</sup>NOTE: Triplicate ECGs do not need to be repeated on Day 1 of Cycle 1 if ECG<sub>r</sub> was performed within 7 days of the date of randomization.

b. For patients in the ECG Group 1, plasma PK samples were to be obtained at the times indicated for ECGs right after ECG assessment. One additional plasma PK sample was to be collected predose on Day 14 of Cycle 2. For all other patients (ECG Group 2), plasma PK samples were to be collected prior to dosing (predose) on Day 14 of Cycle 1 and Cycle 2.

*Reviewer's Comment: Based on the Tmax of 5.9 hr (1.9-8.2 hr) for palbociclib, the timing of ECGs are acceptable.*

#### 4.2.6.5 Baseline

Time-matched baseline was used. Baseline is defined as time-matched triplicate measurements on Day 0 (HR 0, 2, 4, 6, 8 respectively).

#### 4.2.7 ECG Collection

All ECGs were performed using a 12-lead (with a 10-second rhythm strip) tracing. ECG interval readings by the ECG recorder's algorithm were read and interpreted at the investigational site for eligibility determination, and patient safety monitoring and documentation stored in the source documents. For reporting purposes and future QT-PK analysis, all ECGs were centrally read by (b) (4). Triplicate ECGs were performed for all patients to determine the mean QTc for eligibility purpose.

#### 4.2.8 Sponsor's Results

##### 4.2.8.1 Study Subjects

Between 28 February 2013 and 29 July 2014, 666 women were randomized at 186 sites in 17 countries (Table 12 and Table 16.2.4.1.2). Four hundred and forty-four (444) patients were randomized to the palbociclib plus letrozole arm, and 222 patients were randomized to the placebo plus letrozole arm. All randomized patients were treated.

In the ECG subgroup (Group 1), a total of 125 patients were enrolled. Of these patients, 77 were randomized to the palbociclib plus letrozole treatment arm and 48 were randomized to the placebo plus letrozole arm. Due to the differences in the patient recruitment rate at various sites participating in Group 1 and the need to replace the

patients who could not complete PK-matched ECG measurements on both Day 0 and Day 14 of Cycle 1, more patients were enrolled than the planned 60 patients in this subgroup.

Unless specified otherwise, subjects from the ECG subgroup in this Phase 3 study who had at least 1 pair of time-matched baseline (Day 0) and palbociclib postdose (Day 14 of Cycle 1) ECG measurements will be used as the study population for this QT report.

#### 4.2.8.2 Statistical Analyses

##### 4.2.8.2.1 Central Tendency Analysis

The sponsor performed analysis of change from baseline of QTc using QTc analysis set. The QTc Analysis Set is a subset of all treated patients, who were enrolled at selected sites (Group 1) and had their QTc monitored to evaluate the effect of palbociclib on QT interval via serial triplicate ECGs time-matched with PK draws, who had at least 1 pair of time-matched baseline (Day 0) and palbociclib postdose (Day 14 of Cycle 1) ECG measurements.

For analysis of QTc in Group 1 on Cycle 1 Day 14, mean of change from baseline of QTc and 2-sided 90% CI for each mean were provided from a random effect model by treatment group. A random effect model with the nominal time point as a fixed effect and the patient as a random effect was used to estimate the mean change in ECG parameter from baseline at each postbaseline nominal time point. Results were presented in the table below.

**Table 3: QTcF Interval Time-Matched Change from Baseline (msec) by Time Point on Cycle 1 Day 14 (Vendor Data) – QTc Analysis Population**

Planned Time Postdose	Palbociclib plus Letrozole			Placebo plus Letrozole		
	n	LS Mean (Standard Error) Change from Baseline	90% CI of LS Mean Change from Baseline	n	LS Mean (Standard Error) Change from Baseline	90% CI of LS Mean Change from Baseline
0 h	76	1.10 (1.508)	(-1.39, 3.58)	46	3.06 (1.922)	(-0.11, 6.23)
2 h	71	3.68 (1.548)	(1.12, 6.23)	47	1.73 (1.913)	(-1.43, 4.88)
4 h	71	2.86 (1.548)	(0.31, 5.41)	47	1.54 (1.913)	(-1.62, 4.70)
6 h	71	4.57 (1.548)	(2.01, 7.12)	47	0.71 (1.913)	(-2.44, 3.87)
8 h	70	1.21 (1.554)	(-1.36, 3.77)	47	2.84 (1.913)	(-0.31, 6.00)

Source: Sponsor’s Study Report Page 243

*Reviewer’s Comments: The statistical reviewer performed independent analysis. Please refer to section 5.2.*

##### 4.2.8.2.2 Assay Sensitivity

There is no positive control in this study. No assay sensitivity analysis was performed.

##### 4.2.8.2.3 Categorical Analysis

In the QTc analysis population, no patients in the palbociclib plus letrozole arm had a maximum QTcF of  $\geq 480$  msec, or had a maximum increase from time-matched baseline in QTcF of  $\geq 60$  msec. In the placebo plus letrozole arm, no patients had a maximum QTcF of  $\geq 500$  msec and 1 (2.1%) patient had a value between 480 to  $< 500$  msec. No patients had a maximum increase from time-matched baseline in QTcF of  $\geq 60$  msec. Results were presented in the table below.

**Table 4: Categorical Summary of ECG Maximum Postbaseline Absolute Values and Maximum Increase from Baseline QTcF (Vendor Data) – QTc Analysis Population**

Parameter	Criteria	Palbociclib plus Letrozole		Placebo plus Letrozole	
		N	n (%)	N	n (%)
Maximum QTcF (Fridericia's Correction) (msec)	<450	76	69 (90.8)	48	41 (85.4)
	450-<480	76	7 (9.2)	48	6 (12.5)
	480-<500	76	0	48	1 (2.1)
	$\geq 500$	76	0	48	0
Maximum QTcF (Fridericia's Correction) increase from baseline (msec)	Change <30	76	71 (93.4)	48	46 (95.8)
	$30 \leq$ Change <60	76	5 (6.6)	48	2 (4.2)
	Change $\geq 60$	76	0	48	0

Source: Sponsor's Study Report Page 245

#### 4.2.8.3 Safety Analysis

The sponsor provided safety analysis for this Phase 3 study overall. No separate safety analysis was provided for the QTc analysis population.

#### 4.2.8.4 Clinical Pharmacology

##### 4.2.8.4.1 Pharmacokinetic Analysis

The plasma palbociclib steady-state PK parameters on at Cycle 1 on day 14 are shown in table below. Figure below shows the median concentration-time profile of palbociclib.

**Table 5: Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameters Following 125 mg QD Oral Doses of Palbociclib in Combination with 2.5 mg QD Oral Doses of Letrozole – Dose Compliant PK Analysis Population (Group 1, Cycle 1 Day 14)**

Parameter [Units]	Palbociclib PK Parameter Summary Statistics <sup>a</sup> by Administration Group		
	Palbociclib plus Letrozole Administration Group A <sup>†</sup>	Palbociclib plus Letrozole Administration Group B <sup>†</sup>	Palbociclib plus Letrozole All Group 1 Patients
N, n <sup>b</sup>	9,9	34,32	43,41
AUC <sub>24</sub> [ng·hr/mL] <sup>c</sup>	1721 (39)	2076 (33)	1992(35)
C <sub>max</sub> [ng/mL]	100.7 (40)	113.1 (34)	110.4 (35)
T <sub>max</sub> [hr]	4.58 (1.87-8.00)	5.90 (1.90-8.18)	5.83 (1.87-8.18)
CL/F [L/hr]	72.61 (39)	60.17 (33)	62.71 (35)

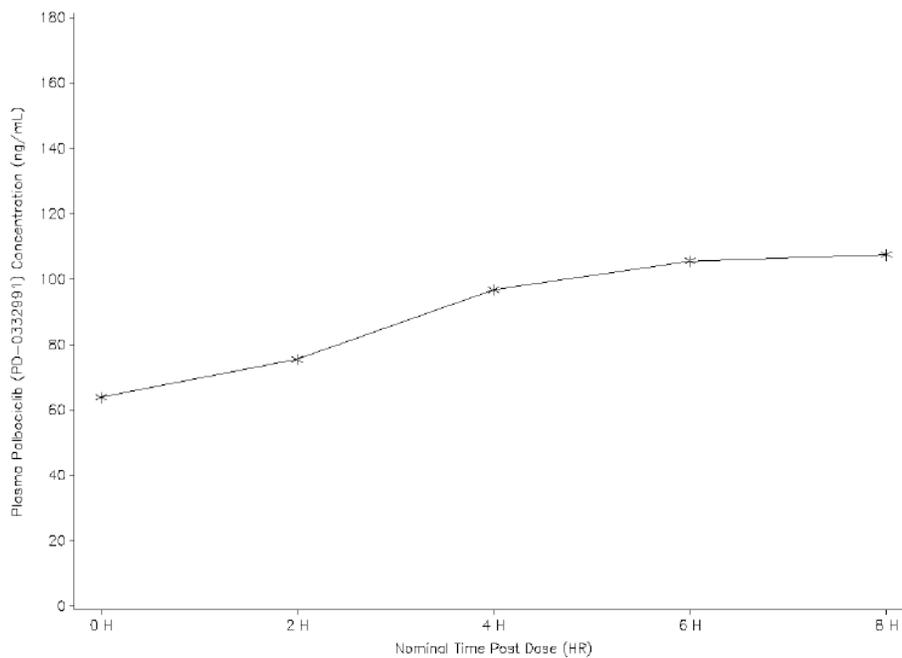
a. Geometric mean (geometric %CV) for all except: median (range) for T<sub>max</sub>.

b. N=Number of patients contributing to the summary statistics for C<sub>max</sub> and T<sub>max</sub>; n=Number of patients contributing to the summary statistics for AUC<sub>24</sub> and CL/F.

c. AUC<sub>24</sub> was calculated by using predose (0 hr) sample as the 24-hour value assuming steady-state conditions.

<sup>†</sup> Group A: patients under fasted condition taking any local antacids, H<sub>2</sub>-receptor antagonists or proton pump inhibitors at the time of PK sampling; Group B: patients under fasted condition not taking antacids at the time of PK sampling; PK=Pharmacokinetic.

**Figure 1: Median Palbociclib Concentration time profile on Day 14 of Cycle 1, Group 1 only**

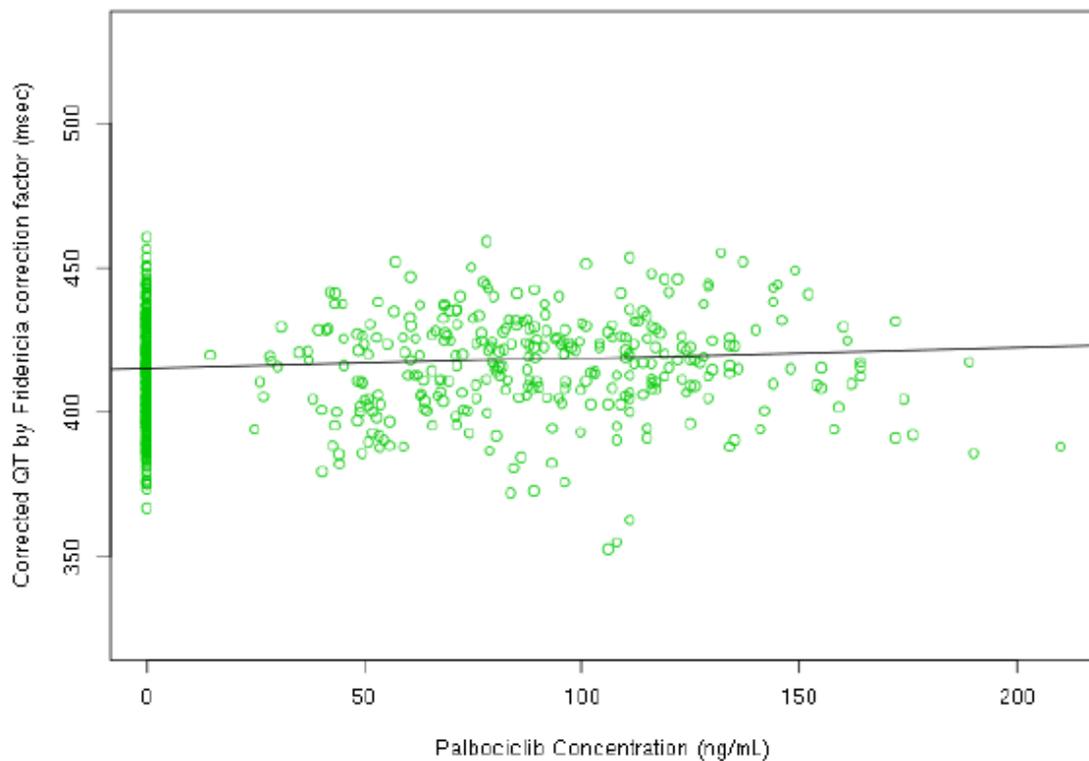


#### 4.2.8.4.2 Exposure-Response Analysis

The linear mixed effects model with random effects on both intercept and slope was utilized to evaluate the effect of palbociclib concentrations on the mean QTcS, QTcF, and QTcB endpoints. Nominal collection time was included as a covariate on the intercept to account for the time effect in all base models for RR-C and QTcX-C. Additive error models appeared to be adequate for the base models. A slight positive linear relationship was observed between palbociclib concentrations and QTcS or QTcF; however, the predicted upper bound of the 1-sided 95% CI for the increase in QTcX at the mean or median maximal steady-state palbociclib concentrations at the therapeutic dose was less than 10 msec.

**Figure 2: QTcF Versus Palbociclib Concentration Relationship**

Slope = 0.0355 (95% CI: 0.00826 to 0.0628 )



*Reviewer's Analysis: A plot of  $\Delta QTc$  vs. drug concentrations is presented in Figure 4.*

## 5 REVIEWERS' ASSESSMENT

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

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

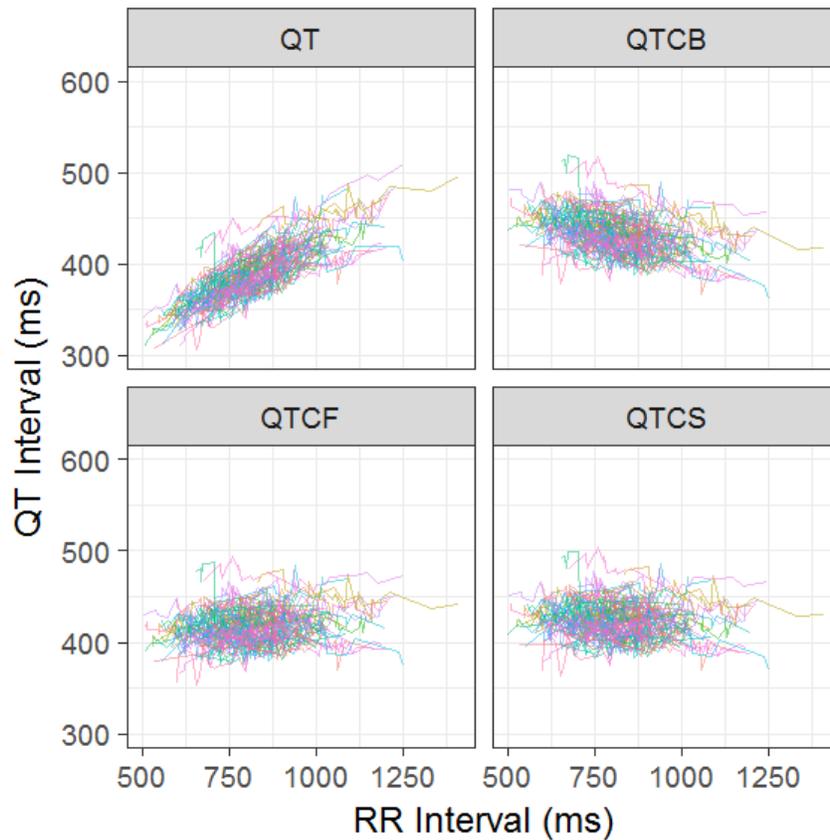
We used criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 6, it appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis.

**Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

Method	Treatment					
	Palbociclib (PD-0332991) + Letrozole		Placebo + Letrozole		All	
	N	MSSS	N	MSSS	N	MSSS
QTcB	71	0.0143	47	0.0192	118	0.0163
QTcF	71	0.0095	47	0.0110	118	0.0101
QTcS	71	0.0095	47	0.0127	118	0.0108

The relationship between different correction methods and RR is presented in Figure 3: QT, QTcB, QTcF, and QTcS vs. RR (Each Subject's Data Points are Connected with a Line)Figure 3.

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



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 Central Tendency Analysis

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcF effect. The model includes treatment, time, time\*treatment as fixed effects and SUBJECT as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

**Table 7: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF by Time Point on Cycle 1 Day 14 for Treatment Group= Palbociclib (PD-0332991) + Letrozole**

	$\Delta$ QTcF Palbociclib + Letrozole	$\Delta$ QTcF Placebo+ Letrozole	$\Delta\Delta$ QTcF	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0	-0.6	2.7	-3.3	(-7.5, 1.0)
2	3.1	3.9	-0.8	(-5.3, 3.6)
4	2.3	3.8	-1.4	(-5.8, 2.9)
6	3.3	2.7	0.6	(-3.9, 5.1)
8	0.1	4.7	-4.7	(-9.1, -0.3)

### 5.2.1.2 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcF values are  $\leq 450$  ms, between 450 ms and 480 ms, and between 480 ms and 500 ms. Two subjects treated with Placebo + Letrozole had QTcF values between 480 ms and 500 ms.

**Table 8: Categorical Analysis for QTcF**

Treatment Group	Total N		Value $\leq$ 450 ms		450 ms<Value $\leq$ 480 ms		480 ms<Value $\leq$ 500 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Palbociclib + Letrozole	71	689	65 (91.5%)	668 (97.0%)	6 (8.5%)	21 (3.0%)	0 (0.0%)	0 (0.0%)
Placebo + Letrozole	47	439	39 (83.0%)	398 (90.7%)	6 (12.8%)	38 (8.7%)	2 (4.3%)	3 (0.7%)

Table 9 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline was above 60 ms.

**Table 9: Categorical Analysis of  $\Delta$ QTcF**

Treatment Group	Total N		Value $\leq$ 30 ms		30 ms<Value $\leq$ 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Palbociclib + Letrozole	71	688	62 (87.3%)	673 (97.8%)	9 (12.7%)	15 (2.2%)
Placebo + Letrozole	47	439	42 (89.4%)	430 (97.9%)	5 (10.6%)	9 (2.1%)

**5.2.2 HR Analysis**

Table 10 lists the categorical analysis results for HR. Five subjects treated with Palbociclib + Letrozole and seven subjects treated with Placebo + Letrozole had HR values above 100 bpm, respectively.

**Table 10: Categorical Analysis of HR**

Treatment Group	Total N		Value $\leq$ 100 bpm		Value $>$ 100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Palbociclib + Letrozole	71	690	66 (93.0%)	677 (98.1%)	5 (7.0%)	13 (1.9%)
Placebo + Letrozole	47	439	40 (85.1%)	419 (95.4%)	7 (14.9%)	20 (4.6%)

### 5.2.3 PR Analysis

The outlier analysis results for PR are presented in Table 11. Seven subjects treated with Palbociclib + Letrozole and six subjects treated with Placebo + Letrozole had PR values above 200 ms, respectively.

**Table 11: Categorical Analysis for PR**

Treatment Group	T		Value≤200 ms		Value>200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Palbociclib + Letrozole	71	690	64 (90.1%)	656 (95.1%)	7 (9.9%)	34 (4.9%)
Placebo + Letrozole	46	432	40 (87.0%)	403 (93.3%)	6 (13.0%)	29 (6.7%)

### 5.2.4 QRS Analysis

The outlier analysis results for PR are presented in Table 12. Five subjects treated with Palbociclib + Letrozole and six subjects treated with Placebo + Letrozole had QRS values above 110 ms, respectively.

**Table 12: Categorical Analysis for QRS**

Treatment Group	T		Value≤100 ms		100 ms<Value≤110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Palbociclib + Letrozole	71	690	59 (83.1%)	625 (90.6%)	7 (9.9%)	26 (3.8%)	5 (7.0%)	39 (5.7%)
Placebo + Letrozole	47	439	37 (78.7%)	372 (84.7%)	4 (8.5%)	27 (6.2%)	6 (12.8%)	40 (9.1%)

## 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

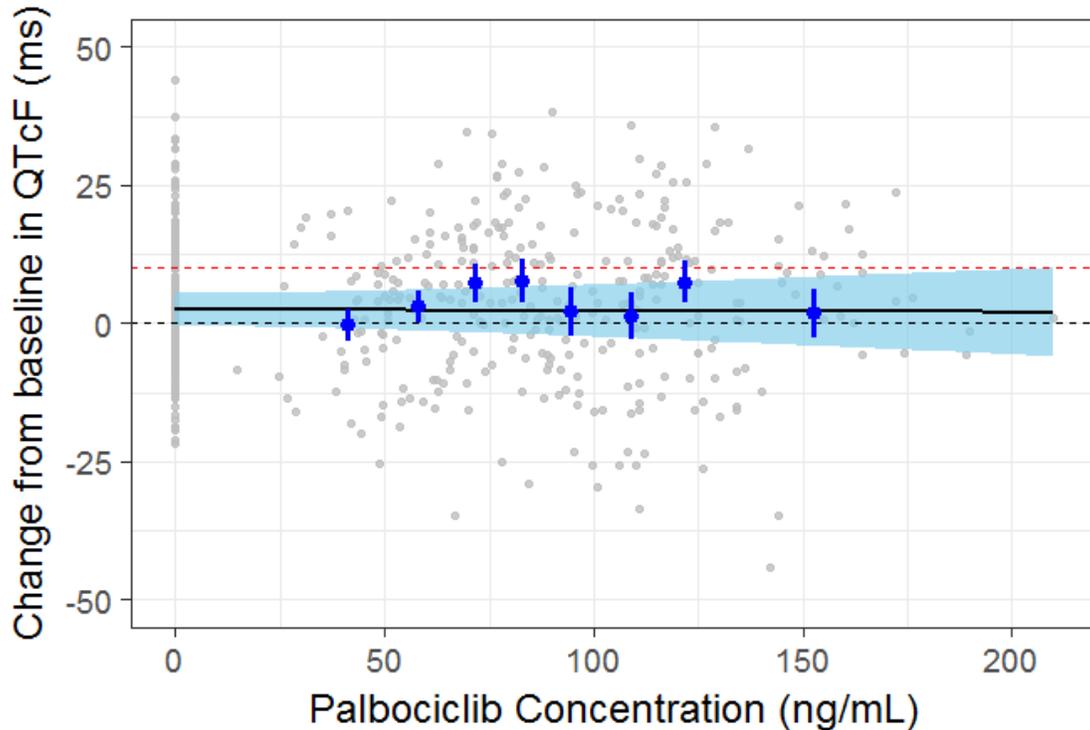
The mean palbociclib concentration-time profile is illustrated in Figure 4.

The relationship between  $\Delta$ QTc and palbociclib was investigated by linear mixed-effects modeling with QTcF change from baseline ( $\Delta$ QTcF) as the dependent variable. The final C-QTc model was a linear model with random effect on the intercept only. Random effect was not added on the slope of palbociclib concentration due to convergence issue.

The letrozole arm was treated as placebo. Time and treatment terms were included in the

C-QT model as categorical factors. According to the final model, no evident exposure-response relationship was established.

**Figure 4:  $\Delta$  QTcF vs. palbociclib concentration**



Note: The bins were determined based on the palbociclib concentration at the treatment arm.

## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

Grade 3 AEs related to QT prolongation were reported for 1 patient in each treatment arms.

### 5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

### 5.4.3 PR and QRS Interval

There was no evidence of clinically significant effects of palbociclib plus letrozole on PR interval or QRS complex.

- Seven subjects treated with Palbociclib + Letrozole had post-baseline PR > 200 ms. None of the subjects had change  $\geq 25\%$  increase from baseline.

- Five subjects treated with Palbociclib + Letrozole had post-baseline QRS>110 ms. Two subjects had a change  $\geq 25\%$  increase from baseline.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

#### Highlights of Clinical Pharmacology and Cardiac Safety

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 reactions (incidence $\geq 10\%$ ) of any grade reported in patients treated with palbociclib across studies A5481008 and A5481023 were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, and pyrexia.  Overall, the most common dose limiting adverse events were hematologic toxicities.	
Maximum dose tested	Single Dose	225 mg
	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	<ul style="list-style-type: none"> <li>• Primary by CYP3A and SULT2A1 metabolism</li> <li>• Following a single oral administration of 125 mg [<sup>14</sup>C]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.</li> <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>	<b>Mean (Std Dev):</b> <ul style="list-style-type: none"> <li>• Palbociclib: 28.8 hrs (5 hrs)</li> <li>• M17 (PF-05089326): ~21 hrs (2.5 – 4.0 hrs)</li> </ul>
	CL/F or CL	<b>Geometric Mean (%CV):</b> Palbociclib CL/F: 63.1 L/hr (29%)
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	While palbociclib geometric mean AUC <sub>inf</sub> and C <sub>max</sub> values were 30% and 35% higher in Japanese healthy subjects compared with those in demographic matched non-Asian healthy subjects in Study A5481032, palbociclib steady-state AUC <sub>τ</sub> , C <sub>max</sub> , and C <sub>trough</sub> values for Japanese and/or Asian (excluding Japanese) patients with advanced breast cancer were comparable with those in non-Asian patients with advanced breast cancer in some study populations but were higher in others. Based on analysis of the cumulative PK, safety, and efficacy data, no dose adjustment based on Asian race is necessary.
Hepatic & Renal Impairment	<p>Population PK analysis indicates that mild hepatic impairment, as defined based on the NCI scale, has no impact on the exposure of palbociclib. Effect of moderate or severe hepatic impairment on palbociclib exposure has not been evaluated.</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	<b>Midazolam (Sensitive CYP3A substrate):</b> <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-</li> </ul>

		<p>dependent inhibitor of CYP3A.</p> <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>Modafinil (Moderate CYP3A Inducer):</u></b></p> <ul style="list-style-type: none"> <li>• Coadministration of modafinil and palbociclib decreased palbociclib AUC<sub>inf</sub> and C<sub>max</sub> by approximately 32% and 11%, 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 68.2% (61.6%-75.5%) and 88.5% (80.6%-97.3%), respectively, following administration of palbociclib with multiple doses of modafinil (Test), relative to palbociclib administered alone (Reference).</li> </ul> <p><b><u>Itraconazole (Strong CYP3A Inhibitor):</u></b></p> <ul style="list-style-type: none"> <li>• Coadministration of itraconazole and palbociclib increased palbociclib AUC<sub>inf</sub> and C<sub>max</sub> by approximately 87% and 34%, 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 187% (173%-202%) and 134% (126%-143%), respectively, following administration of palbociclib with multiple doses of itraconazole (Test), relative to palbociclib administered alone (Reference).</li> </ul> <p><b><u>Rabeprazole (Proton-pump Inhibitor):</u></b></p> <p>Under fasted conditions</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>Under fed conditions</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</li> </ul>
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	<p>alone (Reference).</p> <p><b>Famotidine (an H2-receptor antagonist)</b></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><b>Mi-Acid Maximum Strength Liquid (local antacid)</b></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>• 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).</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 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).</li> </ul> <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). These results indicate that it is not necessary to adjust palbociclib dose when coadministering with tamoxifen.</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<sub>[0-24]</sub> 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<sub>[0-24]</sub> and 91.3% [85.2%-97.8%] for C<sub>max</sub>).</li> </ul>
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	<ul style="list-style-type: none"> <li>Therefore, there is no DDI between palbociclib and letrozole when the 2 drugs are coadministered.</li> </ul>
Food Effects	<p><b>Free Base Final Ph3/Commercial Formulation:</b></p> <ul style="list-style-type: none"> <li>The ratios (90% CIs) of the adjusted geometric means for <math>C_{max}</math> of palbociclib 125 mg after a high-fat meal, a lowfat 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 <math>AUC_{inf}</math> 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 <math>AUC_{inf}</math> and <math>C_{max}</math>. from 39% for <math>AUC_{inf}</math> and 73% for <math>C_{max}</math> under the overnight fasted condition to 23%-27% for <math>AUC_{inf}</math> and 21%-24% for <math>C_{max}</math> 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 <math>AUC_{inf}</math> and <math>C_{max}</math>.</li> <li>Based on these study results, palbociclib should be taken with food.</li> </ul> <p><b>Isethionate Capsule Formulation:</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 no effect on palbociclib <math>AUC_{inf}</math> and <math>C_{max}</math>. The 90% CIs for both <math>AUC_{inf}</math> and <math>C_{max}</math> fell within the established bioequivalence limits (80%-125%).</li> </ul>
Expected High Clinical Exposure Scenario	<p>In theory, high clinical exposure scenarios include:</p> <ol style="list-style-type: none"> <li>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>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>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 <math>APD_{90}</math> at 10 <math>\mu</math>M (4475 ng/mL) in the dog Purkinje fiber assay, and had an <math>IC_{50}</math> of 3.2 <math>\mu</math>M (1432 ng/mL) in a hERG assay. The potential for QTc interval prolongation was identified from conscious telemetered dogs at unbound plasma concentrations <math>\geq</math>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 <math>C_{max}</math> 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 <math>\geq</math>140 ng/mL. No cardiovascular effects are anticipated at</p>

	plasma concentrations <4 times those associated with the unbound Cmax at the human clinical dose of 125 mg QD (17 ng/mL).															
Clinical Cardiac Safety	The exposure of subjects to different drug levels is summarized in Table 1:															
	<b>Table 2: Exposure by Dose (by Indication)</b>															
	<b>Advanced breast cancer</b>															
	<b>Dose of Exposure</b> <sup>Error!</sup> Reference source not found.a	<b>Persons</b>	<b>Person Time (years)</b>													
	Dose < 75 mg/day	6	0.6													
	Dose 75 mg/day	121	57.7													
	Dose 100 mg/day	321	136.8													
	Dose 125 mg/day	891	534.1													
	Dose > 125 mg/day	5	0.2													
	<b>Total</b>	<b>898</b> <sup>Error!</sup> Reference source not found.b	<b>729.3</b>													
<b>Advanced cancer</b> <sup>c</sup>																
<b>Dose of Exposure</b> <sup>Error!</sup> Reference source not found.a	<b>Persons</b>	<b>Person Time (years)</b>														
Dose < 75 mg/day	16	2.6														
Dose 75 mg/day	153	62.7														
Dose 100 mg/day	380	150.3														
Dose 125 mg/day	940	553.8														
Dose > 125 mg/day	40	10.9														
<b>Total</b>	<b>1044</b> <sup>Error!</sup> Reference source not found.b	<b>780.2</b>														
	<p>a. Patient may be in more than one exposure category as patients are counted once for each dose level they took during the study</p> <p>b. Total number of patients that received at least 1 dose of palbociclib</p> <p>c. Advanced cancer includes advanced breast cancer</p> <p>Study A5481001 patients treated with Palbociclib (PD-0332991) (date of data cutoff: 02 January 2015).</p> <p>Studies A5481002 and A5481004 patients treated with Palbociclib (PD-0332991) (clinical study report data).</p> <p>Study A5481003 Phase I and Phase II patients treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 02 January 2015).</p> <p>Study A5481008 patients treated with Palbociclib (PD-0332991) + Letrozole (date of data cutoff: 26 February 2016).</p> <p>Study A5481010 Phase 1 Part 1 (date of data cutoff: 31 March 2015) and Part 2 (date of data cutoff: 04 March 2016).</p> <p>Study A5481023 patients treated with Palbociclib (PD-0332991) + Fulvestrant (date of data cutoff: 31 July 2015).</p> <p>Exposure (person-time) is based on overall exposure to Palbociclib (PD-0332991) doses only.</p>															
	<p>Pertinent cardiac safety events per ICH E14 guidance are summarized from the 3 pivotal breast cancer studies are summarized in Table 2. The following data cutoffs were used: For Study A5481003: January 2, 2015; for Study A5481023: October 23, 2015; for Study A5481008: February 26, 2016.</p>															
	<b>Table 2: ICH E14 Relevant Preferred terms reported in Studies A5481003, A5481008, and A5481023</b>															
	<table border="1"> <thead> <tr> <th></th> <th colspan="2">Pablociclib arm [N=872]</th> <th colspan="2">Comparator arm [N=471]</th> </tr> <tr> <th></th> <th>n</th> <th>%</th> <th>n</th> <th>%</th> </tr> </thead> <tbody> <tr> <td>Electrocardiogram QT</td> <td>6</td> <td>0.7</td> <td>3</td> <td>0.6</td> </tr> </tbody> </table>		Pablociclib arm [N=872]		Comparator arm [N=471]			n	%	n	%	Electrocardiogram QT	6	0.7	3	0.6
	Pablociclib arm [N=872]		Comparator arm [N=471]													
	n	%	n	%												
Electrocardiogram QT	6	0.7	3	0.6												

prolonged				
Syncope	9	1.0	6	1.3
Seizure	2	0.2	0	N/A
Ventricular tachycardia	1*	0.1	0	N/A
Ventricular fibrillation	0	N/A	0	N/A
Ventricular flutter	0	N/A	0	N/A
Torsade de pointes	0	N/A	0	N/A
Sudden death	0	N/A	0	N/A

\*This event was graded as ‘Grade 1’ by the investigator [upon querying this adverse event, it was stated that it was entered in error and was subsequently removed from the CRF]  
N/A= not applicable

In a substudy from Study A5481008 that was conducted as the definitive QT interval prolongation evaluation for the palbociclib program, triplicate ECG data were collected at clock time-matched baselines and at 5 time points (pre-dose and 2, 4, 6, and 8 hours postdose) on Day 14 after palbociclib had reached steady-state concentrations following a therapeutic dosing schedule (125 mg QD on Schedule 3/1 in combination with letrozole). A random effect analysis of the ECG data from this substudy demonstrated that the upper bounds of the 1-sided 95% CIs for the mean changes from clock time-matched baseline for QTcF (Fridericia’s correction), QTcS (study-specific correction), and QTcB (Bazett’s correction) were <8 msec at all 5 time points in the QTc assessment period. In addition, the exposure/response analysis using the same ECG data along with the time-matched PK data showed that while a slight positive linear relationship was observed between palbociclib concentration and QTcS, at the mean steady-state palbociclib C<sub>max</sub>, the mean QTcS increase was 4.04 msec, with the upper bound of the 1-sided 95% CI less than 10 msec. Similar results were obtained with QTcF and QTcB. Both of these analyses indicate that QTc prolongation is not a safety concern with palbociclib in combination with letrozole treatment at the recommended dosing regimen.

Based on the available adverse event data from Studies A5481003, A5481008, and A5481023, there is no evidence to suggest that palbociclib causes cardiac arrhythmias.

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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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DALONG HUANG  
01/24/2017

QIANYU DANG  
01/24/2017

CHAO LIU  
01/24/2017

LARS JOHANNESSEN  
01/24/2017

MICHAEL Y LI  
01/24/2017

CHRISTINE E GARNETT  
01/24/2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207103Orig1s004**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



IND 069324

**MEETING PRELIMINARY COMMENTS**

Pfizer Inc.  
Attention: Michelle Y. Kite  
Associate Director, Worldwide Safety and Regulatory  
10646 Science Center Drive  
San Diego, CA 92121

Dear Ms. Kite:

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

We also refer to your April 28, 2016, correspondence, received April 28, 2016, requesting a teleconference to discuss both the Top-Line Summary results from the global, randomized Phase 3 confirmatory Study A5481008 and the proposed content and format of the upcoming sNDA submission.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact me at 301-796-3994 or [amy.tilley@fda.hhs.gov](mailto:amy.tilley@fda.hhs.gov).

Sincerely,

*{See appended electronic signature}*

Amy R. Tilley  
Regulatory Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comment



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** Type B  
**Meeting Category:** Pre-sNDA

**Meeting Date and Time:** July 20, 2016  
**Meeting Location:** Teleconference

**Application Number:** IND 069324  
**Product Name:** Ibrance (palbociclib)  
**Indication:** in combination with [REDACTED] <sup>(b) (4)</sup> for the treatment of (HR)-positive, HER2-negative advanced or metastatic breast cancer  
**Sponsor/Applicant Name:** Pfizer Inc.

**SPONSOR ATTENDEES:**

Erling Donnelly, PhD, Asset Team Leader  
Keith Wilner, PhD, Franchise Clinical Lead  
Ave Mori, MD, Study A5481008 Clinical Lead and Medical Monitor  
Eric Gauthier, PharmD, PhD, Study A5481008 Lead Study Clinician  
Patrick Schnell, MD, Safety Risk Lead  
Albert L. Kraus, PhD, Oncology Global Regulatory Portfolio Lead  
Patrizia Salmoiraghi, Global Regulatory Lead  
Michelle Yu Kite, MS, RAC, US Regulatory Lead  
Bethany Rappoli, MA, MS, US Regulatory  
Xin Huang, PhD, Statistics Lead  
Dongrui Ray Lu, MS, Study A5481008 Statistics Lead  
Yuqiu (John) Jiang, PhD, Translational Oncology Lead  
Diane Wang, PhD, Clinical Pharmacology Lead  
Rebecca Hintze, Oncology Programming Lead  
Norihiko Oharu, Programming Lead  
Shrividya Iyer, PhD, Global Outcomes & Evidence Lead

**Introduction:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for July 20, 2016, 1:00 – 2:00 pm, between Pfizer Inc. and the Division of Oncology Products 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine

that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

## **1.0 BACKGROUND**

Pfizer has requested a Type B meeting to discuss submission of a sNDA for full approval of the following indication:

*IBRANCE (palbociclib) is a kinase inhibitor indicated in combination with [REDACTED] (b) (4) [REDACTED] with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.*

The accelerated approval of the initial NDA for palbociclib was based on data from the randomized Phase 2 Study 1003 (PALOMA-1). Study 1008 (PALOMA-2) is the confirmatory Phase 3 study with a population similar to that in Study 1003. The following studies will be included in the sNDA:

Study #	Title	N	Study Status at the time of sNDA submission	Safety	Efficacy	Pharmacokinetics
<b>Patients with metastatic breast cancer treated with palbociclib plus letrozole</b>						
A5481008	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	666	Completed*	Yes	Yes	Yes
A5481003	Phase 1/2, Open-Label, Randomized Study of the Safety, Efficacy, and Pharmacokinetics of Letrozole Plus PD-0332991 (Oral CDK 4/6 Inhibitor) and Letrozole Single Agent for the First Line Treatment of ER Positive, HER2 Negative Advanced Breast Cancer in Postmenopausal Women	Phase 1: 12 Phase 2: 165	Completed	Yes	No	No
<b>Patients with solid tumors treated with single-agent Palbociclib</b>						
A5481001 (supplemental CSR)	A Phase 1 Clinical, Pharmacokinetic, and Pharmacodynamic Evaluation of Two Schedules of PD-0332991, A Cyclin-Dependent Kinase Inhibitor, in Patients with Advanced Cancer	74	Completed	Yes	No	No
<b>Patients with metastatic breast cancer treated with palbociclib plus fulvestrant</b>						
A5481023	A Randomized, Multicenter, Double Blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Fulvestrant Versus Placebo Plus Fulvestrant for the Treatment of Women With HR (+), HER2-negative metastatic breast cancer following disease progression after prior therapy	521	Completed	Yes	Yes	No
A5481034	An Expanded Access Study of Palbociclib in Combination With Letrozole as Treatment of Post-Menopausal Women With Hormone Receptor Positive, HER2 Negative Advanced Breast Cancer for Whom Letrozole Therapy is Deemed Appropriate	93	Ongoing	Yes	No	No
<b>Patients with solid tumors treated with single-agent palbociclib Or with Breast Cancer with palbociclib plus letrozole (Japan-only study)</b>						
A5481010	A Phase 1/2 Study of the Efficacy, Safety and Pharmacokinetics of Oral PD-0332991, a Cyclin-Dependent Kinase 4 and 6 (CDK 4/6) Inhibitor, in Japanese Patients With Advanced Solid Tumors or in Combination With Letrozole in First-Line Treatment of Japanese Postmenopausal Patients with ER-Positive, HER2-Negative Advanced Breast Cancer	18 (Phase 1) 32 (Phase 2)	Ongoing	Yes	No	Yes

\* Continuing therapy is provided to all patients and no crossover is implemented at this time. Final analysis for overall survival is anticipated in ~4Q2018.  
Abbreviations: N =number of patients

Study 1008 was an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 clinical trial comparing the efficacy and safety of palbociclib in combination with letrozole versus placebo in combination with letrozole in postmenopausal women with estrogen receptor-positive, HER2-negative advanced breast cancer (ABC). Eligible patients had histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease and were candidates to receive letrozole as first-line treatment for their advanced disease. Patients with advanced symptomatic visceral metastases, and those at risk of life-threatening complications in the short term were excluded from this study. Patients who received anastrozole or letrozole as a component of their (neo)adjuvant regimen could only enter the study if their disease did not progress while on or within 12 months from completion of their anastrozole/letrozole-containing (neo)adjuvant therapy. Patients could not have received any prior systemic anti-cancer therapies for their advanced disease and were not candidates for curative therapies. Patients had to have measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 or bone disease as their only site of disease. Tumor tissue availability was required for patient participation. The primary endpoint was investigator-assessed PFS.

The interim analyses of efficacy and safety were performed after 236 PFS events occurred (68% of total expected PFS events) and were reviewed by the External Data Monitoring Committee (E-DMC). The data cut-off date was May 1, 2015. At that time, the E-DMC recommended that the study continue as planned. The final PFS analysis was based on the available data at the cut-off date of February 26, 2016. Among 331 patients with disease progression or death, 194 (43.7% of 444 patients) were from the palbociclib plus letrozole arm and 137 (61.7% of 222 patients) were from the placebo plus letrozole arm, respectively. The estimated hazard ratio (HR) was 0.576 (95% Confidence Interval (CI): 0.463-0.718; stratified 1-sided p-value <0.000001) in favor of palbociclib plus letrozole. The median PFS was 24.8 months (95% CI: 22.1 to NE) for palbociclib plus letrozole and 14.5 months (95% CI: 12.9-17.1) for placebo plus letrozole.

A Blinded Independent Central Review (BICR) of all patients in Study 1008 was performed to verify the analyses based on investigator assessment. The observed HR from the stratified analysis was 0.653 (95% CI: 0.505-0.844) in favor of palbociclib plus letrozole, with a stratified log-rank 1-sided p-value of 0.000532. The median PFS was 30.5 months (95% CI: 27.4-NE) for palbociclib plus letrozole versus 19.3 months (95% CI: 16.4-30.6) for placebo plus letrozole.

No OS conclusions can be made due to the immaturity of the data. No statistically significant differences were observed in any of the PRO endpoints between the palbociclib plus letrozole arm and the placebo plus letrozole arm (HR of 1.042 [95% CI 0.838-1.295]; p-value=0.663).

No major unexpected safety findings were observed. In the palbociclib plus letrozole arm, 9.7% of patients permanently discontinued treatment with either or both study drugs (ie, palbociclib and letrozole) due to an AE, and 5.9% of patients permanently discontinued treatment in the placebo plus letrozole arm.

## 2.0 DISCUSSION

### Summary of the Top-Line Results of Study 1008 (PALOMA-2)

1. Based on the final results from the Phase 3 Study 1008 (PALOMA-2) and the completed Study 1003 (PALOMA-1) and Study 1023 (PALOMA-3), does the FDA support submission of a sNDA to seek full approval for palbociclib in combination with (b) (4) with hormone receptor positive, HER2 negative advanced or metastatic breast cancer?

**FDA Response: Yes. Please also include any data available regarding the safety and efficacy of (b) (4)**

**In addition to Rb expression, please provide available data regarding other biomarker analyses (CCND1 amplification, CDKN2A deletion, RNA expression of cdk4 and cdk6, and protein expression of Ki67, cyclin E, and p16).**

### NDA Content and Format

2. Does the Agency agree with the proposed content of the sNDA presented in the proposed sNDA Table of Contents (Appendix 1) or have any comments or suggestions?

**FDA Response: Yes.**

3. Does the FDA agree with the proposal for the inclusion of separate adverse reaction (AR) tables for Studies 1008 and 1023 in the IBRANCE United States Package Insert (USPI) given the different combination therapies?

**FDA Response: Yes.**

4. Does the Agency agree with the criteria for providing the patient safety narratives and Case Report Forms (CRF) in the sNDA, as described in Section 11.4, and that efficacy narratives are not required?

**FDA Response: Yes.**

5. The Sponsor proposes to submit legacy (non-CDISC) data as .xpt files (similar structure as original NDA and 1023 sNDA), including define.pdf, and annotated CRF (where available), as well as Text (.txt), and documentation (\*.pdf files) for pharmacokinetic modeling and simulation output. We will also provide a dataset reviewer guide detailing the datasets being provided with the submission. We will provide the production version of SAS programming codes used to generate efficacy analyses and patient reported outcomes analyses in the Study 1008 CSR, as well as simplified SAS codes to replicate the key efficacy analysis results. Does the FDA consider the proposal along with the types and format of datasets appropriate to support the proposed sNDA?

**FDA Response: Yes.**

6. Population pharmacokinetic analysis and exposure/response analysis for efficacy and safety endpoints (PFS and ECG, respectively) from Study 1008 will be conducted and the report of these analyses will be included in the sNDA submission. However, due to the timing of the availability of PK and clinical data from Study 1008, the summary of these analyses will not be included in either the Summary of Clinical Pharmacology (SCP) or the Clinical Overview (CO). Instead these analyses will be provided as standalone documents and will be submitted within 30 days of the sNDA submission. Does FDA agree with this will neither affect the Prescription Drug User Fee Act (PDUFA) review clock nor the FDA's ability to determine whether the application can be accepted?

**FDA Response: We strongly encourage you to submit the summary of population pharmacokinetic and exposure-response analyses with your sNDA submission. Whether your proposed delay affects review clock and/or filability will be a review issue.**

7. Does FDA agree with the proposal for the presentation of patient reported outcomes data in the sNDA Clinical Summary Sections as described in this BD in Section 10.1.6.4?

**FDA Response: Yes.**

8. A second updated efficacy analysis for Study 1023 (PALOMA-3) was performed with a data cutoff date of 23 October 2015 and is summarized in Section 10.2. Does FDA agree this updated analysis can be included in the 1008 sNDA for consideration of inclusion in the USPI?

**FDA Response: Yes.**

9. Given the Breakthrough Therapy Designation and the Sponsor's plan to request Priority Review, does FDA agree with the Sponsor's proposal to submit a 90-Day Safety Update during the review period rather than the standard 120-Day Safety Update?

**FDA Response: Your proposal to submit the 120-Day Safety Update by day 90 is acceptable.**

10. Referring to submissions dated 25 April 2014 and 28 July 2014 containing the Initial Pediatric Study Plan (iPSP) and FDA's final agreement to grant the Sponsor's request for a PREA Waiver of Palbociclib in hormone receptor-positive (Appendix 2), HER2-negative advanced breast cancer dated 12 September 2014. A PREA Waiver will also be included in the planned sNDA submission. Does FDA agree the iPSP applies to this Study 1008 as well and a separate iPSP does not need to be submitted?

**FDA Response: The iPSP with the request for full waivers can be submitted with the sNDA submission.**

### **3.0 OTHER IMPORTANT MEETING INFORMATION**

#### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our April 29, 2016, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

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

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

## **PREA REQUIREMENTS**

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

## **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after

June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [\*PLR Requirements for Prescribing Information\*](#) and [\*Pregnancy and Lactation Labeling Final Rule\*](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

### **Office of Scientific Investigations (OSI) Requests**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

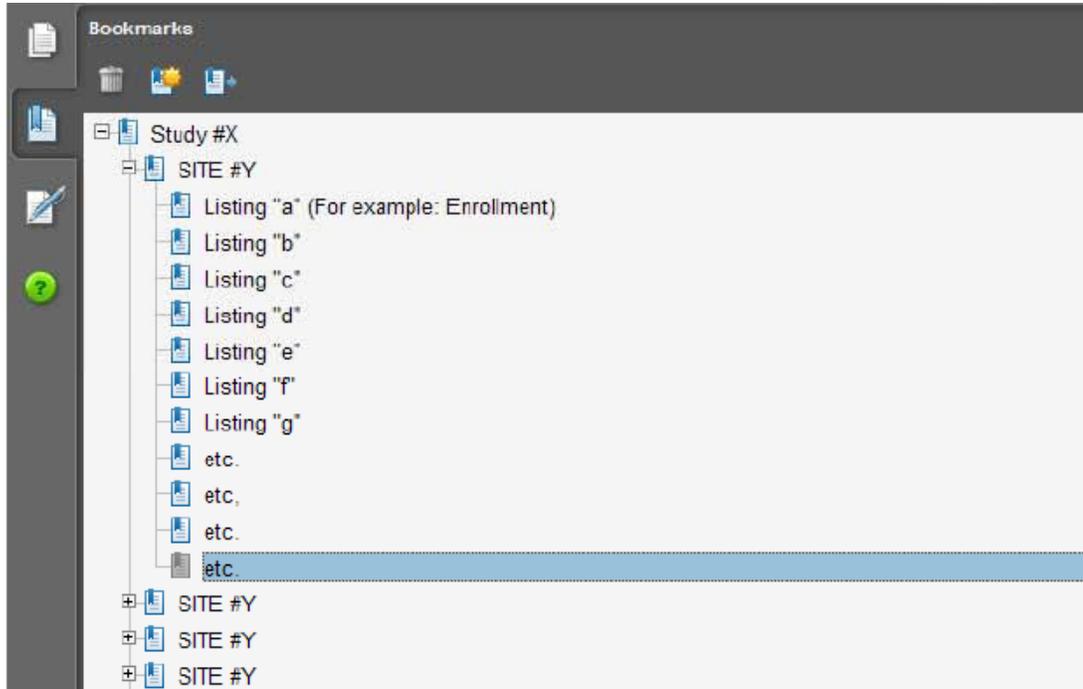
**I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
  - a. Number of subjects screened at each site
  - b. Number of subjects randomized at each site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
  - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.
  - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
  - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

## **II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
  - b. Subject listing for treatment assignment (randomization)
  - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
  - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

## Attachment 1

### Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item <sup>1</sup>	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1:  
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page:  
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

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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  
07/11/2016