CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

207103Orig1s002

Trade Name: **Ibrance**

Generic Name: **palbociclib**

Sponsor: **Pfizer Inc.**

Approval Date: 02/19/2016

Indications: 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:

- letrozole as initial endocrine based therapy in postmenopausal women, or
- fulvestrant in women with disease progression following endocrine therapy.

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207103/S-002

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING COMMITMENT

Pfizer Inc.
Attention: Michelle Y. Kite
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Ms. Kite:

Please refer to your Supplemental New Drug Application (sNDA) dated October 15, 2015, received October 15, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ibrance® (palbociclib) Capsule 75 mg, 100 mg, and 125 mg.

This Prior Approval supplemental new drug application provides for use of Ibrance® (palbociclib) Capsules as indicated 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. The clinical pharmacology information (Summary of Clinical Pharmacology Update and Pop-PK exposure analysis) was also provided.

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 the 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 includes 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

We acknowledge your February 27, 2015, submission containing final printed carton and container labels.

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 because the disease does not exist in children.

FULFILLMENT OF POSTMARKETING COMMITMENT

We have received your submission dated October 15, 2015, containing the final report for the following postmarketing commitment listed in the February 3, 2015, approval letter.

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

We have reviewed your submission and conclude that the above commitment was fulfilled.

We remind you that there are postmarketing requirements and a postmarketing commitment listed in the February 3, 2015, approval letter that are still open.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We also remind you of your new postmarketing commitment:

3040-1 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."

The timetable you submitted on February 11, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	07/2013 (Submitted)
Trial Completion:	12/2017
Final Report Submission:	06/2018

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.

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.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Content of Labeling

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

/s/

GEOFFREY S KIM
02/19/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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)	2/2016
Dosage and Administration (2.1, 2.2)	2/2016
Warnings and Precautions (5.1, 5.2, 5.3)	2/2016

---------- 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:

- letrozole as initial endocrine based therapy in postmenopausal women (1), or
- fulvestrant in women with disease progression following endocrine therapy.

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. (1)

----------DOSAGE AND ADMINISTRATION----------

IBRANCE capsules are taken orally with food in combination with letrozole 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 14 of the first 2 cycles, and as clinically indicated. (2.2, 5.1)
- Pulmonary Embolism: Monitor patients for signs and symptoms of pulmonary embolism and treat as medically appropriate. (2.2, 5.2)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.3, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------

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

---------- 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: 2/2016

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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:

- letrozole as initial endocrine based therapy in postmenopausal women, or
- fulvestrant in women with disease progression following endocrine therapy.

The indication in combination with letrozole is approved under accelerated approval based on progression-free survival (PFS) *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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)]*.

When coadministered with palbociclib, the recommended dose of letrozole is 2.5 mg taken once daily continuously throughout the 28-day cycle. Please refer to the full prescribing information of letrozole.

When coadministered with palbociclib, 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[a]

Monitor complete blood counts prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 14 of the first 2 cycles, and as clinically indicated.	
CTCAE Grade	**Dose Modifications**
Grade 1 or 2	No dose adjustment is required.
Grade 3	Day 1 of cycle: Withhold IBRANCE, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the *same dose*. Day 14 of first 2 cycles: Continue IBRANCE at current dose to complete cycle. Repeat complete blood count on Day 21. Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia in subsequent cycles.
Grade 3 neutropenia[b] with fever ≥38.5 ºC and/or infection	Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose*.
Grade 4	Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose*.

Grading according to CTCAE 4.0.
CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal.
[a] Table applies to all hematologic adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
[b] Absolute neutrophil count (ANC): Grade 1: ANC < LLN - 1500/mm^3; Grade 2: ANC 1000 - <1500/mm^3; Grade 3: ANC 500 - <1000/mm^3; Grade 4: ANC <500/mm^3

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

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade ≥3 non-hematologic toxicity (if persisting despite optimal medical treatment)	Withhold until symptoms resolve to: • Grade ≤1; • Grade ≤2 (if not considered a safety risk for the patient) Resume at the *next lower dose*.

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 both Study 1 (75%) and Study 2 (83%). A Grade ≥3 decrease in neutrophil counts was reported in 62% 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 ≥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 14 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 about 1% of patients exposed to IBRANCE. 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 Pulmonary Embolism

Pulmonary embolism has been reported at a higher rate in patients treated with IBRANCE plus letrozole in Study 1 (5%) and in patients treated with IBRANCE plus fulvestrant in Study 2 (1%) compared with no cases in patients treated either with letrozole alone or fulvestrant plus placebo. Monitor patients for signs and symptoms of pulmonary embolism and treat as medically appropriate.

5.3 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 ≥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 topics are described below and elsewhere in the labeling:

- Neutropenia *[see Warnings and Precautions (5.1)]*
- Pulmonary Embolism *[see Warnings and Precautions (5.2)]*

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 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 letrozole alone was evaluated in Study 1. The data described below reflect exposure to IBRANCE in 83 out of 160 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of treatment in Study 1. The median duration of treatment for IBRANCE was 13.8 months while the median duration of treatment for letrozole on the letrozole-alone arm was 7.6 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 7 of 83 (8%) patients receiving IBRANCE plus letrozole and in 2 of 77 (3%) patients receiving letrozole alone. Adverse reactions leading to discontinuation for those patients receiving IBRANCE plus letrozole included neutropenia (6%), asthenia (1%), and fatigue (1%).

The most common adverse reactions (≥10%) of any grade reported in patients in the IBRANCE plus letrozole arm were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis.

The most frequently reported serious adverse reactions in patients receiving IBRANCE plus letrozole were pulmonary embolism (3 of 83; 4%) and diarrhea (2 of 83; 2%).

An increased incidence of infections was observed in the IBRANCE plus letrozole arm (55%) compared to the letrozole alone arm (34%). Febrile neutropenia has been reported in the IBRANCE clinical program, although no cases were observed in Study 1. Grade ≥3 neutropenia was managed by dose reductions and/or dose delay or temporary discontinuation consistent with a permanent discontinuation rate of 6% due to neutropenia *[see Dosage and Administration (2.2)]*.

Adverse reactions (≥10%) reported in patients who received IBRANCE plus letrozole or letrozole alone in Study 1 are listed in Table 4.

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

Adverse Reaction	IBRANCE plus Letrozole (N=83)			Letrozole Alone (N=77)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
URI[a]	31	1	0	18	0	0
Blood and lymphatic system disorders						
Neutropenia	75	48	6	5	1	0
Leukopenia	43	19	0	3	0	0
Anemia	35	5	1	7	1	0
Thrombocytopenia	17	2	0	1	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	7	0	0
Nervous system disorders						
Peripheral neuropathy[b]	13	0	0	5	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	11	0	0	1	0	0
Gastrointestinal disorders						
Stomatitis[c]	25	0	0	7	1	0
Nausea	25	2	0	13	1	0
Diarrhea	21	4	0	10	0	0
Vomiting	15	0	0	4	1	0
Skin and subcutaneous tissue disorders						
Alopecia	22[d]	N/A	N/A	3[e]	N/A	N/A
General disorders and administration site conditions						
Fatigue	41	2	2	23	1	0
Asthenia	13	2	0	4	0	0

Grading according to CTCAE 3.0.
CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable; URI=Upper respiratory infection.

[a] URI includes: influenza, influenza like illness, laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection.

[b] Peripheral neuropathy includes: neuropathy peripheral, peripheral sensory neuropathy.

[c] Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oral discomfort, oropharyngeal pain, stomatitis.

[d] Grade 1 events – 21%; Grade 2 events – 1%.

[e] Grade 1 events – 3%.

Table 5. Laboratory Abnormalities in Study 1

Laboratory Abnormality	IBRANCE plus Letrozole (N=83)			Letrozole Alone (N=77)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
WBC decreased	95	44	0	26	0	0
Neutrophils decreased	94	57	5	17	3	0
Lymphocytes decreased	81	17	1	35	3	0
Hemoglobin decreased	83	5	1	40	3	0
Platelets decreased	61	3	0	16	3	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. 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 treatment in Study 2.

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 (≥10%) of any grade reported in patients in the IBRANCE plus fulvestrant arm were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, headache, diarrhea, thrombocytopenia, constipation, vomiting, alopecia, rash, decreased appetite, and pyrexia.

The most frequently reported serious adverse reactions in patients receiving IBRANCE plus fulvestrant were infections (3%), pyrexia (1%), neutropenia (1%), and pulmonary embolism (1%).

Adverse reactions reported in patients who received IBRANCE plus fulvestrant or placebo plus fulvestrant in Study 2 are listed in Table 6.

Table 6. Adverse Reactions 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[a]	47	3	1	31	3	0
Blood and lymphatic system disorders						
Febrile neutropenia	1	1	0	1	0	1
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	3	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Eye disorders						
Vision blurred	6	0	0	2	0	0
Lacrimation increased	6	0	0	1	0	0
Dry eye	4	0	0	2	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	8	1	0
Nervous system disorders						
Headache	26	1	0	20	0	0
Dysgeusia	7	0	0	3	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	7	0	0	2	0	0
Gastrointestinal disorders						
Nausea	34	0	0	28	1	0
Stomatitis[b]	28	1	0	13	0	0
Diarrhea	24	0	0	19	1	0
Constipation	20	0	0	16	0	0
Vomiting	19	1	0	15	1	0
Skin and subcutaneous tissue disorders						
Alopecia	18[c]	N/A	N/A	6[d]	N/A	N/A
Rash[e]	17	1	0	6	0	0
Dry skin	6	0	0	1	0	0
General disorders and administration site conditions						
Fatigue	41	2	0	29	1	0
Asthenia	8	0	0	5	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.

[a] Most common infections (>1%) include: nasopharyngitis, upper respiratory infection, urinary tract infection, influenza, bronchitis, rhinitis, conjunctivitis, pneumonia, sinusitis, cystitis, oral herpes, respiratory tract infection.

[b] Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.

[c] Grade 1 events – 17%; Grade 2 events – 1%.

[d] Grade 1 events – 6%.

[e] Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.

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

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 with administration of midazolam alone. The dose of the sensitive CYP3A substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus) may need to be reduced as IBRANCE may increase their 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 ≥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 up to 300 mg/kg/day and 20 mg/kg/day palbociclib, respectively, during the period of organogenesis. The maternally toxic dose of 300 mg/kg/day was fetotoxic in rats, resulting in reduced fetal body weights. At doses ≥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.

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, nor 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

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.

8.5 Geriatric Use

Of 84 patients who received IBRANCE in Study 1, 37 patients (44%) were ≥65 years of age and 8 patients (10%) were ≥75 years of age. Of 347 patients who received IBRANCE in Study 2, 86 patients (25%) were ≥65 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 ≤ ULN and AST > ULN, or total bilirubin >1.0 to 1.5 × 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 × ULN and any AST) *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

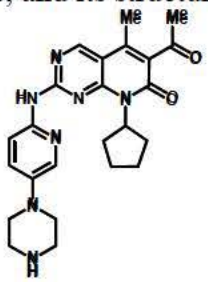
Based on a population pharmacokinetic analysis that included 183 patients, where 73 patients had mild renal impairment (60 mL/min ≤ CrCl <90 mL/min) and 29 patients had moderate renal impairment (30 mL/min ≤ CrCl <60 mL/min), mild and moderate renal impairment had no effect on the exposure of palbociclib. 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 $C_{24}H_{29}N_7O_2$. 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; and 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 kinase (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 protein (Rb) 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 leads to increased cell senescence, which was sustained for up to 6 days following drug removal. 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.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of palbociclib on the QTc interval was evaluated in 184 patients with advanced cancer. No large change (i.e., >20 ms) in the QTc interval was detected at the mean observed maximal steady-state palbociclib concentration following a therapeutic schedule (e.g., 125 mg daily for 21 consecutive days followed by 7 days off to comprise a complete cycle of 28 days).

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 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 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 (26% CV).

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 (± standard deviation) plasma elimination half-life was 29 (±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_{inf} and the C_{max} 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_{inf} and C_{max} 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_{inf} and C_{max} 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_{inf} and the C_{max} values by 61% and 37%, respectively, as compared with 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_{max} by 41%, but had limited impact on AUC_{inf}

(13% decrease), when compared to a single dose of IBRANCE administered alone. Given the reduced effect on gastric pH of H2-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, H2-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_{inf} and C_{max} 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.

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 ≥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 ≥30 mg/kg/day in rats and ≥0.2 mg/kg/day in dogs included decreased organ weight, atrophy or degeneration, hypospermia, intratubular cellular debris, lower sperm motility and density, 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 ≥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 at 100 mg/kg/day with projected exposure levels [AUC] of 20 times the exposure in humans at the recommended dose.

13.2 Animal Toxicology and/or Pharmacology

Altered glucose metabolism (glycosuria, hyperglycemia, decreased insulin) associated with changes in the pancreas (islet cell vacuolation), eye (cataracts, lens degeneration), teeth (degeneration/necrosis of ameloblasts in actively growing teeth), kidney (tubule vacuolation, chronic progressive nephropathy), and adipose tissue (atrophy) were identified in the 27-week repeat-dose toxicology study in rats and were most prevalent in males at doses ≥30 mg/kg/day (approximately 11 times the human exposure [AUC] at the recommended dose). Some of these findings (glycosuria/hyperglycemia, pancreatic islet cell vacuolation, and kidney tubule vacuolation) were present in the 15-week repeat-dose toxicology study in rats, but with lower incidence and severity. The rats used in these studies were approximately 7 weeks old at the beginning of the studies. Altered glucose metabolism or associated changes in pancreas, eye, teeth, kidney, and adipose tissue were not identified in dogs in repeat-dose toxicology studies up to 39 weeks duration.

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 was a randomized, open-label, multicenter study of IBRANCE plus letrozole versus letrozole alone 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 165 patients were randomized in Study 1. Randomization was stratified by disease site (visceral versus bone only versus other) and by disease-free interval (>12 months from the end of adjuvant treatment to disease recurrence versus ≤12 months from the end of adjuvant treatment to disease recurrence or de novo advanced disease). 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 progressive disease, unmanageable toxicity, or consent withdrawal. The major efficacy outcome measure of the study was investigator-assessed PFS evaluated according to Response Evaluation Criteria in Solid Tumors Version 1.0 (RECIST).

Patients enrolled in this study had a median age of 63 years (range 38 to 89). The majority of patients were White (90%) and all patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Forty-three percent of patients had received chemotherapy and 33% had received antihormonal therapy in the neoadjuvant or adjuvant setting prior to their diagnosis of advanced breast cancer. Forty-nine percent of patients had no prior systemic therapy in the neoadjuvant or adjuvant setting. The majority of patients (98%) had metastatic disease. Nineteen percent of patients had bone only disease and 48% 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, disease site and prior therapy. The treatment effect of the combination on PFS was also supported by a retrospective independent review of radiographs with an observed hazard ratio (HR) of 0.621 (95% CI: 0.378, 1.019). Overall response rate in patients with measurable disease as assessed by the investigator was higher in the IBRANCE plus

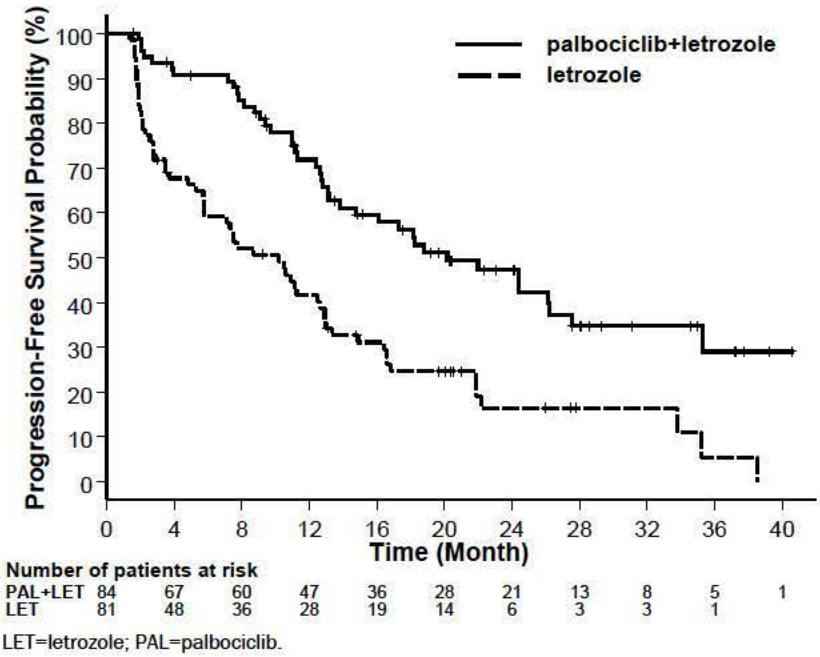
letrozole compared to the letrozole-alone arm (55.4% versus 39.4%). At the time of the final analysis of PFS, overall survival (OS) data were not mature with 37% of events.

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

	IBRANCE plus Letrozole (N=84)	Letrozole (N=81)
Progression-Free Survival (PFS)		
Number of PFS Events (%)	41 (48.8%)	59 (72.8%)
Hazard ratio (95% CI)	0.488 (0.319, 0.748)	
Median PFS [months] (95% CI)	20.2 (13.8, 27.5)	10.2 (5.7, 12.6)

CI=confidence interval; N=number of patients.

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



LET=letrozole; PAL=palbociclib.

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 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.

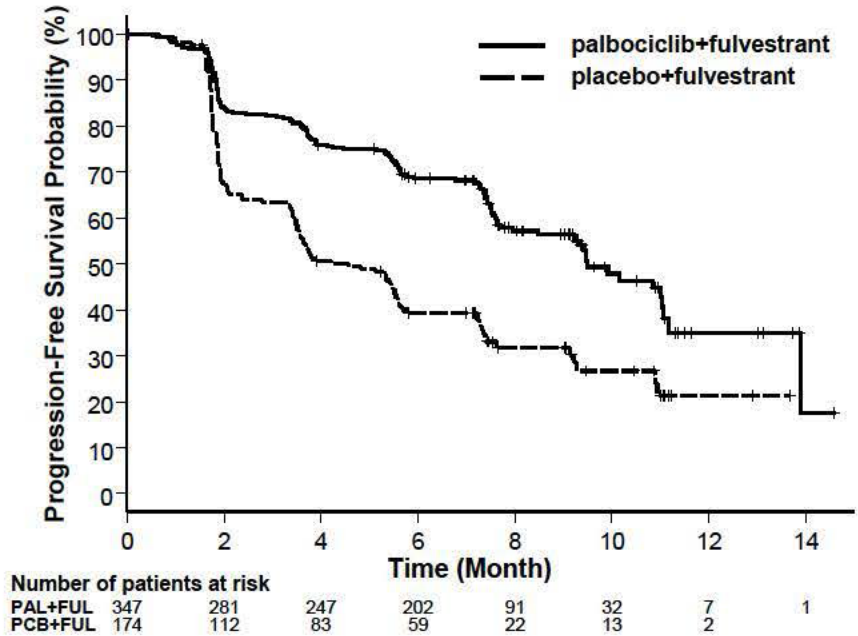
The results from the investigator-assessed PFS from Study 2 are summarized in Table 9 and Figure 2. Consistent results were observed across patient subgroups of disease site, sensitivity to prior hormonal therapy and menopausal status. Confirmed overall response rate in patients with measurable disease as assessed by the investigator was 24.6% in the IBRANCE plus fulvestrant and was 10.9% in the placebo plus fulvestrant arm. Duration of response was 9.3 months in the IBRANCE plus fulvestrant arm compared with 7.6 months in the placebo plus fulvestrant arm. At the time of final analysis of PFS, OS data were not mature with 29% of events.

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

	IBRANCE plus Fulvestrant (N=347)	Placebo plus Fulvestrant (N=174)
Progression-Free Survival Number of PFS Events (%)	145 (41.8%)	114 (65.5%)
Hazard ratio (95% CI) and p-value	0.461 (0.360-0.591), p<0.0001	
Median PFS [months] (95% CI)	9.5 (9.2-11.0)	4.6 (3.5-5.6)

CI=confidence interval; 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:

IBRANCE Capsules			
Package Configuration	**Capsule Strength (mg)**	**NDC**	**Capsule Description**
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, "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 ^{o}C to 25 ^{o}C (68 ^{o}F to 77 ^{o}F); excursions permitted between 15 ^{o}C to 30 ^{o}C (59 ^{o}F to 86 ^{o}F).

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)]*.

Pulmonary Embolism

- Advise patients to immediately report any signs or symptoms of pulmonary embolism, such as shortness of breath, chest pain, tachypnea, and tachycardia *[see Warnings and Precautions (5.2)]*.

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 (5.3) 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.

LAB-0723-2.0

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.

Blood clots in the arteries of your lungs (pulmonary embolism or PE). IBRANCE may cause serious or life-threatening blood clots in the arteries of your lungs. Tell your healthcare provider right away if you have any of the following signs and symptoms of a PE:

- shortness of breath
- sudden, sharp chest pain that may become worse with deep breathing
- rapid heart rate
- rapid breathing

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:

- letrozole 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
- headache
- diarrhea
- constipation
- 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 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.

Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

LAB-0724-2.0

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: February 2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207103Orig1s002

OFFICER/EMPLOYEE LIST

Officer / Employee List
Application: sNDA 207103/002

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
Bloomquist, Erik
Chen, Xiao
Chen, Wei
Chen, Wen-Hung
Cleck-Derenick, Jessica
Dinatale, Miriam
Fedenko, Katherine
Fourie-Zirkelbach, Jeanne
Fu, Wentao
Fuller, Barbara
Iacono-Connor, Lauren
Ibrahim, Amna
Kacuba, Alice
Kim, Geoffrey
Kovacs, Sarrit
Jenney, Susan
Liu, Qi
Mills, Sharon
Papadopoulos, Elektra
Palmby, Todd
Pierce, William
Senior, Nicholas
Tang, Shenghui
Thompson, Susan
Tilley, Amy
Trentacosti, Anne Marie
Walker, Amanda
Walker, Morgan
Wang, Yaning
Wedam, Suparna
Yu, Jingyu (Jerry)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207103Orig1s002

OFFICE DIRECTOR MEMO

Division Director Summary Review for Regulatory Action

Date	February 19, 2016
From	Geoffrey Kim
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	207103/S002
Applicant	Pfizer, Inc.
Date of Submission	October 15, 2015
PDUFA Goal Date	April 15, 2016
Proprietary Name / **Non-Proprietary Name**	Ibrance/palbociclib
Dosage Form(s) / Strength(s)	Capsules/ 75 mg, 100 mg, 125 mg
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Action/Recommended Action for sNDA:	*Approval*
Approved/Recommended Indication/Population(s) (if applicable)	In combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, HER2-negative advanced or metastatic cancer with disease progression following prior endocrine therapy.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Suparna Wedam; Amanda Walker
Statistical Review	Erik Bloomquist; Shenghui Tang
Clinical Pharmacology Review	Wentao Fu, Jeanne Fourie Zirkelbach, Qi Liu; Jerry Yu

OPDP	Nick Senior
OSI	Lauren Iacono-Connors
Pharm Tox	Wei Chen; Todd Palmby
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 1023 (PALOMA-3), a favorable benefit-risk profile has been demonstrated for patients with HR-positive, HER2-negativeadvanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy. The regulatory action for this supplement is approval. As summarized by the clinical review team:

*"*The benefit-risk assessment in this sNDA is based on the phase 3 Study 1023 (PALOMA-3). Study 1023 was a randomized, double-blind, placebo- controlled study in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy. This was a well-designed trial with an appropriate comparator arm. The primary endpoint was investigator assessed PFS. The median PFS in the palbociclib plus fulvestrant arm at the time of the preplanned interim analysis was 9.2 months compared to 3.8 months in the placebo plus fulvestrant arm (HR=0.42; 95%CI: 0.32, 0.56; p<0.000001). The results were consistent at the time of the updated and final analysis with a median PFS of 9.5 months in the palbociclib plus fulvestrant arm compared to 4.6 months n the placebo plus fulvestrant arm (HR=0.46; 95% CI: 0.36, 0.59; p<0.000001). Palbociclib plus fulvestrant showed a 4.9 month improvement in median PFS compared to placebo plus fulvestrant which is both clinically meaningful and statistically significant. Results of a BICR audit, subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results. Overall survival (OS) results are immature at this time.

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 event across the entire clinical program with palbociclib occurring in >70% of patients. It is reassuring, however, that there were very few cases of neutropenic fever and neutropenic sepsis. Additional common adverse reactions with palbociclib include leukopenia (53%), infections (47%), fatigue (41%), nausea (34%), anemia (30%), stomatitis (28%), and headache (26%). There was a numerical increase in the number of pulmonary emboli reported in patients receiving palbociclib plus endocrine therapy compared to letrozole alone (Study 1003) or placebo plus fulvestrant (Study 1023). 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.

In conclusion, based on a favorable risk-benefit profile for palbociclib in combination with fulvestrant, the reviewers recommend regular approval for the following indication "IBRANCE is a kinase inhibitor indicated in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic cancer with disease progression following prior endocrine therapy."

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
Analysis of Condition	In 2016, it is estimated that breast cancer will be diagnosed in 246,660 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%.	Breast cancer is a serious and life-threatening condition.
Current Treatment Options	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. 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.	There are unmet medical needs to improve the outcomes in patients with HR-positive, HER2-negative advanced or metastatic breast cancer.
Benefit	The clinical data from a randomized, double-blind, placebo controlled Phase 3 Trial (Study 1023, A5481023, PALOMA-3) in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy presented in this sNDA demonstrates an improvement in PFS for palbociclib plus fulvestrant compared to placebo plus fulvestrant. The median PFS in the palbociclib plus fulvestrant arm was 9.5 months compared to 4.6 months in the placebo plus fulvestrant arm (HR =0.46; 95% CI: 0.36, 0.59; p<0.000001). OS results were immature at the time of analysis with only 29% of the planned 198 events. Overall response rate	The PFS benefit derived from palbociclib is statistically significant and clinically meaningful. It is unclear if there will be an OS benefit.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(ORR) was 24.6% in the palbociclib plus fulvestrant arm compared with 10.9% in the placebo plus fulvestrant arm for patients with measurable disease at baseline. Duration of response (DOR) was 9.3 months in the palbociclib plus fulvestrant arm and 7.6 months in the placebo plus fulvestrant arm.	
Risk	Neutropenia was reported in >70% of patients taking palbociclib and was the most common reason for temporary discontinuation and/or dose reduction; however, there were very few cases of neutropenic fever and neutropenic sepsis. Additional common adverse reactions with palbociclib include leukopenia (53%), infections (47%), fatigue (41%), nausea (34%), anemia (30%), stomatitis (28%), and headache (26%). There was a numerical increase in the number of pulmonary emboli reported in patients receiving palbociclib compared to letrozole alone (Study 1003) or placebo plus fulvestrant (Study 1023). With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2, and rates of treatment discontinuation for adverse reactions were generally low. No new safety concerns have been identified based on the cumulative safety data submitted in this sNDA.	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.
Risk Management	• There is no proposal for a formal Risk management Plan.	

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 ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

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.
April 9, 2013: FDA granted Breakthrough Designation to palbociclib for the treatment of patients with breast cancer.
July 31, 2014: The protocol for Study 1023 was submitted to the IND (SDN 222, eCTD 211). Amendments to this protocol are explained in detail in Section 6.1.1. There was no special protocol assessment requested for Study 1023.
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.

Intended Population
From the Clinical Review:
Endocrine therapy options for postmenopausal women with HR-positive MBC that do not respond to first line therapy 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 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.

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Drug Class

Letrozole	First and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer	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 (p=0.5136)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor
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
Fulvestrant	Treatment of HR+ MBC in postmenopausal women with disease progression following antiestrogen therapy.	2002	250mg once a month intramuscularly	vs. anastrozole (2 studies) ORR: 17% vs 17%; 20.3%vs 14.9% TTP: 165 vs 103 days; 166 vs 156 days	Hot flushes, GI disturbances, hepatic impairment	Estrogen receptor antagonist
		2010	500mg on days 1, 15, 29 and once monthly thereafter intramuscularly	vs fulvestrant 250mg ORR: 13.8% (500 mg) vs. 14.6% (250 mg) PFS: 6.5 vs. 5.4 months (p=0.006)		
Everolimus	postmenopausal women with advanced HR+, HER2negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole.	2012	10mg daily by mouth	Vs exemestane ORR: 12.6% vs. 1.7% PFS: 11.0 months vs. 4.1 months HR=0.38 (p<0.0001) (independent review); 7.8 months vs. 3.2 months HR=0.45 (p<0.0001); (investigator assessed)	Infections, non-infectious pneumonitis, oral ulceration, angioedema, renal failure, impaired wound healing, diarrhea	mTOR inhibitor
Paclitaxel	After failure of initial chemotherapy in MBC	1994	175 mg/m^2 intravenously every 3 weeks	Data from 83 patients accrued in three Phase 2 open label studies and from 471 patients enrolled in a Phase 3 randomized study were available to support the use of paclitaxel in patients with MBC. ORR: 26% (175 mg and 135 mg combined) PFS: 3.5 months	Neuropathy, hepatic toxicity, myelosuppression, hypersensitivity	Microtubule stabilizing agent

Docetaxel	In the treatment of locally advanced or MBC after chemotherapy failure	1996	60 mg/m^2 to 100 mg/m^2 intravenously every 3 weeks	Vs mitomycin/vinblastine ORR: 28.1% vs. 9.5% (p<0.0001) TTP: 4.3 vs. 2.5 (p=0.01)	Fluid retention, neuropathy, hepatic toxicity, myelosuppression, hypersensitivity	Microtubule stabilizing agent
Nab-paclitaxel	In the treatment of MBC after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.	2005	260mg/m2 intravenously every 3 weeks	Vs paclitaxel ORR: 21.5% vs. 11.1% (p=0.003)	Myelosuppression, neuropathy,	Microtubule stabilizing agent
Capecitabine	As monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen	1998	1250 mg/m2 twice daily orally for 2 weeks followed by a one week rest period in 3-week cycles	ORR: 18.5 (all); 25.6 (subgroup) PFS: 3 months for all	Coagulopathy, hand foot syndrome, diarrhea, cardiac toxicity,	Oral prodrug of 5'-DFUR to 5-FU
	In combination with docetaxel after failure of prior anthracycline containing therapy for MBC	2001	1250 mg/m2 twice daily for 2 weeks followed by a 7-day rest period, combined with docetaxel at 75 mg/m2 as a 1-hour IV infusion every 3 weeks	Vs docetaxel alone ORR: 32% vs. 22% PFS: 6.2 months vs. 4.3 months		

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 (b) applicable for action on an NDA resulting in an increase in use but the estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 part per billion. The calculated Expected Introduction Concentration (EIC) is provided in the attachment. The applicant claims that to the best of its knowledge no extraordinary circumstances exist. The claim for claims 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:

"Since the male fertility index was decreased compared to concurrent control and there were corroborating effects on the male reproductive organs in repeat-dose toxicity studies, this finding was included in the product label despite the fact that this was within the historical control range for fertility index of 78.3-100% provided by the Applicant.

The Applicant proposed to change the duration of contraception use following the last dose of palbociclib in females of reproductive potential from 2 to 3 weeks. This was based on the aneugenic mechanism of genotoxicity of palbociclib. The window of sensitivity for an aneugen spans periovulation to approximately 24 hours after the end of ovulation when the unfertilized oocyte is destroyed (Marchetti et al. 2015). On a molecular level, the sensitive stage of oocyte maturation is the transition between end of meiosis I and beginning of meiosis II, which corresponds to approximately 14 days (The Developing Human: Clinically Oriented Embryology, 10th edition). Thus, 21 days of contraception post treatment was proposed to allow for clearance (5 half-lives or approximately 7 days) and account for the sensitive stage of oocyte development. This proposed change was acceptable.

Contraception use in males with female partners of reproductive potential for 3 months after the last dose of palbociclib was added to the label based on two periods of spermatogenesis. The term "teratogenic" was removed from the risk summary in section 8.1 upon the Applicant's request. This was based on a re-evaluation of the findings in the embryofetal developmental toxicity studies in rats and rabbits. The skeletal variations observed in the presence of maternal toxicity are thought to be related to maternal toxicity and may be secondary effects. In addition, those findings are expected to resolve later in development and are not likely to lead to permanent effects in the offspring."

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).The current submission fulfills the postmarketing requirement identified in the February 3, 2015 approval letter as 2860-3 "Submit the final report for your ongoing drug interaction trial (A5481039) entitled, "A phase 1, open-label, fixed-sequence, 2-cohort, 2-period study to investigate the effect of modafinil and pioglitazone given as multiple doses on single dose pharmacokinetics of palbociclib (PD-0332991) in healthy volunteers", to assess the effect of modafinil (a moderate CYP3A inducer) on the pharmacokinetics of palbociclib in healthy volunteers"."

Major findings from the review are as follows:

- At the fixed dose of 125 mg palbocicib, there was a flat exposure-response relationship for PFS in women enrolled in trial 1023.

- In vivo, coadministration of multiple doses of a modafinil (moderate CYP3A inducer) had no clinically significant effect on palbociclib exposure. There was no drug interaction between palbociclib and fulvestant, or between palbociclib and goserelin when these drugs were co-administered in trial 1023.

- In vivo, palbociclib exposure was increased by 30% in Japanese subjects (N=13) versus non-Asian subjects (N=12). No initial dose adjustment is needed for patients with Japanese ethnicity, and dose adjustments based on adverse events (as in the current Ibrance Package Insert) for all patients taking palbociclib should be followed.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical-Efficacy

This efficacy supplement is supported by a single, well-controlled, randomized, multicenter, multinational trial (Study 1023; PALOMA-3) conducted in 521 women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy. 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 Study 1023:

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.

(b) (4)

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

I concur with the review team's recommendation to remove "Infections" as a stand-alone warning and precaution in section 5 of the product label. Although the incidence of infections was higher on the Ibrance arm as compared to the placebo arm (47% vs. 31%, respectively), the rate of grade 3-4 infections were similar in both arms. In addition, the rate of serious infections and/or infections leading to death, were relatively low in the context of the rates of infections observed with other anti-cancer agents available for the treatment of breast cancer. In addition, the true risk of serious infection is in the context of neutropenia. Thus, the warning for "Neutropenia" was updated to inform prescribers of the risk of serious and life-threatening neutropenic infections.

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

The initial palbociclib approval was granted under the provisions of 21 CFR 314.510 (accelerated approval). 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] is outstanding.

I concur with the review team that this submission does not fulfill the applicant's postmarketing requirement to submit the safety and efficacy data from the ongoing, fully-accrued Study 1008 (PALOMA-2). This study is optimally designed to address the uncertainty regarding the results of PALOMA-1 trial. (b) (4)

OSI
The OSI consultants conclude: "Based on the review of preliminary inspectional findings for clinical investigator Dr. Dennis Slamon, M.D. (Site 1137; Study A5481023), data submitted to the Agency in support of sNDA 207103 S-002 appear reliable and can be used in support of the application."

There are no other unresolved relevant regulatory issues.

12. Labeling

Agreement has been reached on the physician labeling. The final indication is for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with 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.

The applicant has agreed to the following post marketing commitment:

3040-1 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."

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

/s/

GEOFFREY S KIM
02/18/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207103Orig1s002

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	02/11/2016
From	Laleh Amiri-Kordestani, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	207103 002
Applicant	Pfizer, Inc.
Date of Submission	October 15, 2015
PDUFA Goal Date	April 15, 2016
Proprietary Name / Non-Proprietary Name	Ibrance®/ palbociclib
Dosage form(s) / Strength(s)	Capsules: 75 mg, 100 mg and 125 mg
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	In combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, HER2-negative advanced or metastatic cancer with disease progression following prior endocrine therapy.

1. Benefit-Risk Assessment

Source: Clinical Review (Drs. Suparna Wedam and Amanda Walker)

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 2016, it is estimated that breast cancer will be diagnosed in 246,660 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 MBC.

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 received prior endocrine therapy. 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. 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.

The benefit-risk assessment in this sNDA is based on the phase 3 Study 1023 (PALOMA-3). Study 1023 was a randomized, double-blind, placebo- controlled study in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy. This was a well-designed trial with an appropriate comparator arm. The primary endpoint was investigator assessed-PFS. The median PFS in the palbociclib plus fulvestrant arm at the time of the preplanned interim analysis was 9.2 months compared to 3.8 months in the placebo plus fulvestrant arm (HR=0.42; 95%CI: 0.32, 0.56; $p<0.000001$). The results were consistent at the time of the updated and final analysis with a median PFS of 9.5 months in the palbociclib plus fulvestrant arm compared to 4.6 months in the placebo plus fulvestrant arm (HR=0.46; 95% CI: 0.36, 0.59; $p<0.000001$). Palbociclib plus fulvestrant showed a 4.9 month improvement in median PFS compared to placebo plus fulvestrant which is both clinically meaningful and statistically significant. Results of a BICR audit, subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results.

Neutropenia was the most common adverse event across the entire clinical program with palbociclib occurring in >70% of patients. There were very few cases of neutropenic fever and neutropenic sepsis. Additional common adverse reactions with palbociclib include leukopenia (53%), infections (47%), fatigue (41%), nausea (34%), anemia (30%), stomatitis (28%), and headache (26%). There was a numerical increase in the number of pulmonary emboli reported in patients receiving palbociclib plus endocrine therapy compared to letrozole alone (Study 1003) or placebo plus fulvestrant (Study 1023). 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.

Study 1023 used a different endocrine therapy than that used in the pivotal trial (Study 1003, PALOMA-1) that granted accelerated approval to palbociclib. Fulvestrant is an estrogen antagonist and letrozole is an aromatase inhibitor. Thus, the safety and activity of the combination of palbociclib with fulvestrant vs letrozole may differ. In addition, the study populations were different. The results of the postmarketing required study (Study 1008, PALOMA-2) used to confirm the benefit of palbociclib used in combination with letrozole as initial endocrine therapy are not available yet. The interim analysis for Study 1008 has occurred but the data monitoring committee (DMC) recommended continuation of the study at this time. (b) (4) the benefit-risk profile from Study 1023 supports regular approval for the new indication listed above, (b) (4)

(b) (4)

In conclusion, based on a favorable risk-benefit profile for palbociclib in combination with fulvestrant, the reviewers recommend regular approval for the following indication "IBRANCE is a kinase inhibitor indicated in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic cancer with disease progression following prior endocrine therapy."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	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%.	HR-positive/HER2-negative advanced or metastatic breast cancer is a serious and life-threatening condition.
Current Treatment Options	Endocrine therapies are the preferred options for the initial treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer. Endocrine therapy options for postmenopausal women 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 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.	Although multiple treatment options are available for patients with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy, there is still a need for improved therapy.
Benefit	In a well-designed, well-conducted, randomized, double-blind, placebo-controlled Phase 3 Trial (Study 1023, A5481023, PALOMA-3) in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy, there was a clinically meaningful and statistically significant improvement in PFS for palbociclib plus fulvestrant compared to placebo plus fulvestrant. The study had one planned interim analysis of PFS, when 143 events had occurred (60% of the final planned events). The study was stopped for efficacy at the time of the interim analysis. The median PFS in the palbociclib plus fulvestrant arm at the time of the preplanned interim analysis was 9.2 months compared to 3.8 months in the placebo plus fulvestrant arm (HR=0.42; 95% CI: 0.32, 0.56, p-value < 0.000001. After the interim analysis, the Applicant continued to follow-up all	Treatment with palbociclib in combination with fulvestrant resulted in a clinically meaningful and statistically significant improvement in progression-free survival.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	enrolled subjects for an additional four months. The median PFS in the palbociclib plus fulvestrant arm at the time of the updated analysis was 9.5 months compared to 4.6 months in the placebo plus fulvestrant arm (HR=0.47; 95% CI: 0.36, 0.60; p<0.000001). Results of a BICR audit, subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results.	
Risk	Neutropenia was reported in >70% of patients taking palbociclib and was the most common reason for temporary discontinuation and/or dose reduction; however, febrile neutropenia has only been reported in about one percent of patients receiving palbociclib in combination with fulvestrant. Additional common adverse reactions with palbociclib include leukopenia (53%), infections (47%), fatigue (41%), nausea (34%), anemia (30%), stomatitis (28%), and headache (26%). There was a numerical increase in the number of pulmonary emboli reported in patients receiving palbociclib compared to letrozole alone (Study 1003) or placebo plus fulvestrant (Study 1023). With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2, and rates of treatment discontinuation for adverse reactions were generally low. No new safety concerns have been identified based on the cumulative safety data submitted in this sNDA.	The overall safety profile of palbociclib plus letrozole or fulvestrant is acceptable for patients with advanced breast cancer.
Risk Management	Serious risks were mitigated in the protocol by patient selection criteria, mandated supportive therapies, close monitoring for known serious risks, and dose modifications.	Labeling includes instructions for dose reductions for hematological toxicities. Risk of pulmonary embolism was discussed in Warnings and Precautions section of labeling.

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 second-line endocrine treatment in HR-positive/HER2-negative disease depend on patient and tumor characteristics. The aromatase inhibitors, fulvestrant, everolimus (mTOR inhibitor) in combination with exemestane, 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 whose disease has progressed on prior endocrine therapy, 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 October 15, 2015, Applicant submitted Supplement 002 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 (b) (4) The application was complete upon submission and was filed as a priority review because the topline results indicated that palbociclib plus fulvestrant combination therapy provided an advantage over available therapy. Pfizer proposes a new indication, (b) (4)

(b) (4)

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.

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

- July 31, 2014: The protocol for Study 1023 was submitted to the IND (SDN 222, eCTD 0211). There was no special protocol assessment requested for Study 1023.

- 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.

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 (b) applicable for action on an NDA resulting in an increase in use but the estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 part per billion. Per Dr. Xiao Hong Chen (CMC reviewer) this claim is acceptable.

There is no device associated with this sNDA.

4. Nonclinical Pharmacology/Toxicology

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

Pharmacology Toxicology Team Recommendation: Approval

Nonclinical studies including 27-week repeat-dose study in rats, 39-week repeat-dose study in dogs and fertility study in male rats were submitted in this application.

Pharmacology:

A study on the mechanism of bone marrow toxicity was evaluated *in vitro*. Treatment of human bone marrow mononuclear cells (hBMNCs) with palbociclib at concentrations up to 1 μM caused a concentration-dependent increase of cells in G1 phase, and decrease in S and G2/M phases, consistent with G1 cell cycle arrest. This was characterized by a fully reversible, concentration-dependent inhibition of proliferation without apoptosis, cellular senescence, or DNA damage. By contrast, chemotherapeutic agents, including paclitaxel, doxorubicin, and carboplatin, primarily caused apoptotic cell death in bone marrow. The study results suggested that the mechanism of palbociclib induced bone marrow suppression was different from that induced by cytotoxic chemotherapeutic agents.

General toxicology:

In the 39-week repeat-dose toxicity study in dogs, no new toxicities were observed in animals treated with PD332991. The bone marrow, lymphoid tissues, and male reproductive organs were the target organs associated with primary palbociclib-related toxicities. Male reproductive organ effects included degeneration of seminiferous tubules in the testes and hypospermia and increased intratubular cellular debris in the epididymis. Partial to complete reversibility of findings in the hematolymphopoietic and male reproductive systems was demonstrated following a 12-week recovery period.

Reproductive toxicology:

Testicular and epididymal effects (minimal to marked seminiferous tubule degeneration in the testis, and minimal to moderate or marked increases in cellular debris and hypospermia in the epididymides) were identified at ≥ 30 mg/kg/day in rats. These effects correlated with macroscopic changes in the testis, and lower male reproductive organ weights, sperm motility, cauda epididymal sperm density and testicular spermatid density at 100 mg/kg/day. There were no effects on mating and embryonic survival at any dose level. Fertility index was lower (89%) when untreated females were mated with treated males at 100 mg/kg, compared to 100% in treated males at control or lower dose groups.

5. Clinical Pharmacology

Source: Clinical Pharmacology Review (Drs. Wentao Fu, Jeanne Fourie Zirkelbach, Jingyu Yu)

Clinical Pharmacology Team Recommendation: Approval

Population PK Analysis and Exposure-response Analysis:

At the fixed dose of 125 mg palbociclib, there was a flat exposure-response relationship for PFS in women enrolled in trial 1023. PK/PD analysis for safety endpoints (e.g., neutropenia) suggested that higher exposure of palbociclib was associated with lower neutrophil counts, which is consistent with findings in original NDA submission. These findings support the proposed dosing regimen in the overall patient population.

Drug-drug interactions:

For approximately 40 patients included in an early safety review, plasma PK samples were drawn predose on Day 1 and Day 15 of Cycle 1 and Cycle 2, and Day 1 of Cycle 3 for DDI assessments in Study 1023. There was no drug interaction between palbociclib and fulvestrant, or between palbociclib and goserelin when these drugs were co-administered in trial 1023.

In vivo evaluation of the effect of a moderate CYP3A inducer, modafinil, on the single dose palbociclib pharmacokinetics in healthy volunteers was assessed in Study A5481039. *In vivo*, coadministration of multiple doses of a modafinil (moderate CYP3A inducer) had no clinically significant effect on palbociclib exposure. Per Clinical Pharmacology review team, the submission of the final report of study A5481039 fulfills Post Marketing Requirement 2860-3 identified in the 2/3/2015 Original Approval Letter as follows:

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

Demographic interactions/specific populations:

In vivo, palbociclib exposure was increased by 30% in Japanese subjects (N=13) versus non-Asian subjects (N=12). No initial dose adjustment is needed for patients with Japanese ethnicity, and dose adjustments based on adverse events (as in the current Ibrance Package Insert) for all patients taking palbociclib should be followed.

6. Clinical Microbiology

This application did not include clinical microbiology information.

7. Clinical/Statistical- Efficacy

Source: Statistical and Clinical Reviews

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 fulvestrant for the treatment of women with hormone receptor (HR)-positive, HER2-negative advanced or metastatic cancer with disease progression following prior endocrine therapy.

Efficacy Summary

Study 1023 Design:

This sNDA contains data from Study 1023, entitled "Multi-center, randomized, double-blind, placebo-controlled, phase 3 trial of fulvestrant (Faslodex®) with or without PD-0332991 (Palbociclib) +/- goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy". Patients were treated with either palbociclib 125 mg/day or placebo orally for 3 of 4 weeks. Patients also received fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and every 28 days thereafter starting from Day 1 of Cycle 1. In both arms, pre- and peri-menopausal women also received the LHRH agonist goserelin (Zoladex® or generic). The primary objective was to demonstrate an improvement in investigator-assessed progression free survival with palbociclib plus fulvestrant over fulvestrant alone. 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 planned to randomize 417 patients (278 in the fulvestrant plus palbociclib arm and 139 in the placebo plus fulvestrant arm) in a 2:1 randomization ratio. Approximately 238 PFS events were required in the two treatment arms for the study to have a 90% power to detect an increase in PFS assuming a true HR of 0.64 (representing a 56% increase in median PFS from 6 to 9.38 months), if tested at a 1-sided significance level of alpha=0.025. The primary efficacy analysis population was the intent-to-treat (ITT) population. Overall survival was a key secondary endpoint. The final analysis of OS will occur when 198 deaths have occurred. An interim analysis for OS will occur when 97 events have occurred; the Applicant has pre-specified an O'Brien-Fleming boundary for the OS interim analysis.

The study had one planned interim analysis of PFS when 143 events had occurred (60% of the final planned events). The Haybittle-Peto efficacy boundary was to be used at the IA. If the value of the test-statistic from the log-rank test for PFS exceeds the efficacy boundary ($z \geq 3$, $p \leq 0.00135$) the trial may have been stopped for efficacy.

The protocol had two amendments; neither altered the study's integrity:

1) April 4th, 2014: The study drug administration instructions were revised from administration of palbociclib in a fasted state to administration with food and to prohibit the concomitant use of proton-pump inhibitors based on preliminary results from two clinical pharmacology (Studies 1018 and 1021) which suggested that palbociclib taken with food results in more consistent drug absorption and exposure than in a fasted state, and palbociclib exposure may be decreased in a subgroup of patients taking palbociclib concomitantly with proton-pump inhibitors.
2) September 30th, 2014: The protocol was amended in order to prospectively characterize whether or not palbociclib affects glucose metabolism through monitoring of appropriate laboratory measurements given the nonclinical findings in rats and taking into account the limited laboratory glucose data in the current clinical dataset. Prospective monitoring of hemoglobin A1c was added to characterize whether or not palbociclib affected glucose metabolism.

Study 1023 Efficacy Results:

The study was stopped for efficacy at the time of the preplanned interim analysis. The median PFS in the palbociclib plus fulvestrant arm at the time of the preplanned interim analysis (05 December 2014 Cutoff) was 9.2 months compared to 3.8 months in the placebo plus fulvestrant arm (HR=0.42; 95% CI: 0.32, 0.56, p-value < 0.000001. After the interim analysis, the Applicant continued to follow-up all enrolled subjects for an additional four months. The median PFS in the palbociclib plus fulvestrant arm at the time of the updated analysis (16 March 2015 Cutoff) was 9.5 months compared to 4.6 months in the placebo plus fulvestrant arm (HR=0.47; 95% CI: 0.36, 0.60; p<0.000001). See Table 1 and Figure 1 Figure 2 for summary of Efficacy Results.

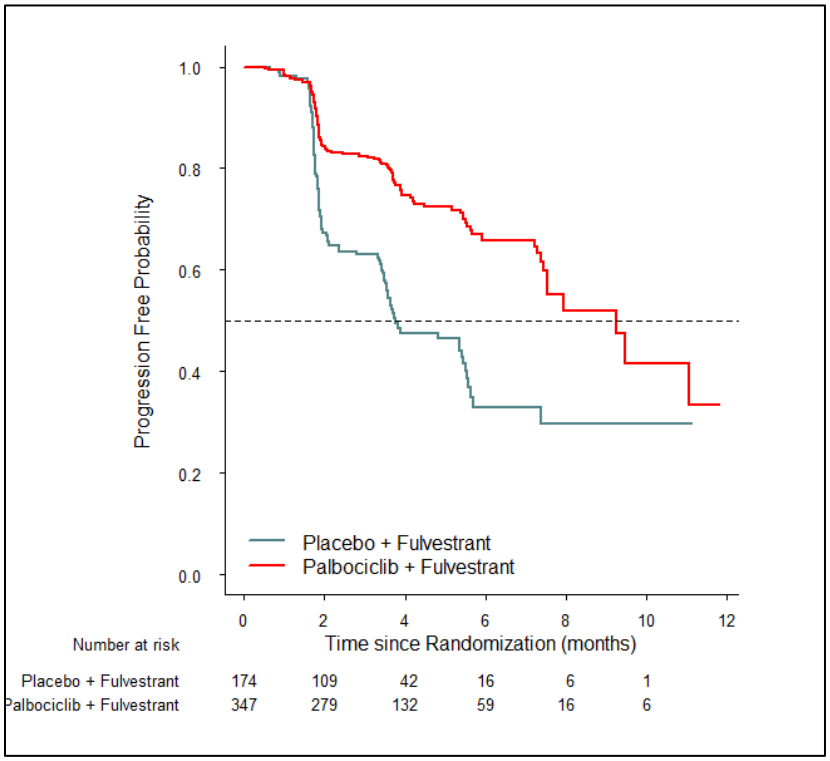
At the March 16, 2015 cutoff, the overall survival (OS) results were not mature with only 57 total death events between the two arms. Per Statistical reviewer, based on the currently available information for OS, the estimated HR = 0.811 and the 95% CI= (0.473, 1.390).

Table 1. Efficacy Results: Investigator Assessment, Intent-to-Treat Population

	Interim/Final Analysis (05 December 2014 Cutoff)		**Updated Analysis (16 March 2015 Cutoff)**	
	Palbociclib plus Fulvestrant (N=347)	**Placebo plus Fulvestrant (N=174)**	**Palbociclib plus Fulvestrant (N=347)**	**Placebo plus Fulvestrant (N=174)**
PFS				
Number of PFS Events (%) at Interim Analysis	102 (29.4%)	93 (53.4%)	145 (41.8%)	114 (65.5%)
Censored	245 (70.6%)	81 (46.6%)	202 (58.2%)	60 (34.5%)
In-follow up	227 (65.4%)	70 (40.2%)	177 (51.0%)	48 (27.6%)
Hazard ratio (95% CI) and p-value at Interim Analysis	0.42 (0.32-0.56), p<0.0001		0.46 (0.36-0.59), p<0.0001	
Median PFS [months] (95% CI)	9.2 (7.5-NE)	3.8 (3.5-5.5)	9.5 (9.2-11.0)	4.6 (3.5-5.6)
ORR	10.4%	6.3%	19.0%	8.6%
ORR (measurable disease)	13.4%	8.0%	24.6%	10.9%
CBR	34.0%	19.0%	66.6%	39.7%
DOR (months)	9.3	5.7	9.3	7.6

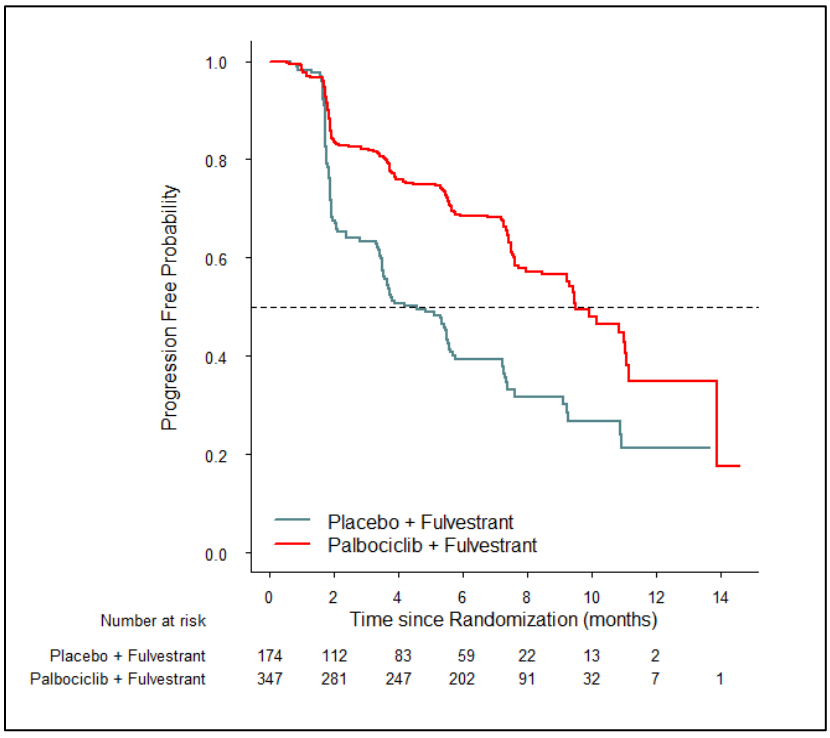
N=number of patients; PFS=progression-free survival; CI=confidence interval; NE=not estimable; ORR=objective response rate; CBR=clinical benefit response; DOR=duration of response.

Figure 1. Primary PFS Results (Dec 5, 2014 cutoff)



Source: Statistical Reviewer Analysis

Figure 2. Primary PFS Results (March 16, 2015 cutoff)



Source: Statistical Reviewer Analysis

Blinded Independent Central Review:

To help assess whether any potential bias occurred with the primary investigator-assessed PFS results, a BICR PFS audit study was conducted. In this study, a random sample (selection done by a third party) of 40% of the total sample (N=211) was selected for additional review by a BICR. Per Statistical reviewer's conclusion, the BICR audit results of the PFS results supported the results of the primary analysis.

Patient Reported Outcome Results:

Patient reported outcomes (PRO) were collected using three specific instruments: the EORTC QLQ-C30, the EORTC QLQ-BR23, and the EQ-5D. Patient reported outcomes data, based upon questionnaires, was taken on day 1 of cycle 1,2,3,4, and then every other cycle, e.g. 6, 8, 10.

PRO endpoints were not pre-specified as primary or key secondary endpoints and results were not adjusted for multiple comparisons. In addition, it is not clear that the results from the instruments used are clinically relevant. Per PRO review, Dr. Sarrit Kovacs, even if the PRO measures were pre-specified and there were no multiplicity concerns, we would need to examine the analyses to make sure that the applicant assessed the clinical meaningfulness of the statistically significant findings (e.g., anchor-based analyses to define clinically meaningful responders, as well as cumulative distribution function curves using an anchor measure such as a patient global impression of severity). For further details, please see Statistical, Clinical Reviews and COA staff consult.

Conclusions on the Substantial Evidence of Effectiveness:

The efficacy results of clinical trial 1023 provide substantial evidence of effectiveness. Study 1023 demonstrated a statistically significant and clinically meaningful improvement in the primary efficacy endpoint of PFS). Improvement in PFS based on a single, adequate, and well-controlled trial has been used in previous FDA approvals for the treatment of patients with advanced or metastatic breast cancer.

8. Safety

Source: Clinical Review (Dr. Amanda Walker)

Clinical Team Recommendation: Approval

I concur with the clinical reviewer's (Dr. Amanda Walker's) conclusions regarding the relative safety of palbociclib. The safety profile observed in Study 1023 was well-tolerated and generally consistent with the known safety profiles of single-agent palbociclib and fulvestrant.

Neutropenia was the most common adverse event across the entire clinical program with palbociclib occurring in >70% of patients. There were very few cases of neutropenic fever and neutropenic sepsis. Additional common adverse reactions with palbociclib include leukopenia

(53%), infections (47%), fatigue (41%), nausea (34%), anemia (30%), stomatitis (28%), and headache (26%). There was a numerical increase in the number of pulmonary emboli reported in patients receiving palbociclib plus endocrine therapy compared to letrozole alone (Study 1003) or placebo plus fulvestrant (Study 1023). 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 2 for details on Deaths on study and Table 3 for serious adverse events.

Table 2. FDA Analysis of Deaths within 28 Days of Study Drug

	Palbociclib plus Fulvestrant (n= 345)	**Placebo plus Fulvestrant (n=172)**
Deaths within 28 Days	4 (1.2%)	3 (1.7%)
DIC	1[1]	0
Disease progression	2	2
Intracerebral hemorrhage	0	1[2]
Neutropenic sepsis	1[3]	0

[1]DIC related to underlying malignancy or sepsis
[2]Intracerebral hemorrhage likely caused by AVM or single brain metastases not visible on baseline MRI
[3]Cause of death reported by Investigator was Deterioration of General Condition due to underlying malignancy.

Table 3. Serious Adverse Events Occurring in >1 Patients Sorted by Descending Frequency in the Palbociclib plus Fulvestrant Arm

	Palbociclib plus Fulvestrant N=345	Placebo plus Fulvestrant N=172
Any	53 (15%)	31 (18%)
Pyrexia	5	1
Neutropenia	4	0
Pulmonary embolism	3	0
Deep vein thrombosis	2	0
Disease progression	2	0
Dyspnea	2	1
Febrile neutropenia	2	1
General physical health deterioration	2	0
Pharyngitis	2	0
Pleural effusion	2	3
Suicide attempt	2	0
Pneumonia	1	2
Ascites	0	3
Pathological Fracture	0	2

Includes data up to 28 days of last dose of study drug.

9. 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.

10. Pediatrics

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. PeRC held a meeting on 1/20/2016 to discuss the PREA waiver requirement for palbociclib. The waiver was granted.

11. 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 two clinical sites (Site # 1137 and 1201) for inspection based on the size of the enrolled study population. Site # 1201 was not available for inspection prior to planned Action Date. Site # 1137 received interim classifications as VAI or voluntary action indicated.

I agree with the clinical reviewer that based on preliminary inspectional findings, data submitted to the Agency from Site 1137 appear reliable. Site 1201 only enrolled 9 patients, and it is unlikely that data from this site would impact study outcome analysis.

12. Labeling

Prescribing Information

Labeling negotiations were ongoing at the time of this review and have not been finalized. The following are the key clinical labeling recommendations:

- INDICATIONS AND USAGE section:

Revised the proposed indication to add the following to the already approved 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 fulvestrant in women with disease progression following endocrine therapy".

Rationale:

(b) (4)

- Study 1023 used a different endocrine therapy and different population than that used in the pivotal trial (Study 1003, PALOMA-1) that granted accelerated approval to palbociclib. The results of the postmarketing required study (Study 1008, PALOMA-2)

used to confirm the benefit of palbociclib used in combination with letrozole as initial endocrine therapy are not available yet. The interim analysis for Study 1008 has occurred but the DMC recommended continuation of the study at this time. (b) (4) the benefit-risk profile from Study 1023 supports regular approval for the new indication listed above (b) (4)

- WARNINGS AND PRECAUTIONS sections:

Recommended deletion of " infections" from the WARNINGS AND PRECAUTIONS section, as the incidence was low.

- USE IN SPECIFIC POPULATIONS sections:

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

- Since the male fertility index was decreased compared to concurrent control and there were corroborating effects on the male reproductive organs in repeat-dose toxicity studies, this finding was included in the product label

- Twenty one days of contraception post treatment was proposed to allow for clearance (5 half-lives or approximately 7 days) and account for the sensitive stage of oocyte development.

- Contraception use in males with female partners of reproductive potential for 3 months after the last dose of palbociclib was added to the label based on two periods of spermatogenesis.

- Based on a re-evaluation of the findings in the embryofetal developmental toxicity studies in rats and rabbits, the term "teratogenic" was removed from the risk summary in section 8.1.

- CLINICAL STUDIES section:

(b) (4)

Other Labeling

- **Patient labeling:** The FDA Patient Labeling team participated in labeling discussions of the Prescribing Information and the Patient Information. Refer to the FDA Patient Labeling NDA Reviews for their recommendations.

- **Office of Prescription Drug Promotion (OPDP):** OPDP participated in labeling discussions. Refer to OPDP review in DARRTS for OPDP labeling recommendations.

13. 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.

OS results were immature at the time of analysis with only 29% of the planned 198 events. 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."*

14. Recommended Comments to the Applicant

None

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

/s/

LALEH AMIRI KORDESTANI
02/11/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207103Orig1s002

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	207,103/002
Priority or Standard	Priority
Submit Date(s)	October 15, 2015
Received Date(s)	October 15, 2015
PDUFA Goal Date	April 15, 2016
Division/Office	DOP1/OHOP
Reviewer Name(s)	Suparna Wedam, MD/Amanda Walker, MD
Review Completion Date	February 11, 2016
Established Name	Palbociclib
(Proposed) Trade Name	Ibrance®
Applicant	Pfizer Inc.
Formulation(s)	75mg, 100mg and 125mg oral capsule
Dosing Regimen	125mg orally daily for 21 days followed by 7 days off treatment
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s)	In combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, HER2-negative advanced or metastatic cancer with disease progression following endocrine therapy.

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Glossary

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

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

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 supplemental indication for the IBRANCE label:

(b) (4)

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 kinase inhibitor indicated in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, HER2-negative advanced or metastatic cancer with disease progression following endocrine therapy."

The basis for this recommendation is a favorable benefit-risk profile for palbociclib when added to fulvestrant in women with HR-positive, HER2-negative advanced or metastatic breast cancer that has progressed on prior endocrine therapy. In the pivotal randomized, double-blind, placebo- controlled Phase 3 study, Study 1023 (A5481023, PALOMA-3) a clinically meaningful and statistically significant improvement in median progression free survival (PFS) was observed favoring the palbociclib plus fulvestrant treatment arm. Results of a blinded independent central review (BICR) audit, subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results. The median PFS in the palbociclib plus fulvestrant arm at the time of the preplanned interim analysis was 9.2 months compared to 3.8 months in the placebo plus fulvestrant arm (HR=0.42; 95%CI: 0.32, 0.56; p<0.000001). The results were consistent at the time of the updated and final analysis with a median PFS of 9.5 months in the palbociclib plus fulvestrant arm compared to 4.6 months in the placebo plus fulvestrant arm (HR=0.46; 95% CI: 0.36, 0.59; p<0.000001).

Study 1023 used a different endocrine therapy than that used in the pivotal trial (Study 1003, PALOMA-1) that granted accelerated approval to palbociclib. Fulvestrant is an estrogen receptor antagonist and letrozole is an aromatase inhibitor. Thus, the safety and activity of the combination of palbociclib with fulvestrant vs letrozole may differ. In addition, the study populations were different. The results of the postmarketing required study (Study 1008,

PALOMA-2) used to confirm the benefit of palbociclib used in combination with letrozole as initial endocrine therapy are not available yet. The interim analysis for Study 1008 has occurred but the Data Monitoring Committee (DMC) recommended continuation of the study at this time. (b) (4) the benefit-risk profile from Study 1023 supports regular approval for the new indication listed above (b) (4)

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 event across the entire clinical program with palbociclib occurring in >70% of patients. It is reassuring, however, that there were very few cases of neutropenic fever and neutropenic sepsis. Additional common adverse reactions with palbociclib include leukopenia (53%), infections (47%), fatigue (41%), nausea (34%), anemia (30%), stomatitis (28%), and headache (26%). There was a numerical increase in the number of pulmonary emboli reported in patients receiving palbociclib plus endocrine therapy compared to letrozole alone (Study 1003) or placebo plus fulvestrant (Study 1023). 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. The safety profile is acceptable for this patient population with a serious and life-threatening disease.

1.3. Benefit-Risk Assessment

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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 2016, it is estimated that breast cancer will be diagnosed in 246,660 women in the United States and that approximately 40,000 women will die of their disease (1). 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 (2,3). 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% (2). 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 received prior endocrine therapy. 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 (4,5). 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 (6).

The benefit-risk assessment in this sNDA is based on the phase 3 Study 1023 (PALOMA-3). Study 1023 was a randomized, double-blind, placebo- controlled study in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy. This was a well-designed trial with an appropriate comparator arm. The primary endpoint was investigator assessed PFS. The median PFS in the palbociclib plus fulvestrant arm at the time of the preplanned interim analysis was 9.2 months compared to 3.8 months in the placebo plus fulvestrant arm (HR=0.42; 95%CI: 0.32, 0.56; p<0.000001). The results were consistent at the time of the updated and final analysis with a median PFS of 9.5 months in the palbociclib plus fulvestrant arm compared to 4.6 months in the placebo plus fulvestrant arm (HR=0.46; 95% CI: 0.36, 0.59; p<0.000001). Palbociclib plus fulvestrant showed a 4.9 month improvement in median PFS compared to placebo plus fulvestrant which is both clinically meaningful and statistically significant. Results of a BICR audit, subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results. Overall survival (OS) results are immature at this time.

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 event across the entire clinical program with palbociclib occurring in >70% of patients. It is reassuring, however, that there were very few cases of neutropenic fever and neutropenic sepsis. Additional common adverse reactions with palbociclib include leukopenia (53%), infections (47%), fatigue (41%), nausea (34%), anemia (30%), stomatitis (28%), and headache (26%). There was a numerical increase in the number of pulmonary emboli reported in patients receiving palbociclib plus endocrine therapy compared to letrozole alone (Study 1003) or placebo plus fulvestrant (Study 1023). 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.

In conclusion, based on a favorable risk-benefit profile for palbociclib in combination with fulvestrant, the reviewers recommend regular approval for the following indication "IBRANCE is a kinase inhibitor indicated in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic cancer with disease progression following prior endocrine therapy."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2016, it is estimated that breast cancer will be diagnosed in 246,660 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%.	Breast cancer is a serious and life-threatening condition.
Current Treatment Options	• 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	There is an unmet medical need to improve the outcomes in patients with HR-positive, HER2-negative advanced or metastatic breast cancer.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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.	
Benefit	• The clinical data from a randomized, double-blind, placebo-controlled Phase 3 Trial (Study 1023, A5481023, PALOMA-3) in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy presented in this sNDA demonstrates an improvement in PFS for palbociclib plus fulvestrant compared to placebo plus fulvestrant. The median PFS in the palbociclib plus fulvestrant arm was 9.5 months compared to 4.6 months in the placebo plus fulvestrant arm (HR =0.46; 95% CI: 0.36, 0.59; p<0.000001). OS results were immature at the time of analysis with only 29% of the planned 198 events. Overall response rate (ORR) was 24.6% in the palbociclib plus fulvestrant arm compared with 10.9% in the placebo plus fulvestrant arm for patients with measurable disease at baseline. Duration of response (DOR) was 9.3 months in the palbociclib plus fulvestrant arm and 7.6 months in the placebo plus fulvestrant arm.	The PFS benefit derived from palbociclib is statistically significant and clinically meaningful. It is unclear if there will be an OS benefit.
Risk	• Neutropenia was reported in >70% of patients taking palbociclib and was the most common reason for temporary discontinuation and/or dose reduction; however, there were very few cases of neutropenic fever and neutropenic sepsis. Additional common adverse reactions	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,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with palbociclib include leukopenia (53%), infections (47%), fatigue (41%), nausea (34%), anemia (30%), stomatitis (28%), and headache (26%). There was a numerical increase in the number of pulmonary emboli reported in patients receiving palbociclib compared to letrozole alone (Study 1003) or placebo plus fulvestrant (Study 1023). With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2, and rates of treatment discontinuation for adverse reactions were generally low. No new safety concerns have been identified based on the cumulative safety data submitted in this sNDA.	with adverse reactions manageable through the use of palbociclib dose reduction, temporary treatment discontinuation, and/or standard medical care.
Risk Management	• There is no proposal for a risk management plan.	None

2 Therapeutic Context

Analysis of Condition

Endocrine therapy options for postmenopausal women with HR-positive MBC that do not respond to first line therapy 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 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 (7,8).

2.2. Analysis of Current Treatment Options

Multiple endocrine and chemotherapy agents have been approved for treatment of MBC. The table below (Table 1) is a summary of FDA-approved available therapies for patients with locally advanced or metastatic breast cancer who have progressed through at least one line of therapy.

Table 1. Available Therapies for Patients with Locally Advanced or Metastatic Breast Cancer Who Have Progressed on Prior Endocrine Therapy

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Drug Class
Letrozole	First and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer	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 (p=0.5136)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor
Exemestane	Treatment of advanced	1999	25mg daily by mouth	Vs megestrol acetate	Bone mineral density decrease,	Aromatase inhibitor

	breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy			TTP: 20.3 weeks vs 16.6 weeks (HR 0.84)	hot flashes, and arthralgias	
Fulvestrant	Treatment of HR+ MBC in postmenopausal women with disease progression following antiestrogen therapy.	2002	250mg once a month intramuscularly	vs. anastrozole (2 studies) ORR: 17% vs 17%; 20.3%vs 14.9% TTP: 165 vs 103 days; 166 vs 156 days	Hot flushes, GI disturbances, hepatic impairment	Estrogen receptor antagonist
		2010	500mg on days 1, 15, 29 and once monthly thereafter intramuscularly	vs fulvestrant 250mg ORR: 13.8% (500 mg) vs. 14.6% (250 mg) PFS: 6.5 vs. 5.4 months (p=0.006)		
Everolimus	postmenopausal women with advanced HR+, HER2negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole.	2012	10mg daily by mouth	Vs exemestane ORR: 12.6% vs. 1.7% PFS: 11.0 months vs. 4.1 months HR=0.38 (p<0.0001) (independent review); 7.8 months vs. 3.2 months HR=0.45 (p<0.0001); (investigator assessed)	Infections, non-infectious pneumonitis, oral ulceration, angioedema, renal failure, impaired wound healing, diarrhea	mTOR inhibitor
Paclitaxel	After failure of initial chemotherapy in MBC	1994	175 mg/m^2 intravenously every 3 weeks	Data from 83 patients accrued in three Phase 2 open label studies and from 471 patients enrolled in a Phase 3 randomized study were available to support the use of paclitaxel in patients with MBC. ORR: 26% (175 mg	Neuropathy, hepatic toxicity, myelosuppression, hypersensitivity	Microtubule stabilizing agent

				and 135 mg combined) PFS: 3.5 months		
Docetaxel	In the treatment of locally advanced or MBC after chemotherapy failure	1996	60 mg/m^2 to 100 mg/m^2 intravenously every 3 weeks	Vs mitomycin/vinblastine ORR: 28.1% vs. 9.5% (p<0.0001) TTP: 4.3 vs. 2.5 (p=0.01)	Fluid retention, neuropathy, hepatic toxicity, myelosuppression, hypersensitivity	Microtubule stabilizing agent
Nab-paclitaxel	In the treatment of MBC after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.	2005	260mg/m2 intravenously every 3 weeks	Vs paclitaxel ORR: 21.5% vs. 11.1% (p=0.003)	Myelosuppression, neuropathy,	Microtubule stabilizing agent
Capecitabine	As monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen	1998	1250 mg/m2 twice daily orally for 2 weeks followed by a one week rest period in 3-week cycles	ORR: 18.5 (all); 25.6 (subgroup) PFS: 3 months for all	Coagulopathy, hand foot syndrome, diarrhea, cardiac toxicity,	Oral prodrug of 5'-DFUR to 5-FU
	In combination with docetaxel after failure of prior anthracycline containing therapy for MBC	2001	1250 mg/m2 twice daily for 2 weeks followed by a 7-day rest period, combined with docetaxel at 75 mg/m2 as a 1-hour IV infusion every 3 weeks	Vs docetaxel alone ORR: 32% vs. 22% PFS: 6.2 months vs. 4.3 months		

HR=hormone receptor; MBC=metastatic breast cancer

Reviewer comment: *The treatment of patients with metastatic breast cancer is palliative in nature. Patients with metastatic HR-positive, HER2-negative breast cancer may be treated with another endocrine therapy once they have had progression of disease on a prior endocrine therapy or with single agent or combination chemotherapy. This decision to use endocrine therapy or chemotherapy is based on several factors. These factors include, but are not limited to, tumor burden of disease, symptoms from the disease, toxicity from previous therapy, patient comorbidities, patient performance status and patient preference.*

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

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 ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

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.

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

July 31, 2014: The protocol for Study 1023 was submitted to the IND (SDN 222, eCTD 0211). Amendments to this protocol are explained in detail in Section 6.1.1. There was no special protocol assessment requested for Study 1023.

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.

3.3. Foreign Regulatory Actions and Marketing History

Palbociclib is not approved in any country outside of the United States.

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

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) audit was requested for this sNDA. The OSI inspected the one site that accrued the highest number of patients in the United States. A summary of the site inspection is provided in Table 2.

Table 2. OSI Findings in Study 1023

Inspection	Site #, and # of Subjects	Inspection Date	Interim Classification
Dr. Dennis Slamon UCLA Medical Center Los Angeles, CA, USA	Site #: 1137 # of subjects: 14	January 14-28, 2016	VAI. No major issues

VAI=Voluntary Action Indicated

The preliminary classification (based on information in 483 and preliminary communication with inspector) for this inspection site was voluntary action indicated (VAI). 19 subjects were screened at Site 1137 and 14 were enrolled. Records for all 14 enrolled subjects were reviewed. A summary of issues found at Site 1137 are listed below:

- 3 subjects had one or more tumor assessment scan performed out of window between 1 and 28 days.
- 4 subjects failed to complete one or more health-related quality of life and health status using protocol specified questionnaires.
- 5 subjects' records revealed some discrepancies between source and case report forms (CRF)s pertaining to adverse event (AE)s. Most were Grade1/2 and had start dates and end dates in source/AE logs, but were listed as ongoing in eCRFs.

See Clinical Inspection Summary written by Lauren Iacono-Connors, Ph.D, Good clinical Practice Assessment Branch, Division of Good clinical Practice Compliance, OSI for full details.

Reviewer Comments: *Based on preliminary inspectional findings, data submitted to the Agency from Site 1137 appear reliable. It is unlikely that any of the issues found at Site 1137 impacted*

subject safety or study outcome analysis.

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 Pharmacology/Toxicology review by Dr. Wei Chen. The nonclinical studies adequately support the safety of oral palbociclib in women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

Nonclinical studies including 27-week repeat-dose study in rats, 39-week repeat dose study in dogs and fertility study in male rats were submitted in this application.

Pharmacology:

The *in vitro* bone marrow toxicity assay results demonstrated that palbociclib-induced bone marrow suppression manifested through cell cycle arrest without apoptosis; by contrast, chemotherapeutic agents, including paclitaxel, doxorubicin, and carboplatin, primarily caused apoptotic cell death in bone marrow. The study results suggested that the mechanism of palbociclib induced bone marrow suppression was different from that induced by cytotoxic chemotherapeutic agents.

General toxicology:

Palbociclib was assessed in 39-week toxicology study in dogs. Repeat-dose toxicology studies were conducted with daily administration for 21 days followed by 7-day non dosing period. No new toxicities were identified in the 39-week study compared to the 15-week study in dogs. All PD-0332991-related hematology effects exhibited reversibility or reversible tread during the 12-week recovery phase. In the male reproductive system, degeneration of the seminiferous tubules was present in the testes of males in all dosed groups. Following the 12-week recovery phase, PD-0332991-related microscopic findings were limited to the testes and epididymis.

Reproductive toxicology:

Palbociclib was administered to Sprague-Dawley rats at doses up to 100 mg/kg/day in males.

Male rats were administered palbociclib once daily during a 15- week period in a scheduled dosing regimen of 3 weeks of consecutive daily dosing followed by a 1-week non-dosing period (a total of 4 cycles). Treated males were paired with untreated females for 5 days during the last 2 weeks of the dosing period. Testicular and epididymal effects (minimal to marked seminiferous tubule degeneration in the testis, and minimal to moderate or marked increases in cellular debris and hypospermia in the epididymides) were identified at ≥ 30 mg/kg/day. These effects correlated with macroscopic changes in the testis, and lower male reproductive organ weights, sperm motility, cauda epididymal sperm density and testicular spermatid density at 100 mg/kg/day. There were no effects on mating and embryonic survival at any dose level. Fertility index was lower (89%) when untreated females were mated with treated males at 100 mg/kg, compared to 100% in treated males at control or lower dose groups.

4.5. Clinical Pharmacology

For full details, please see Clinical Pharmacology/ Pharmacometrics Reviews by Drs. Wentao Fu, Jeanne Fourie Zirkelbach and Jerry Yu.

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 (4,5). For further details see original NDA submission.

4.5.2. Pharmacodynamics

At the fixed dose of 125 mg palbociclib, there was a flat exposure-response relationship for PFS in women enrolled in Study 1023.

4.5.3. Pharmacokinetics

Drug Interactions

In vivo, coadministration of multiple doses of a modafinil (moderate CYP3A inducer) had no clinically significant effect on palbociclib exposure.

There was no drug interaction between palbociclib and fulvestrant or between palbociclib and goserelin when these drugs were co-administered in Study 1023.

Pharmacokinetics in Special Populations

Japanese Ethnicity

In an open-label parallel study that investigated the effect of Japanese ethnicity on palbociclib PK, when single oral doses of palbociclib 125 mg were administered with food, palbociclib geometric mean AUCinf and Cmax values were 30% and 35% higher, respectively, in Japanese subjects (N=13) when compared with the demographic matched non-Asian subjects (N=12). No initial dose adjustment is needed for patients with Japanese ethnicity, and dose adjustments based on adverse events (as in the current palbociclib Package Insert) for all patients taking palbociclib should be followed.

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

5.1. Table of Clinical Studies

Data from 9 studies were submitted to the sNDA. This included the pivotal Phase 3 study (A5481023/PALOMA-3) and two other clinical studies (A5481003/PALOMA-1 and A5481008/PALOMA-2). Additional studies submitted included three PK and tolerability studies (A5481001, A5481010, A5481039), an intrinsic factor PK study (A5481032), an extrinsic factor PK study (A5481016) and an expanded access study (A5481034).

The primary evidence to support this supplement application is derived from Study 1023 as seen in Table 3.

Table 3. Listing of Clinical Trials Relevant to this sNDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
A5481023	Randomized, double-blind phase 3 study	Palbociclib 125mg daily for 3 weeks on 1 week off with	Investigator assessed PFS	Median days on treatment: palbociclib-144, fulvestrant-	571	Women with HR+, HER2 negative advanced or	144 centers in 17 countries

		fulvestrant 500mg days 1,15,29 and monthly thereafter vs fulvestrant alone (at same dose listed above)		148 vs fulvestrant-128,placebo-120		metastatic breast cancer whose disease has progressed on prior endocrine therapy	
Studies to Support Safety							
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	Ongoing	666	Women with newly diagnosed ER+, HER2- advanced breast cancer	186 centers in 17 countries
A5481034	Open-label expanded access protocol	Palbociclib 125mg daily for 3 weeks on 1 week off with letrozole	AEs, deaths, tumor response, and PRO endpoints	Ongoing	240	Women with HR+, HER2-, advanced breast cancer	18 centers in 1 country (USA)

5.2. Review Strategy

The efficacy review was conducted by Dr. Suparna Wedam and the safety review by Dr. Amanda Walker. A 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 1023

4. Review of selected case report forms (CRFs) for Study 1023
5. Review of selected patient narratives for serious adverse events and deaths in Study 1023
6. Review of response to clinical and biostatistical queries sent to Sponsor
7. Review of consultation reports from the Office of Scientific Investigations
8. Consultation with other disciplines, including Biostatistics, Clinical Outcomes Assessment, Clinical Pharmacology and Toxicology was undertaken

6 Review of Relevant Individual Trials Used to Support Efficacy

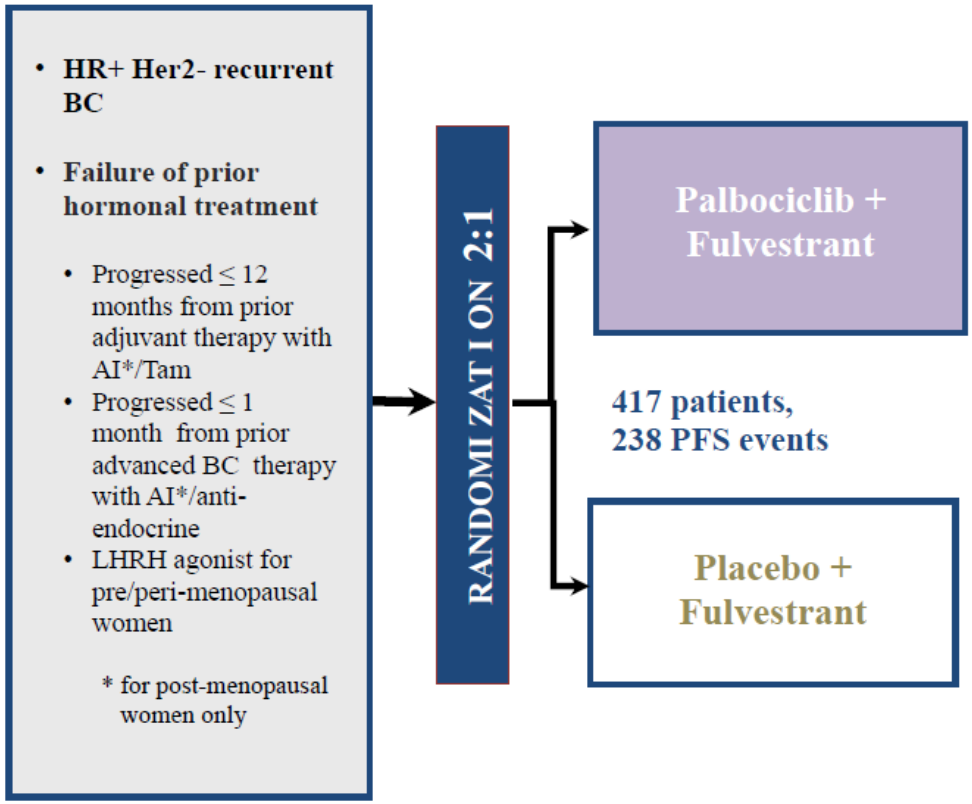
A5481023 (Study 1023 or PALOMA-3)

6.1.1. Study Design

Overview and Objective

This sNDA contains data from Study 1023, entitled "Multi-center, randomized, double-blind, placebo-controlled, phase 3 trial of fulvestrant (Faslodex®) with or without PD-0332991 (Palbociclib) +/- goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy"(Figure 1). Patients were treated with either palbociclib 125 mg/day or placebo orally for 3 of 4 weeks. Patients also received fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and every 28 days thereafter starting from Day 1 of Cycle 1. In both arms, pre- and peri-menopausal women also received the LHRH agonist goserelin (Zoladex® or generic). The primary objective was to demonstrate an improvement in investigator-assessed progression free survival with palbociclib plus fulvestrant over fulvestrant alone. Key secondary objectives include overall survival, objective response rates, duration of response, and clinical benefit response (CR or PR or SD ≥ 24 weeks).

Figure 1. 1023 Study Design



Patients on either arm were allowed to continue treatment after initial investigator-assessed RECIST v 1.1-defined progression if it was considered to be in the best interest of the patient and no new anticancer treatment is initiated. Cross-over between arms was not permitted.

Choice of Control Group

Fulvestrant is a potent anti-estrogen drug that binds and degrades ER and is currently indicated for the treatment of postmenopausal women with metastatic HR-receptor positive breast cancer following the failure of anti-estrogen therapy. The Applicant chose fulvestrant as the comparator arm due to its significant antitumor activity in patients whose tumors had progressed after anti-estrogen or AI therapy.

Diagnostic Criteria

Patients were required to have histologically or cytologically proven hormone receptor positive, HER2 negative breast cancer with evidence of metastatic or locally advanced disease that is not amenable to therapy with curative intent. The documentation of an ER-positive and/or PR-positive and HER2 negative tumor must be based on the most recent tumor biopsy (unless bone only disease) utilizing an assay consistent with local standards. Hormone receptor positivity is defined as ≥ 1% positive stained cells, and HER2-negativity is defined as an immunohistochemistry score 0/1+ or negative *by in situ* hybridization (FISH/CISH/SISH/DISH) defined as a HER2/CEP17 ratio < 2 or a HER2 copy number < 4 for a single probe assessment.

Reviewer comment: *The Agency recommends the documentation of ER, PR, and HER2 status using an assay consistent with central standards.*

Inclusion/Exclusion Criteria

Inclusion Criteria:

- Women 18 years of age or older who are either:
  - Post-menopausal, as defined by at least one of the following:
    - Age ≥ 60 years;
    - Age < 60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and serum estradiol and FSH level within the laboratory's reference range for postmenopausal females;
    - Documented bilateral oophorectomy;
    - Medically confirmed ovarian failure

OR

- Pre/perimenopausal (i.e. not meeting the criteria for being postmenopausal).
  - Pre/perimenopausal women can be enrolled if amenable to be treated with the LHRH agonist goserelin. Patients must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to randomization. But, if patients have received an alternative LHRH agonist prior to study entry, they must switch to goserelin for the duration of the trial.

- Histologically or cytologically proven diagnosis of breast cancer with evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent.
- Documentation of ER-positive and/or PR-positive tumor (≥1% positive stained cells) based on most recent tumor biopsy (unless bone-only disease, see below) utilizing an assay consistent with local standards.
- Documented HER2-negative tumor based on local testing on most recent tumor biopsy: HER2-negative tumor is determined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH/DISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4.
- Patients must satisfy the following criteria for prior therapy:
  - Progressed during treatment or within 12 months of completion of adjuvant therapy with an aromatase inhibitor if postmenopausal, or tamoxifen if pre- or perimenopausal.

  OR

  - Progressed while on or within 1 month after the end of prior aromatase inhibitor therapy for advanced/metastatic breast cancer if postmenopausal, or prior endocrine treatment for advanced/metastatic breast cancer if pre- or perimenopausal. One previous line of chemotherapy for advanced/metastatic disease is allowed in addition to endocrine therapy.
- Except where prohibited by local regulations, all patients must agree to provide and have available a formalin-fixed paraffin embedded (FFPE) tissue biopsy sample taken at the time of presentation with recurrent or metastatic disease. A de novo biopsy is required if no archived tissue taken at the time of presentation with recurrent/metastatic disease is available. The sole exception is those patients with bone only disease for whom provision of previous archival tissue only is acceptable. Patients who had surgery within the last 3 years (but without neoadjuvant chemotherapy prior to surgery) and relapsed while receiving adjuvant therapy may provide a tumor specimen from that surgery.

- Measurable disease as defined by RECIST v 1.1, or bone-only disease. Patients with bone-only metastatic cancer must have a lytic or mixed lytic-blastic lesion that can be accurately assessed by CT or MRI. Patients with bone-only disease and blastic-only metastasis are not eligible.
- Patients must satisfy the following criteria for prior therapy:
    - Progressed during treatment or within 12 months of completion of adjuvant therapy with an aromatase inhibitor if postmenopausal, or tamoxifen if pre- or perimenopausal.

      OR
    - Progressed while on or within 1 month after the end of prior aromatase inhibitor therapy for advanced/metastatic breast cancer if postmenopausal, or prior endocrine treatment for advanced/metastatic breast cancer if pre- or perimenopausal. One previous line of chemotherapy for advanced/metastatic disease is allowed in addition to endocrine therapy.
- ECOG performance status 0-1.
- Adequate organ and marrow function defined as follows:
    - ANC ≥1,500/mm3 (1.5 x 109/L);
    - Platelets ≥100,000/mm3 (100 x 109/L);
    - Hemoglobin ≥9 g/dL (90 g/L);
    - Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≤60 ml/min as calculated using the method standard for the institution;
    - Total serum bilirubin ≤1.5 x ULN (<3ULN if Gilbert's disease);
    - AST and/or ALT ≤3 x ULN (≤5.0 x ULN if liver metastases present);
    - Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN if bone or liver metastases present).
- Resolution of all acute toxic effects of prior therapy or surgical procedures to National Cancer Institute (NCI) CTCAE Grade ≤1 (except alopecia).
- 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.
- Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion Criteria:

- Prior treatment with any CDK inhibitor, or fulvestrant, or with everolimus, or any agent whose mechanism of action is to inhibit the PI3K-mTOR pathway.
- Patients with advanced/metastatic, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and
  over 50% liver involvement).
- 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 (eg, radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.
- Current use of food or drugs known to be potent CYP3A4 inhibitors, drugs known to be potent CYP3A4 inducers, and drugs that are known to prolong the QT interval.
- Major surgery, chemotherapy, radiotherapy, or other anti-cancer therapy within 2 weeks before randomization. Patients who received prior radiotherapy to ☐25% of bone marrow are n
- 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 interval > 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.
- Any of the following within 6 months of randomization: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥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.
- Impairment of gastro-intestinal (GI) function or GI disease that may significantly alter the absorption of palbociclib, such as history of GI surgery with may result in intestinal blind loops and patients with clinically significant gastroparesis, short bowel syndrome, unresolved nausea, vomiting, active inflammatory bowel disease or diarrhea of CTCAE Grade >1.
- Prior hematopoietic stem cell or bone marrow transplantation.
- Known abnormalities in coagulation such as bleeding diathesis, or treatment with anticoagulants precluding intramuscular injections of fulvestrant or goserelin (if applicable).
- Known or possible hypersensitivity to fulvestrant, goserelin, any of their excipients or to any palbociclib/placebo excipients.
- Known human immunodeficiency virus infection.

APPEARS THIS WAY ON ORIGINAL

- Other severe acute or chronic medical or psychiatric condition, including recent or active suicidal ideation or behavior, 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.
- Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, 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 4 weeks before randomization in the current study.

Reviewer's comments: *Overall, the inclusion/exclusion criteria are appropriate. Of note, men with breast cancer were not eligible for Study 1023.*

Concomitant Radiotherapy or Surgery:

Concurrent radiotherapy or cancer-related surgery was prohibited throughout the duration of the active treatment phase of the study. Palliative radiotherapy was 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. Palliative radiotherapy of any other site was considered alternative cancer treatment resulting in censoring of the PFS endpoint. Caution was advised for any surgical procedures during the study.

Dose Selection

The Applicant chose the palbociclib dose regimen of 125 mg/day for 3 of 4 weeks based upon the results of a Phase I dose escalation study (A5481001). Two dosing schedules were evaluated: Schedule 3/1 (3 weeks on/1 week off) and Schedule 2/1 (2 weeks on/1 week off). A greater proportion of patients on the 2/1 schedule had treatment-related TEAEs than patients on the 3/1 schedule, and a total of 13/37 patients treated with Schedule 3/1 evaluable for efficacy experienced stable disease (SD) including 6 patients with SD lasting 40 weeks or longer. Based on the relatively improved safety profile of Schedule 3/1 and the efficacy results from this study, the Schedule 3/1 was selected for further clinical development. The RP2D for this study schedule was determined to be 125 mg/day. This dose and schedule of palbociclib was further explored in combination with letrozole in a phase 1/2 study (A5481003)

which led to accelerated approval of palbociclib 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.

The 500 mg dose of fulvestrant was used in Study 1023 in combination with palbociclib and placebo given the favorable safety profile and efficacy results of the CONFIRM study, a Phase 3 study that compared two doses of fulvestrant (250 mg and 500 mg). The median PFS was 6.5 months for fulvestrant 500 mg and 5.5 months for fulvestrant 250 mg; a statistically significant difference in favor of the higher dose (HR=0.80; 95% CI: 0.68 0.94; p=0.006).

Study Treatments

Arm A (Investigational Arm):

- Palbociclib capsules of 75 mg, 100 mg, and 125 mg.
    - Starting Dose: 125 mg daily for 21 days followed by 7 days off treatment of each 28-day cycle (3/1 schedule)
    - Palbociclib doses could be reduced to 100 mg daily and 75 mg daily on 3/1 schedule, respectively, or to 75 mg on a 2-week on/2-week off (2/2) schedule.
    - Administration: oral
    - Pfizer Lot Numbers
        - 75 mg capsules: 13-109348, 13-107814, 13-111143
        - 100 mg capsules: 13-107411, 13-109347, 13-111139
        - 125 mg capsules: 13-1007781, 13-109759, 13-109346, 13-111134

In Combination With

- Fulvestrant 250 mg/5 mL syringe solution for injection
    - Dose: 500 mg on Days 1 and 15 of Cycle 1, thereafter every 28 ±7 days every cycle, starting on Day 1 of Cycle 1, according to approved fulvestrant prescribing information.
    - Administration: IM
    - Pfizer Lot Numbers: 13-110227, 13-109742, 14-001237, 13-109468, 14-002736, and 13-110724

Arm B (Comparator arm):

- Palbociclib capsule-matched placebo

- Starting Dose: 125 mg palbociclib-matched placebo daily for 21 days followed by 7 days off treatment of each 28-day cycle (3/1 schedule). Palbociclib-matched placebo doses could be reduced to 100 mg daily and 75 mg daily on 3/1 schedule, respectively, or to 75 mg on a 2-week on/2-week off (2/2) schedule.
- Administration: oral
- Pfizer Lot Numbers: 12-004486, 12-004533, and 12-004572

In Combination With

- Fulvestrant as described above.

Pre- and perimenopausal women started receiving goserelin or an alternative LHRH agonist at least 4 weeks before study treatment start and continued receiving concurrent ovarian function suppression with goserelin administered every 28 days during the active treatment phase.

Reviewer's comment: *The dose and schedule of fulvestrant and goserelin is appropriate. Based on prior studies with palbociclib, the dose and schedule of palbociclib is appropriate.*

Assignment 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 agent. After informed consent was obtained, the clinical site completed a patient pre-randomization form (which included key eligibility criteria and stratification factors) and sent it to the sponsor for approval of randomization. Upon receipt of the sponsor's approval, the site was to contact the centralized internet/telephone registration system for randomization. Subjects were randomized assigned on a 2:1 basis to receive palbociclib plus fulvestrant or placebo plus fulvestrant. Subjects were stratified by documented sensitivity to prior hormonal therapy (yes vs. no), menopausal status at study entry (pre/peri- vs. post-menopausal), and presence of visceral metastases (yes vs. no). Sensitivity to prior hormonal therapy is defined as either: (i) documented clinical benefit (CR, PR, SD ≥ 24 weeks) to at least one prior hormonal therapy in the metastatic setting, or (ii) at least 24 months of adjuvant hormonal therapy prior to recurrence. "Visceral" refers to lung, liver, brain, pleural and peritoneal involvement. There were no plans to change the randomization during the study.

Blinding

Palbociclib and placebo were provided by the Applicant and supplied as indistinguishable capsules matching in size and color. Blinding codes were only broken in emergency situations for reasons of patient safety. Blinding codes could also be broken after a patient discontinued treatment due to disease progression, but only if deemed essential to allow the investigator to select the patient's next treatment regimen and after discussion in agreement with the sponsor. When the blinding code was broken, the date and reason for unblinding was required to be fully documented in source documents and entered on the case report form and every effort made by the site staff to ensure that the treatment arm is not communicated to any sponsor personnel or designee involved in the conduct of the trial.

Reviewer's comment: *The hematologic toxicities of palbociclib likely prevented investigator blinding.*

Dose Modifications

In the event of significant treatment-related toxicities, dose adjustments were permitted for palbociclib/placebo only. Fulvestrant dose adjustments were not allowed; however, dosing delays or interruptions were permitted according to standard practice. When treatment interruption was deemed necessary for just one of the study drugs in the combination, treatment with the other study drug was continue as planned.

In the case of Grade 2 toxicity lasting for > 3 weeks or a Grade ≥ 3 toxicity, dose reduction of palbociclib was recommended for the subsequent cycles. Dose reduction by one, and, if needed, two dose levels was recommended depending on the type and severity of the toxicity. Available dose levels are shown in Table 1 below.

Table 4. Palbociclib Dose Levels

Dose Level	Palbociclib/Placebo for 3 out of 4 weeks (3/1 schedule)	Fulvestrant monthly dosing schedule
Starting dose	125 mg/d	2x 250 mg/injection
-1	100 mg/d	2x 250 mg/injection
-2	75 mg/d*	2x 250 mg/injection

* Palbociclib/placebo dose de-escalation below 75 mg/d is not allowed, but the schedule may be changed to 75 mg/day two weeks on followed by two weeks off (2/2 schedule).

Patients requiring more than two dose reductions were allowed to receive 75 mg/day for 2 weeks followed by 2 weeks off. Once a dose was reduced for a given patient, all subsequent cycles were administered at that dose level, unless further dose reduction is required. Dose re-escalation was not permitted. The pre-specified dose reductions for various treatment-related toxicities are shown in Table 2 below.

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

Toxicity	**Palbociclib/Placebo Treatment at:**
Uncomplicated Grade 3 neutropenia *(ANC ≥ 500 - <1000/mm^3)*	Same dose level; ↓ 1 dose level if neutrophil recovery is delayed beyond 7 days *, **
Grade 3 neutropenia (*ANC<1000/mm^3*) **associated with a documented infection or fever ≥38.5 degrees C**	↓ 1 Dose Level; ↓ 2 dose levels*** if neutrophil recovery is delayed beyond 7 days *
Grade 4 neutropenia (*ANC<500/mm^3*)	↓ 1 Dose Level; ↓ 2 dose levels*** in case of recurrent grade 4 event *
Grade 3 or 4 thrombocytopenia (*Platelet count <50,000/mm^3*)	↓ 1 Dose Level; ↓ 2 dose levels*** in case of recurrent grade 3 event
Grade ≥ 3 non-hematologic toxicity (*including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment*)	↓ 1 Dose Level; ↓ 2 dose levels***, if repeated toxicity is seen in the next cycle or if recovery from grade 3 is delayed beyond 7 days *

* If recovery of neutrophils to ≥ 1000/mm^3 or platelet count to ≥ 50,000/mm^3 takes longer than 2 weeks (which may include dose holding due do toxicity, the scheduled week off treatment and up to 7 days of cycle delay), then reduce by 2 dose levels.

** If uncomplicated Grade 3 neutropenia recurs in 2 consecutive cycles, after recovery as per retreatment criteria (ANC ≥ 1000/mm^3 and no fever), treatment may restart at the next lower dose level at investigator's discretion.

*** If no further dose reduction is possible (ie, patient is already receiving 75 mg/d according to schedule 3/1) consider changing the schedule to 75/mg/d 2 weeks on/2 weeks off), or discontinue palbociclib/placebo and continue with fulvestrant alone.

Administrative Structure:

The applicant utilized an independent External Data Monitoring Committee (E-DMC) for general oversight of safety and efficacy considerations, study conduct, and risk-benefit assessment of this study. The E-DMC acted in an advisory capacity to the sponsor, monitoring patient safety and evaluating available efficacy data for the study. The sponsor designated a biostatistician not affiliated with the project to prepare data for E-DMC review.

A sample-based blinded independent central review (BICR) was used as an auditing tool for PFS in order to corroborate the analysis results of the primary endpoint (i.e., investigator-assessed PFS) and to assist in the evaluation of potential bias.

Procedures and Schedule

The key assessments and procedures for this study were:

Screening

- Eligibility assessment
- Informed consent
- Laboratory tests
- Physical examination including ophthalmic exam
- Baseline tumor assessment
- EKG
- Tumor tissue for biomarker analysis

- PK analysis
- Patient reported outcome measurements

On-study

- Laboratory tests
- Tumor assessments every 8 weeks (+/- 7 days) for the first year, and then every 12 weeks (+/- 7 days) from the date of randomization
- Adverse events assessment
- PK analysis
- Patient reported outcome measurements

Follow-up

- Adverse events followed until 28 days after discontinuation of study treatment (either palbociclib/placebo or fulvestrant).
- In patients who discontinue active study treatment for any reason other than objective disease progression or death will continue to have tumor assessments every 8 weeks) for the first year, and then every 12 weeks from the date of randomization until documented progression or onset of new anticancer therapy.
- For patients who discontinue study treatment due to objective disease progression, survival data (i.e., patient status along with start, stop and type of new anticancer therapy) will be collected every 3 months for the first 9 months then every 6 months starting at Month 15, calculated from the last dose of study treatment.

  A detailed schedule of activities is shown in Table 6 below.

Table 6. Schedule of Activities

Protocol Activity	Screening	Active Treatment Phase [a] - One Cycle = 28 days			End of Treatment/Withdrawal [c]	Post-Treatment Follow-Up [d]
		Cycles 1 and 2		Cycles ≥3		
Study Day	Within 28 days prior to randomization unless specified otherwise	Day 1 [b]	Day 15	Day 1		
Visit Window		±-2 days	±2 days	±7 days [a]		±7 days
Informed Consent [e]	X					
Medical/Oncological History [f]	X					
Baseline Signs/Symptoms [g]		X [g]				
Physical Examination/Vital Signs [h]	X	X [b]		X	X	
Ophthalmic Examination [i]	X			X [i]	X	
ECOG Performance Status	X	X		X	X	
Laboratory Studies						
Hematology [j]	X	X [b]	X	X	X	
Blood Chemistry [j]	X	X [b]	X	X	X	
Pregnancy test, serum estradiol and FSH (if applicable) [j]	X					
12-Lead ECG (in triplicate)	X				X	
Disease Assessment						
CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; Clinical evaluation of superficial disease [k]	X	◄--► [k] Performed every 8 weeks (±7 days) for the first year, and then every 12 weeks (±7 days) from the date of randomization (See tumor assessment requirements flowchart)			X	X
Radionuclide Bone Scan, Whole Body [l]	X	As clinically indicated or to confirm complete response. (See tumor assessment requirements flowchart) [l]			X	X

Protocol Activity	Screening	Active Treatment Phase [a] - One Cycle = 28 days			End of Treatment/Withdrawal [c]	Post-Treatment Follow-Up [d]
		Cycles 1 and 2		Cycles ≥3		
Study Day	Within 28 days prior to randomization unless specified otherwise	Day 1 [b]	Day 15	Day 1		
Visit Window		±-2 days	±2 days	±7 days [a]		±7 days
Other Clinical Assessments						
Adverse Event Reporting [m]	X	X	X	X	X	X
Concomitant Medications/Treatments	◄--► Recorded from 28 days prior to the start of study treatment up to 28 days after the last dose of study treatment					
Pharmacokinetics (PK) [n]		First 40 patients: Sampling at pre-dose on Day 1 and Day 15 of Cycles 1 and 2, and Day 1 of Cycle 3; all other patients: Pre-dose sampling on Day 15 of Cycles 1 and 2				
Banked Blood Biospecimens (Prep D1) [o]		X				
Plasma banking (Prep B1) [p]		X	X		X	
Tumor Tissue for Biomarker Analysis [q]	X				X	
EuroQol-5D (EQ-5D) [r]		Pre-dose on Day 1 of Cycles 1, 2, 3, 4 and Day 1 of every other cycle thereafter starting with Cycle 6 (ie, Cycle 6,8, 10, etc)			X	
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) [r]					X	
European Organisation for Research and Treatment of Cancer Breast Cancer Module (EORTC-QLQ-BR23) [r]					X	
Survival Follow-up [s]						X
Study Treatment						
Randomization		X				
Fulvestrant (both treatment arms) [t]		◄--► [t] IM administration on Days 1 and 15 of Cycle 1, every 28 days (±7 days) thereafter starting from Day 1 of Cycle 1				
Palbociclib or placebo (Arm A only) [u]		◄--► [u] Orally once daily on Days 1 to 21of each Cycle followed by 7 days off treatment				
For pre-/peri-menopausal patients only: Goserelin (both treatment arms, if applicable) [v]	SC administration at least 4 weeks before study treatment start [v]	◄--► [v] SC administration every 28 days				

a. **Active Treatment Phase:** Assessments should be performed prior to dosing on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. One cycle consists of 28 days. A cycle could be longer than 28 days if persistent

toxicity delays initiation of the subsequent cycle. **Day 1 of any cycle visit should coincide with the day the palbociclib/placebo treatment begins.** If there are delays due to toxicity, then the start of the next cycle visit will be delayed until the patient has recovered and can begin study treatment again. Fulvestrant injection will be given every 28 days (+/- 7 days) with the exception of Cycle 1 during which it will be administered on Days 1 and 15 (±2 days allowed according to the protocol visit time windows). Goserelin will be administered every 28 days (+/- number of days allowed according to the protocol visit time windows). The active treatment phase is ongoing as long as the patient is receiving both study drugs (ie, palbociclib/placebo and fulvestrant) or fulvestrant alone.

b. **Cycle 1/Day 1:** Blood chemistry, hematology, and physical examination not required if acceptable screening assessment is performed within 7 days prior to randomization.
c. **End of Treatment/Withdrawal:** Visit to be 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. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).
d. **Post Treatment Follow-up:** Patients who discontinue study treatment should be contacted 28 calendar days (±7 days) after discontinuation of study treatment (palbociclib/placebo or fulvestrant) to assess if there have been any new adverse events and/or any change to any previously reported adverse events. Telephone contact is acceptable. Patients who discontinue active study treatment for any reason other than objective disease progression or death will continue to have tumor assessments performed every 8 weeks (±7 days) for the first year, and then after 1 year every 12 weeks (±7 days) (calculated from the date of randomization) until documented progression or onset of new anticancer therapy. See Tumor Assessment Requirements Flowchart for details. For patients who discontinue study treatment due to objective disease progression, see table footnote s (Survival Follow-up) below.
e. **Informed Consent:** Informed consent must be obtained prior to any protocol required assessments being performed (with the exception of certain imaging assessments if meeting the criteria defined in the Screening Section).
f. **Medical/Oncological History:** To include information on prior anticancer 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. **Physical Examination/Vital signs:** A full physical examination including an examination of all major body systems and breasts, 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. Physical examinations will be carried out at Screening, Day 1 of every cycle and the End of Treatment/Withdrawal visit.
i. **Ophthalmology Examinations:** Upon approval of Amendment 1, newly enrolled lens grading evaluable patients will undergo an ophthalmic examination by an ophthalmologist at screening, during study treatment on Cycle 4 Day 1, on Cycle 7 Day 1, on Cycle 13 Day 1 (ie, after 3, 6 and 12 months), every 12 months thereafter (ie, Days 1 of Cycles 25, 37, etc.) and at the End of Treatment/Withdrawal visit. Additional ophthalmic examinations may be performed as clinically indicated. It is expected that a minimum of 100 evaluable patients will participate in these examinations. Sites will be informed once these examinations are no longer required for patients newly enrolled in this study. Refer to the Ocular Safety Assessments Section for further details.
j. **Laboratory tests:** Hematology includes hemoglobin, WBC, absolute neutrophil count, platelet count. Blood chemistry includes AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, blood urea nitrogen (BUN) (or urea), serum creatinine, and albumin. Additional hematology/chemistries panels may be performed as clinically indicated. Upon approval of Amendment 2, hemoglobin A1c will be measured in all patients every 3 months from the date of randomization (ie, C4D1, C7D1, C10D1, etc), and at the End of Treatment/Withdrawal visit. Pregnancy test (serum) at screening only for women of childbearing potential. Test may be repeated as per request of IRB/IECs or if required

by local regulations. Serum estradiol and Follicle stimulating hormone (FSH) levels are analysed at screening to confirm postmenopausal status of women <60 years old and who have been amenorrheic for at least 12 consecutive months.

k. **CT/MRI Scans of Chest, Abdomen, Pelvis:** Refer to the tumor assessment requirement flowchart for details and timing of procedures
l. **Radionuclide Bone Scan, Whole Body:** Refer to the tumor assessment requirement flowchart for all details and timing of procedures.
m. **Adverse Events (AEs):** Serious Adverse events (SAEs) must be reported from the time the patient provides informed consent through and including 28 calendar days after the last administration of the study drug. SAEs occurring after the active reporting period has ended should be reported if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor. All AEs (serious and non serious) should be recorded on the CRF from the first dose of study treatment through last patient visit. It is expected that telephone contact with the patient will be made in order to assess SAEs and AEs 28 calendar days (+/- 7 days) after the last administration of the study drug.
n. **Pharmacokinetics (PK)**: In approximately the first 40 patients randomized in the study, plasma PK samples will be drawn pre-dose on Day 1 and Day 15 of Cycles 1 and 2, and Day 1 of Cycle 3 for DDI assessment for palbociclib and fulvestrant (and goserelin if applicable). In all other patients, plasma concentrations will be drawn on Day 15 of Cycle 1 and Cycle 2 for palbociclib only. Additional PK blood samples may be collected from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation.
o. **Banked Blood Biospecimens (Prep D1):** A single 4 mL blood sample will be collected pre-dose at the Cycle 1 Day 1 to be retained for potential pharmacogenomics/biomarker analyses related to drug response or adverse drug reactions. Samples will be collected from all patients, unless prohibited by local regulations.
p. **Plasma Banking (Prep B1):** Blood samples for plasma collection (2x 10 mL each) will be drawn for exploratory analyses from all patients pre-dose on Cycle 1 Days 1 and 15 and at End of Treatment/Withdrawal, unless prohibited by local regulations.
q. **Tumor Tissue for Biomarker Assessments:** Tumor tissue is required for patient participation, and patients must agree to provide tissue from the metastatic or recurrent site at the time of study entry. For the purpose of eligibility, documentation of ER-positive and/or PR-positive tumor and HER2-negative tumor will be based on local results utilizing an assay consistent with local standards. Archived formalin-fixed paraffin embedded (FFPE) specimen will be collected. If archived metastatic or recurrent tumor FFPE specimen is not available, a de novo biopsy will be required for patient participation, except for those with bone disease only who will need to provide the original diagnostic FFPE tumor specimen. Patients who relapsed while receiving adjuvant therapy and had surgery within the last 3 years, may provide a tumor specimen from that surgery. Provision of new metastatic tissue from these patients is strongly encouraged but not mandated. An optional de novo tumor biopsy will be collected from the site of progression at the End of Treatment visit. Details on sample preparation, processing, storage, and shipment will be provided in the Study Manual.
r. **Patient Reported Outcomes Assessments:** 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.
s. **Survival Follow-Up:** For patients who discontinue study treatment due to objective disease progression, survival data (ie, patient status along with start, stop and type of new anticancer therapy) will be collected every 3 months for the first 9 months (Month 3, 6, and 9, ±14 days), then every 6 months starting at Month 15 (±14 days), calculated from the last dose of study treatment. Telephone contact is acceptable.
t. **Fulvestrant:** To be administered on-site according to the local Summary of Product Characteristics for fulvestrant (Faslodex®). Fulvestrant injection will be given every 28 days (+/- 7 days) with the exception of Cycle 1 during which it will be administered on Days 1 and 15 (±2 days allowed according to the protocol visit time windows).

u. **Palbociclib or Placebo:** Patients will be required to return all bottles of palbociclib/placebo as well as the completed patient diary on Day 1 of each cycle for drug accountability.
v. **Goserelin (if applicable):** Goserelin will be administered every 28 days (+/- number of days allowed according to the protocol visit time windows). Treatment with goserelin (Zoladex® or generic) as per local practice for all women who are pre- or peri-menopausal at study entry. Patients must have commenced treatment with goserelin or an alternative luteinizing hormone-releasing hormone (LHRH) agonist at least 4 weeks prior to randomization. If patients have not received goserelin as their LHRH agonist prior to study entry, they must switch to goserelin for the duration of the trial. It is recommended to administer goserelin (given every 28 days) on-site when monthly fulvestrant is given. If goserelin is administered at home by the patient, a patient diary will be implemented.

Reviewer comment: *There is preclinical evidence to suggest that the occurrence of ocular toxicities in patients receiving palbociclib may be related to altered glucose metabolism. However, serum glucose measurement was not reported in Study 1023. In order to further explore this association, the protocol was amended in September 2014 to include the measurement of HgbA1c.*

Concurrent medications

Prohibited concurrent medications include anticancer agents, potent (strong/moderate) CYP3A inhibitors/inducers, drugs known to cause QT interval prolongation, hormone replacement therapy, megastrol acetate, selective estrogen-receptor modulators, anticoagulants, and proton-pump inhibitors. The initial protocol was amended based on preliminary results from two clinical pharmacology studies (A5481018 and A5481021) which suggested that palbociclib exposure may be decreased in a subgroup of patients taking with proton-pump inhibitors.

Treatment compliance

Treatment compliance was monitored by drug accountability as well as the patient's treatment diary and medical record. Drug accountability was performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle. To be considered compliant, each study patient must have received at least 80% of the planned number of doses of primary therapy based on the number of days of actual dose administration during the study. Fulvestrant was administered by qualified study personnel at the site in accordance with the fulvestrant label. Fulvestrant administration was documented on the corresponding study drug administration CRF.

Rescue medication

Primary prophylactic use of granulocyte-colony stimulating factors was not permitted but may have been used in the context of treatment-emergent neutropenia. If neutropenic complications were observed in a cycle in which primary prophylaxis with CSFs was not received, secondary prophylaxis may be given at the discretion of the investigator, but only if dose reduction or delay are not considered a reasonable alternative. Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

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 fulvestrant. 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 1023 was investigator-assessed progression-free survival (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 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 had their PFS time censored on the date of randomization with the duration of one day. Additionally, patients who started a new anti-cancer therapy prior to documented PD were 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: CR or PR)
- Duration of Response (DR)
- Clinical Benefit Response (CBR: CR or PR or SD ≥ 24 weeks)
- Type, incidence, severity (as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.0), seriousness and relationship to study medications of AEs and any laboratory abnormalities. AEs were coded using the MedDRA version 17.1)
- Trough plasma concentration of palbociclib, fulvestrant and goserelin (if applicable) in the subgroup of approximately 40 patients included in the initial safety assessment
- PRO endpoints such as health related quality of life scores [EuroQol (EQ-5D) Score; European Organization for Research and Treatment of Cancer Quality of Life Instrument (EORTC QLQ-C30); European Organization for Research and Treatment of Cancer Breast Cancer Module (EORTC QLQ-BR23); minimally important difference (MID) cut-off, and time to deterioration (TTD) composite endpoint
- Tumor tissue biomarkers, including genes (eg, copy numbers of CCND1 and

CDKN2A, PIK3CA mutations), proteins (eg, Ki67, pRb, CCNE1), and RNA expression (eg, cdk4, cdk6)

Efficacy analyses were performed using the local radiologist's/investigator's tumor assessments as the primary data source. Additionally, an independent third-party core imaging laboratory, (b) (4), performed blinded independent central review (BICR) of PFS data for a randomly selected subgroup of patients independent of the investigator assessed determination of progression.

Statistical Analysis Plan

The sample size for this study was determined based on the results of the randomized Phase 2 trial assessing fulvestrant with or without dasatinib in postmenopausal patients with HR-positive metastatic breast cancer previously treated with an aromatase inhibitor. The median PFS for the fulvestrant alone arm was 5.3 months and the median PFS for the combination arm was 6.0 months. The study planned to randomize 417 patients (278 in the fulvestrant plus palbociclib arm and 139 in the placebo plus fulvestrant arm) in a 2:1 randomization ratio. Approximately 238 PFS events were required in the two treatment arms for the study to have a 90% power to detect an increase in PFS assuming a true HR of 0.64 (representing a 56% increase in median PFS from 6 to 9.38 months), if tested at a 1-sided significance level of alpha=0.025. The null hypothesis was that there is no difference in progression free survival between the palbociclib plus fulvestrant arm and the fulvestrant plus placebo arm.

The primary efficacy analysis population was the intent-to-treat (ITT) population. Patients were to be classified according to assigned treatment group, regardless of actual treatment received. PFS was defined as the time from the date of randomization to the date of the documentation of objective progression of disease (PD) or death due to any cause in the absence of documented PD, whichever comes first. If tumor progression data included more than one date, the first date was used. Documentation of progression must have been objective disease assessment based on RECIST v1.1. The length of PFS was calculated as PFS time (months) = [progression/death date (censor date) – randomization date +1]/30.4.

Censorship: Patients last known to be 1) alive 2) not to have started new (non-protocol) anti-cancer treatment and 3) progression-free, and who have a baseline and at least one disease assessment after dosing, were to be censored at the date of the last objective disease assessment that verified the lack of disease progression.

- Patients with no disease assessments after dosing were to be censored at the date of randomization unless death occurred prior to the first planned assessment (in which case the death is an event).
- Patients starting new anti-cancer treatment prior to progression were to be censored at the date of last objective disease assessment documenting no progression prior to the new treatment.
- If patients were removed from the study (withdrew the consent, lost to follow up, etc)

prior to progression and death, then censorship was to be at the date of the last objective disease assessment that verified lack of disease progression.

- Patients with documentation of progression or death after an unacceptably long interval since the last tumor assessment were to be censored at the time of last objective assessment documenting no progression.

The study was designed to have one interim analysis (IA) and the final analysis at 238 events based on the primary PFS endpoint with the investigator assessment. The IA was to be conducted to allow for early stopping of the study due to efficacy or to potentially re-estimate the sample size of the trial based upon the primary endpoint of PFS. The interim analysis was to be performed after approximately 143 investigator-assessed PFS events. The Haybittle-Peto efficacy boundary was to be used at the IA. If the value of the test-statistic from the log-rank test for PFS exceeds the efficacy boundary ($z \geq 3$, $p \leq 0.00135$) the trial may have been stopped for efficacy.

Overall survival (OS) was defined as the time from date of randomization to date of death due to any causes. OS was to be hierarchically tested for significance at the time of PFS analyses, provided the primary PFS endpoint is statistically significant at the interim and/or final PFS analyses. A stratified log-rank test (using the same stratification factors as for the PFS analysis) was to be used to compare OS between the treatment arms. OS for the two treatment arms was to be assessed using Kaplan-Meier methods and displayed graphically where appropriate. Cox regression models were to be used to estimate the treatment hazard ratio and its 95% CI. The 1-year survival probability was to be estimated using the Kaplan-Meier method and a two sided 95% CI for the log [-log(1-year survival probability)] calculated using a normal approximation using the Greenwood's formula, and then back transformed to give a CI for the 1-year survival probability itself. The 2-year and 3-year survival probabilities were to be estimated similarly.

Objective response rate (ORR) was defined as the number of patients with OR (CR or PR per RECIST 1.1) by the number of patient's randomized to the respective treatment arm. A 95% CI for response rates was to be provided. Response rate comparisons between the two treatment arms as randomized were to be assessed using Cochran-Mantel-Haenszel (CMH) test with the same stratification factors as for the PFS analysis. Analyses of ORR were to be performed on the ITT population based on the investigator's assessment as well and also on the review of the blinded independent third-party core imaging laboratory. In addition, the Best Overall Response for each patient was to be summarized by treatment arm.

Duration of response (DR) was defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. DR data was 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 due to any cause while on study. DR was to be calculated for the subgroup of

patients with an OR. DR for the two treatment arms was to be summarized using Kaplan-Meier methods and displayed graphically, where appropriate. The median event time and 95% CI for the median was to be provided for each endpoint.

Clinical Benefit Response (CBR) was defined as CR or PR or SD ≥ 24 weeks. The CBR rate on each randomized treatment arm was to be estimated by dividing the number of patients with CR, PR, or SD ≥ 24 weeks by the number of patients randomized to the treatment arm. A 95% CI for the CBR rates was to be provided. CBR rate comparison between the two treatment arms as randomized was to be assessed using CMH test with the same stratification factors as for the PFS analysis. Analyses for CBR were to be performed on the ITT population based on the investigator's assessment as well and also on the review of the blinded independent third-party core imaging laboratory.

The primary safety analysis population was planned to include all patients who received at least one dose of study treatment (i.e. palbociclib/placebo or fulvestrant), with treatment assignments designated according to actual treatment received.

Protocol Amendments

The applicant submitted 2 protocol amendments. Key changes are summarized here:

Amendment 1 (April 4th, 2014): The study drug administration instructions were revised from administration of palbociclib in a fasted state to administration with food and to prohibit the concomitant use of proton-pump inhibitors based on preliminary results from two clinical pharmacology (Studies 1018 and 1021) which suggested that palbociclib taken with food results in more consistent drug absorption and exposure than in a fasted state, and palbociclib exposure may be decreased in a subgroup of patients taking palbociclib concomitantly with proton-pump inhibitors.

Amendment 2 (September 30th, 2014): The protocol was amended in order to prospectively characterize whether or not palbociclib affects glucose metabolism through monitoring of appropriate laboratory measurements given the nonclinical findings in rats and taking into account the limited laboratory glucose data in the current clinical dataset. Prospective monitoring of hemoglobin A1c was added to characterize whether or not palbociclib affected glucose metabolism.

Reviewer's comment: *These amendments did not alter the study's integrity. The applicant's methods for assuring data quality and integrity are appropriate; however, no information was provided in regards to the sponsor's measures to assure complete and accurate identification of protocol deviations.*

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.

Data Quality and Integrity: Sponsor's Assurance

The Applicant stated that Compliance Oversight Leads (COLs) provided study and site level oversight to ensure that trial was delivered to high quality standards. COLs documented and recorded onsite 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 (SOPs) and local regulation.

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. A total of 17 site audits were conducted during this study until the data cut-off date December 5, 2014.

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 A5481001, A5481003, A5481008, A5481010, A5481023, and A5481034. Of the 3,504 investigators listed, certification was provided for 3,465. Due Diligence activities was required for 1 of the 3,504 clinical investigators. Thirty eight of the 3,504 clinical investigators listed in the study report had financial information to disclose (1.2%).

Study A5481023 (PALOMA-3) included 171 principal investigators and 1061 sub-investigators. Six had financial information to disclose and are summarized in the following table (Table 7).

Table 7. Summary of Financial Disclosures for Study 1023

Clinical Site Number	Investigator Name (PI or SI)	Study A5481023 Patient Enrollment at Site	Disclosure
(b) (6)	(b) (6)	(b) (6)	Honorariums totaling $26,000.00
(b) (6)	(b) (6)	(b) (6)	Equity Pfizer totaling $438,498.72 (as of 1/10/2014)
(b) (6)	(b) (6)	(b) (6)	Consulting and honorariums totaling $50,850.00
(b) (6)	(b) (6)	(b) (6)	Grants totaling $36,675.00
(b) (6)	(b) (6)	(b) (6)	Consulting, honorarium and miscellaneous payments totaling $416,717.82
(b) (6)	(b) (6)	(b) (6)	Miscellaneous payments totaling $100,000.00

Reviewer Comment: *Investigators with significant disclosable interests enrolled approximately 8.8% (N=46) of the total number of patients in Study 1023. Each individual investigator enrolled between 0.19-(b) (6)% 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

From September 26, 2013 to August 26, 2014, a total of 521 patients were randomized at 144 sites in 17 countries. Additional 16 sites received study drug but did not randomize any patients.

At the time of data cutoff on December 5, 2014, 107 (30.8%) in the palbociclib plus fulvestrant arm and 97 (55.7%) patients in the placebo plus fulvestrant arm had discontinued study treatment, while 238 (68.6%) patients in the palbociclib plus fulvestrant arm and 75 (43.1%) patients in the placebo plus fulvestrant arm were still on study treatment (as seen in Table 8).

Table 8. Study 1023 Patient Disposition

	Palbociclib plus Fulvestrant N (%)	Placebo plus Fulvestrant N (%)	Total N (%)
Randomized to study treatment	347	174	521
Randomized and not treated	2 (0.6)	2 (1.1)	4 (0.8)
Randomized and treated	345 (99.4)	172 (98.9)	517 (99.2)
Completed	0	0	0
Discontinued	107 (30.8)	97 (55.7)	204 (39.2)
Ongoing at data cutoff date	238 (68.6)	75 (43.1)	313 (60.1)
Reason for discontinuation			
AE (reason for palbociclib/placebo discontinuation)	9 (2.6)	3 (1.7)	12 (2.3)
AE (reason for fulvestrant discontinuation)	7 (2.0)	3 (1.7)	10 (1.9)
Global deterioration of health status	8 (2.3)	3 (1.7)	11 (2.1)
Lost to Follow-Up	0	0	0
Medication error without associated AE	0	0	0
Objective progression or relapse plus progressive disease	85 (24.5)	87 (50.0)	172 (33.0)
Protocol violation	0	0	0
Study terminated by the sponsor	0	0	0
Patient died	0	1 (0.6)	1 (0.2)
Patient refused to continue treatment for reason other than AE	1 (0.3)	1 (0.6)	2 (0.4)

Source: Modified from Study 1023 CSR Table 11 and Table 12; sbjdsp.xpt

Protocol Violations/Deviations

There were an equal number of protocol deviations reported in both treatment arms, with at least 1 protocol deviation reported in 69.5% of patient in each arm as seen in Table 9. Major protocol deviations occurred with respect to inclusion/exclusion criteria, study drug administration/study treatment, informed consent, disallowed medication, and SAE/AE.

Major protocol deviations were reported in a higher percentage of patients in the palbociclib plus fulvestrant arm than in the placebo plus fulvestrant arm. The difference was due to a higher percentage of patients in the palbociclib plus fulvestrant arm with major protocol deviations related to study drug administration/study treatment (21.0% vs 13.8%), and deviations related to informed consent (12.1% vs 5.7%).

All the protocol violations regarding SAE/AE in both arms were due to reporting not occurring within the required time frame. Proton pump inhibitors were the most common disallowed medication used by patients in both treatment arms. The most common inclusion/exclusion criteria protocol deviations included patients that had not come off of anti-cancer therapy at least two weeks prior to going on study. The majority of protocol deviations related to study drug administration/study treatment were due to patients that took palbociclib/placebo for 1-2 doses more than the scheduled 21 doses per cycle or palbociclib/placebo treatment not interrupted or reduced for toxicity as required by protocol. Informed consent document (ICD) deviations mainly included patients that did not have a properly signed ICD on file (missing time, all boxes not initialed, discordance in answers when different versions of consent signed), did not re-sign an ICD when updated versions became available or had vital signs/physical exam/labs performed prior to ICD being signed.

Table 9. Protocol Deviations in Study 1023

Protocol Deviation Category	Palbociclib plus Fulvestrant N=347 N (%)	Placebo plus Fulvestrant N=174 N (%)
Any protocol deviation	241 (69.5)	121 (69.5)
AE/SAE	5 (1.4)	1 (0.6)
Disallowed medication	16 (4.6)	11 (6.3)
Inclusion/exclusion criteria	20 (5.8)	13 (7.5)
Informed consent	42 (12.1)	10 (5.7)
Study drug administration/study treatment	73 (21.1)	24 (13.8)
Other	15 (4.3)	9 (5.2)
Procedures/tests	192 (55.3)	92 (52.9)
Visit schedule	53 (15.3)	31 (17.8)
Any major protocol deviation	125 (36.0)	51 (29.3)
AE/SAE	5 (1.4)	1 (0.6)
Disallowed medication	16 (4.6)	11 (6.3)
Inclusion/exclusion criteria	20 (5.8)	13 (7.5)
Informed consent	42 (12.1)	10 (5.7)
Study drug administration/study treatment	73 (21.0)	24 (13.8)

Source: Modified from Study 1023 CSR Table 13; Table 16.2.2.2

Reviewer Comment: *All protocol deviations were reviewed. The nature of these deviations should not have affected the efficacy results. In addition, results for Sensitivity Analysis #5*

(influence of deviations in tumor lesion assessment) support 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 Fulvestrant N=347 n (%)	Placebo plus Fulvestrant N=174 n (%)
United States	129 (37)	72 (41)
Ukraine	32 (9)	12 (7)
Korea	24 (7)	19 (11)
Canada	29 (8)	10 (6)
Italy	18 (5)	18 (10)
Japan	27 (8)	8 (5)
Australia	23 (7)	9 (5)
Belgium	20 (6)	7 (4)
Russia	14 (4)	3 (2)
United Kingdom	9 (3)	4 (2)
Netherlands	6 (2)	3 (2)
Romania	4 (1)	4 (2)
Portugal	2 (<1)	4 (2)
Taiwan	4 (1)	0
Germany	2 (<1)	1 (1)
Ireland	3 (1)	0
Turkey	1 (<1)	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, Ukraine, Korea, Canada and Italy, with a 39% of patients enrolled from the United States.*

Table 11. Demographic Characteristics for Study 1023

Demographic Parameters	Palbociclib plus Fulvestrant N=347 N (%)	Placebo plus Fulvestrant N=174 N (%)	Total N=521 N (%)
Sex			
Male	0	0	0
Female	347 (100)	174 (100)	521 (100)
Age			
Mean years (SD)	56.9 (11.7)	56.8 (10.4)	56.9 (11.3)
Median (years)	57	56	57
Min, max (years)	30-88	29-80	29-88
Age Group			
≥ 17 - < 65 years	261 (75.2)	131 (75.3)	392(75.2)
≥ 65 - < 75 years	59 (17.0)	37 (21.3)	96 (18.4)
≥ 75 years	27 (7.8)	6 (3.4)	33 (6.3)
Race			
White	252 (72.6)	133 (76.4)	385 (73.9)
Black or African American	12 (3.5)	8 (4.6)	20 (3.8)
Asian	74 (21.3)	31 (17.8)	105 (20.2)
Other	8 (2.3)	1 (0.6)	9 (1.7)
Ethnicity			
Hispanic or Latino	17 (4.9)	11 (6.3)	28 (5.4)
Not Hispanic or Latino	329 (94.8)	161 (92.5)	490 (94)

Source: Modified from Study 1023 CSR Table 15 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 1023

	Palbociclib plus Fulvestrant N=347 N (%)	Placebo plus Fulvestrant N=174 N (%)	Total N=521 N (%)
Measurable disease			
Yes	268 (77.2)	138 (79.3)	406 (77.9)
No	79 (22.8)	36 (20.7)	115 (22.1)
Adequate baseline assessment			
Yes	346 (99.7)	174 (100)	520 (99.8)
No	1 (0.3)	0	1 (0.2)
Bone Only Disease			
Yes	84 (24.2)	37 (21.2)	121 (23.2)
ER Status			
Positive	339 (97.7)	167 (96.0)	506 (97.1)
Negative	1 (0.3)	2 (1.1)	3 (0.6)
Missing	7 (2.0)	5 (2.9)	12 (2.3)
PR Status			
Positive	243 (70.0)	117 (67.2)	360 (69.1)
Negative	91 (26.2)	48 (27.6)	139 (26.7)
Missing	13 (3.7)	9 (5.2)	22 (4.2)
HER2 status			
Positive	2 (0.6)	2 (1.1)	4 (0.8)
Negative	341 (98.3)	171 (98.3)	512 (98.3)
Equivocal	3 (0.9)	1 (0.6)	4 (0.8)
Missing	1 (0.3)	0	1 (0.2)
Histopathologic classification			
Ductal	233 (67.1)	106 (60.9)	339 (65.1)
Lobular	40 (11.5)	22 (12.6)	62 (11.9)
Other	74 (21.3)	46 (26.4)	120 (23.0)
Histologic Grade			
1	22 (6.3)	16 (9.2)	38 (7.3)
2	162 (46.7)	79 (45.4)	241 (46.3)
3	93 (26.8)	40 (23.0)	133 (25.5)
Stage at Initial Diagnosis			
I	26 (7.5)	13 (7.5)	39 (7.5)
II	120 (34.6)	56 (32.2)	176 (33.8)

III	69 (19.9)	47 (27.0)	116 (22.3)
IV	86 (24.8)	36 (20.7)	122 (23.4)
Other/Unknown	46 (13.3)	22 (12.6)	68 (13.1)
ECOG Performance Status			
0	207 (59.7)	115 (66.1)	322 (61.8)
1	140 (40.3)	59 (33.9)	199 (38.2)
Involved Disease Sites			
Bone	163 (75.8)	129 (74.1)	392 (75.2)
Breast	61 (17.6)	19 (10.9)	80 (15.4)
Liver	127 (36.6)	81 (46.6)	208 (39.9)
Lung	103 (29.7)	44 (25.3)	147 (28.2)
Lymph Node	138 (39.8)	63 (36.2)	201 (38.6)
Other	109 (31.4)	46 (26.4)	155 (29.8)

Source: Modified from Study 1023 CSR Table 16 demog.xpt, and othbas.xpt

Reviewer Comment: *There was a difference (≥5%) in baseline characteristics between treatment arms regarding ECOG performance status, histologic classification, stage at initial diagnosis and involved sites of disease. These differences are unlikely to have affected the efficacy results.*

Stratification Factors:
Patients were stratified by documented sensitivity to prior hormonal therapy (yes vs. no), by menopausal status at study entry (pre-/peri- vs. post-menopausal), and by the presence of visceral metastases (yes vs. no). Sensitivity to prior hormonal therapy was defined as either: 1) documented clinical benefit (complete response, partial response, stable disease ≥24 weeks) to at least 1 prior hormonal therapy in the metastatic setting, OR 2) at least 24 months of adjuvant hormonal therapy prior to recurrence. Postmenopausal status was defined by at least one of the following criteria: age>60 years; age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and serum estradiol and FSH level within the laboratory's reference range for postmenopausal females; documented bilateral oophorectomy; medically confirmed ovarian failure. Visceral metastases refer to lung, liver, brain, pleural, and peritoneal involvement. Stratification factors are well balanced between arms as seen in Table 13.

Table 13. Stratification Factors for Study 1023

	Palbociclib plus Fulvestrant N=347 N (%)	Placebo plus Fulvestrant N=174 N (%)	Total N=521 N (%)
Based on randomization:			
Visceral metastases			
Yes	206 (59.4)	105 (60.3)	311 (59.7)
No	141 (40.6)	69 (39.7)	210 (40.3)
Documented sensitivity to prior hormonal therapy			
Yes	274 (79.0)	136 (78.2)	410 (78.7)
No	73 (21.0)	38 (21.8)	111 (21.3)
Menopausal status			
Pre-/perimenopausal	72 (20.7)	36 (20.7)	108 (20.7)
Postmenopausal	275 (79.3)	138 (79.2)	413 (79.3)
Based on CRF:			
Visceral metastases			
Yes	206 (59.4)	105 (60.3)	311 (59.7)
No	141 (40.6)	69 (39.7)	210 (40.3)
Documented sensitivity to prior hormonal therapy			
Yes	273 (78.7)	133 (76.4)	406 (77.9)
No	74 (21.3)	41 (23.6)	115 (22.1)
Menopausal status			
Pre-/perimenopausal	71 (20.5)	36 (20.7)	107 (20.5)
Postmenopausal	276 (79.5)	138 (79.3)	414 (79.5)

Source: Study 1023 CSR Table 17

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

- **Concomitant Medications**
  Almost all patients in both treatment arms received concomitant drug treatment during the study (95.9% of patients in the palbociclib plus fulvestrant arm and 96.5% of patients in the placebo plus fulvestrant arm).

  The top 5 most commonly used concomitant drug treatment for patients in the palbociclib plus fulvestrant arm vs patients in the placebo plus fulvestrant arm, respectively are as follows: paracetamol (24.6% vs 26.2%), denosumab (21.7% vs 20.3%), goserelin (20.0% vs 20.3%), zoledronic acid (18.3% vs 21.5% of patients) and ergocalciferol (16.8% vs 12.2%). The use of goserelin in approximately 20% of each treatment arm correlates to the 20% peri/premenopausal population in each treatment

arm. Overall, approximately half the patients in each treatment arm were on treatment for bone disease as seen in Table 14.

Table 14. Concomitant Use of Treatment for Bone Disease in Study 1023

	Palbociclib plus Fulvestrant N=345 N (%)	Placebo plus Fulvestrant N=173 N (%)
Drugs for Treatment of Bone Disease	173 (50.1)	83 (47.1)
Actonel combination	0	1 (0.6)
Alendronate sodium	4 (1.2)	1 (0.6)
Clodronic acid	6 (1.7)	0
Denosumab	75 (21.7)	35 (20.3)
Ibandronate sodium	6 (1.7)	1 (0.6)
Ibadronic acid	4 (1.2)	0
Pamidronate disodium	19 (5.5)	8 (4.7)
Pamidronic acid	1 (0.3)	0
Zolendronic acid	63 (18.3)	37 (21.5)

Source: Modified from Study 1023 CSR Table 14.4.2.5

- **Subsequent systemic therapies**
  As of the December 2014 data cutoff date, 19.6% and 40.8% of patients in the palbociclib plus fulvestrant arm and in the placebo plus fulvestrant arm respectively, had started a new anti-cancer therapy. The anti-cancer therapies most commonly administered were capecitabine (8.4% vs 12.1%), paclitaxel (4.6% vs 10.9%), exemestane (3.5% vs 8.0%), and everolimus (3.2% and 8.6%).

Efficacy Results – Primary Endpoint

The primary endpoint for Study 1023 was investigator-assessed PFS. A planned interim analysis of the primary PFS endpoint was to be performed after at least 143 investigator-assessed PFS events (approximately 60% of the total PFS events expected at the time of final analysis). Due to a high accrual rate in Study 1023 and the operational logistics of cleaning the data for the interim analysis, a total of 195 events (82% of the total planned final PFS events expected) were included in the interim analysis.

As of the December 5, 2014 data cutoff for the interim analysis, 195 investigator-assessed PFS events had occurred, 102 (29.4%) patients in the palbociclib plus fulvestrant arm and 93 (53.4%) in the placebo plus fulvestrant arm. At the time of the interim analysis, the median PFS

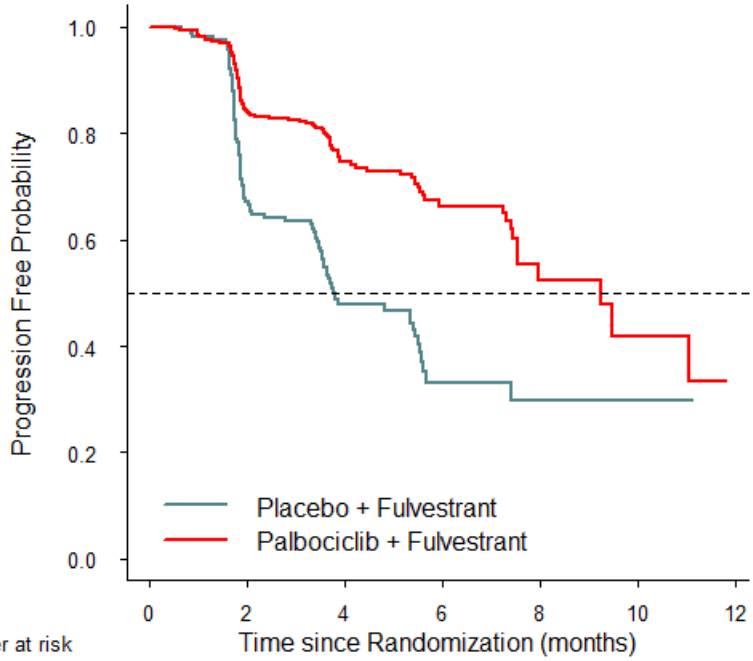
in the palbociclib plus fulvestrant arm was 9.2 months compared to 3.8 months for 174 patients randomized to placebo plus fulvestrant arm (HR=0.42; 95% CI: 0.32, 0.56; p<0.000001), as summarized in Table 15 and Figure 2.

Table 15. Primary endpoint: Investigator-Assessed PFS (December 5, 2014 cut-off)

	Palbociclib plus Fulvestrant (N=347)	**Placebo plus Fulvestrant (N=174)**
Number of events (%)	101 (29.1)	92 (52.9)
Censored (%)	246 (70.9)	82 (47.1)
Median PFS (months) 95% CI	9.2 (7.5, NR)	3.8 (3.5, 5.5)
Hazard Ratio (stratified)* 95% confidence interval	0.42 (0.32, 0.56)	
p-value	<0.0001	

Source: FDA Statistician
**stratified by documented sensitivity to prior hormonal therapy, menopausal status, and by the presence of visceral metastases; NR=not reached*

Figure 2. KM Curve for Investigator-Assessed PFS (December 5, 2014 cut-off)



Source: FDA Statistician

Reviewer Comment: *A clinically meaningful and statistically significant 5.4 months improvement in the primary endpoint of investigator-assessed PFS was seen in the palbociclib treatment arm at the time of interim analysis. The study was stopped for efficacy at the time of the interim analysis.*

Of note, the control arm of (placebo plus fulvestrant) did not perform as well as expected with a median PFS of only 3.8 months compared to a predicted 6.0 months. This difference may be due to the fact that Study 1023 allowed enrollment of peri/premenopausal patients and patients with >1 prior therapy for advanced/metastatic breast cancer. Both of these patient populations were not eligible for the phase 2 study (9) in which the statistical assumptions were based on for Study 1023 and may have conferred a worse prognosis resulting in shorter median PFS.

Sensitivity Analyses:
The applicant performed eight sensitivity analyses for PFS to evaluate the impact of stratification factors and analysis populations, results are shown in Table 16. Briefly, the

sensitivity analyses performed were as follows:

- Sensitivity analysis 1: Influence of analysis population; based on As Treated (AT) population
- Sensitivity analysis 2: A 1-sided unstratified log-rank test was used to compare treatments and the HR was based on an unstratified Cox proportional hazards model.
- Sensitivity analysis 3: To investigate whether the stratification factors and important covariates influenced the outcome of the primary endpoint PFS.
- Sensitivity analysis 4: Influence of disease assessment scheduling. If disease progression was documented between 2 scheduled tumor assessments, then the date of progression was assigned to the earlier scheduled tumor assessment. In the event of death, the date of the endpoint was not adjusted.
- Sensitivity analysis 5: Influence of deviations in tumor lesion assessment.
- Sensitivity analysis 6.1: Influence of bone-only disease patients. Patients with bone-only disease with fracture, radiation therapy, surgery, ECOG at least 2 point increase from baseline or change of therapy were censored at the date of prior tumor assessment with no PD.
- Sensitivity analysis 6.2: Influence of bone-only disease patients: Patients with bone-only disease with fracture, radiation therapy, surgery, ECOG at least 2 point increase from baseline or change of therapy were considered as events.
- Sensitivity analysis 6.3: Influence of bone-only disease patients: Bone-only disease patients were excluded from the analysis.
- Sensitivity analysis 7: Influence of Missing Data: The following missing PFS data that might have resulted in the censored PFS data in the primary analysis were considered PFS events in addition to the documented PD and death: new anti-cancer treatment, lost to follow-up, consent withdrawal, medication error without associated AE.
- Sensitivity analysis 8: Influence of potential investigator bias. Random sample BICR data and investigator assessed PFS (event) data were combined. For events identified by both BICR and investigator, BICR data were used to determine event time. For patients who were censored by both BICR and investigator, BICR (when applicable) data were used to determine the censoring time.

Table 16. PFS Sensitivity Analyses

Sensitivity analysis	HR (95% CI)	p-value	Palbociclib plus fulvestrant events	Placebo plus fulvestrant events
1	0.422 (0.318, 0.560)	<0.000001	102	93
2	0.417 (0.314, 0.553)	<0.000001	102	93
3	0.395 (0.297, 0.525)	<0.000001	102	93
4	0.426 (0.321, 0.565)	<0.000001	102	93
5	0.422 (0.318, 0.560)103	<0.000001	102	93
6.1	0.422 (0.318, 0.560)	<0.000001	102	93
6.2	0.432 (0.326, 0.573)	<0.000001	104	93
6.3	0.411 (0.300, 0.563)	<0.000001	83	77
7	0.438 (0.335, 0.574)	<0.000001	114	101
8	0.378 (0.287, 0.498)	<0.000001	103	103

CI=confidence interval; for sensitivity analyses 1 and 4 to 8, stratified hazard ratios are presented, for sensitivity analyses 2 and 3 unstratified hazard ratios; 1-sided p-values are reported except for sensitivity analysis 3 (2-sided p-value)
Source: Modified from Study 1023 CSR Table 20 modified

The FDA statistician performed an additional sensitivity analyses on PFS assessing the impact of sites with investigators that had financial disclosures.

FDA Sensitivity Analysis: Sites with investigators with financial disclosures were omitted. The results were consistent with the primary findings, with a 5.5 month improvement in PFS (9.2 vs 3.7 months) and a stratified HR = 0.39 (95% CI = 0.293, 0.532).

Reviewer Comment: *The planned sensitivity analyses results are all consistent with the primary efficacy endpoint results. The additional FDA sensitivity analysis also supports the primary efficacy endpoint results.*

Table 17. Censored Patients in Study 1023

	Palbociclib plus fulvestrant N=347 N (%)	**Placebo plus fulvestrant N=174 N (%)**
Number Censored	245 (70.1)	81 (55.1)
Reason for censorship:		
No adequate baseline assessments	1 (<1)	0
No on-study disease assessments	7 (2.0)	7 (4.0)
Given new anti-cancer treatment prior to disease progression and after last dose of study treatment	8 (2.3)	4 (2.3)
Discontinued study without disease progression or death: Withdrew consent for follow-up Other	 1 (<1) 1 (<1)	 0 0
In follow-up for progression	227 (65.4)	70 (40.2)

Source: Modified from Study 1023 CSR Table 19

Reviewer Comment: *Reasons for censoring were appropriate in the two treatment arms of this double-blinded, placebo control study.*

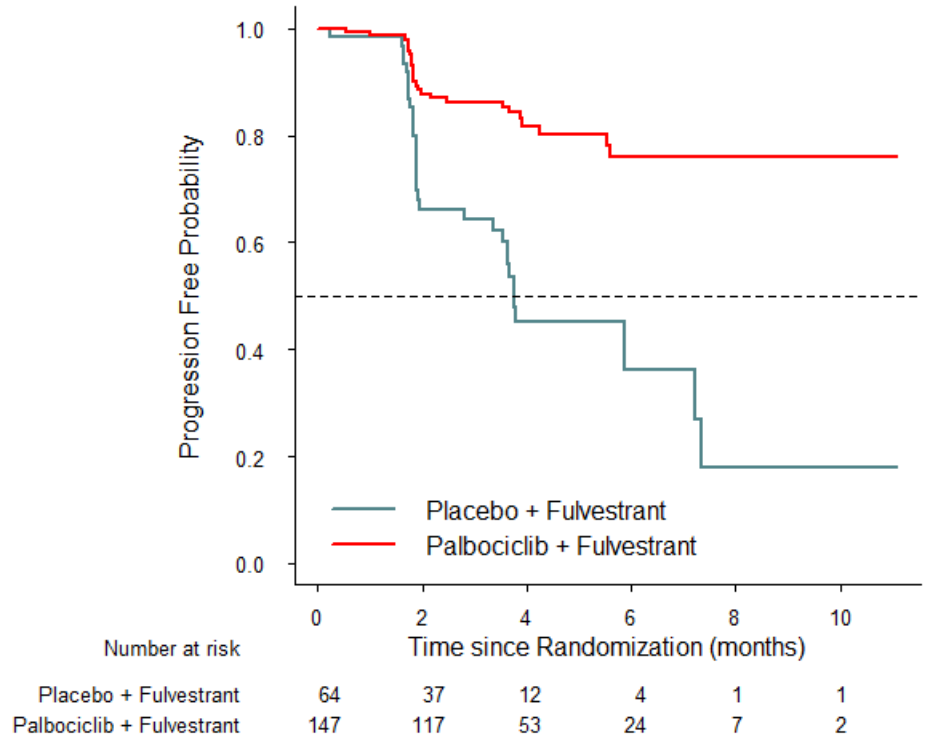
PFS Based on Blinded Independent Central Review (BICR):
A protocol prespecified BICR was conducted by (b) (4) on approximately 40% of the total population to corroborate the investigator-assessed PFS results. A stratified simple random sampling approach was utilized to randomly select patients from each stratum based on the blinded enrollment data. The BICR audit was not intended to provide an alternative means of definitive analysis.

The investigators were not aware, which patients were randomly selected for the BICR review. The independent third-party core imaging laboratory assessed tumor progression based on the review of scans, physical examination data and other data, from the final data cut for this randomly selected subgroup of the study population. The following materials were forwarded for independent review:

- All imaging studies performed on study
- Photographs of sites of disease assessed using clinical methods. Details concerning clinically assessed lesions were collected on the CRFs and made available to the independent core imaging laboratory.

Results for the BICR are seen below in Figure 3.

Figure 3. PFS Results for BICR Audit in Study 1023



Source: FDA Statistician

Reviewer Comment: *In the pivotal study used for the basis of accelerated approval of palbociclib {Study 1003, PALOMA-1 (Part 1)}, there were censoring differences between the investigator and BICR that led to discordant results between the BICR assessed PFS and investigator assessed PFS. Although, Study 1023 did not have a full BICR assessment, no discordance was observed between the BICR audit results and investigator assessed PFS. Based on three different methods (NCI method, Pharma method and a multiple imputation approach developed internally at the FDA), results of the BICR audit support the primary analysis using investigator-assessed PFS. For further details regarding results from the different methods, refer to the Statistical Review by Dr. Erik Bloomquist.*

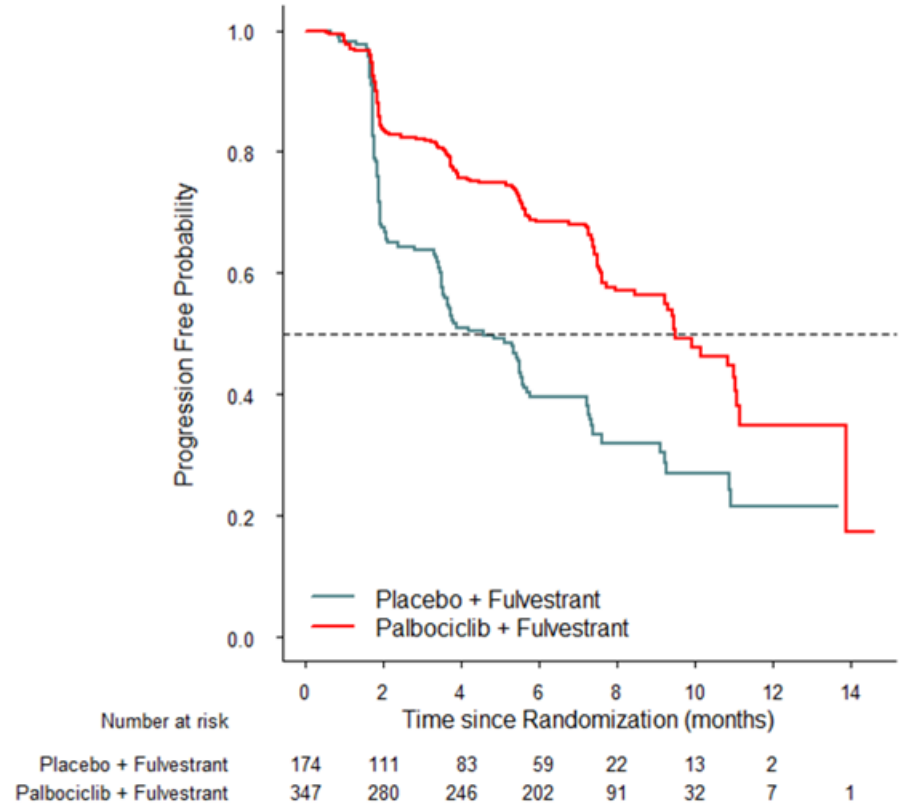
Updated Progression-Free Survival Analysis:
At the recommendation of the European Union (EU) Rapporteurs, the Applicant performed an exploratory updated analysis of PFS. The updated analysis was based on a March 16, 2015 data cut-off date and 259 PFS events (Table 18 and Figure 4).

Table 18. Investigator-Assessed PFS (March 16, 2015 cut-off)

	Palbociclib plus Fulvestrant (N=347)	**Placebo plus Fulvestrant (N=174)**
Number of events (%)	145	113
Censored (%)	202	61
Median PFS (months) 95% CI	9.5 (9.2, 11.0)	4.6 (3.5, 5.6)
Hazard Ratio (stratified)* 95% confidence interval	0.46 (0.36, 0.59)	
p-value	<0.0001	

Source: FDA Statistician
**stratified by documented sensitivity to prior hormonal therapy, menopausal status, and by the presence of visceral metastases*

Figure 4. KM Curve for Investigator-Assessed PFS (March 16, 2015 cut-off)



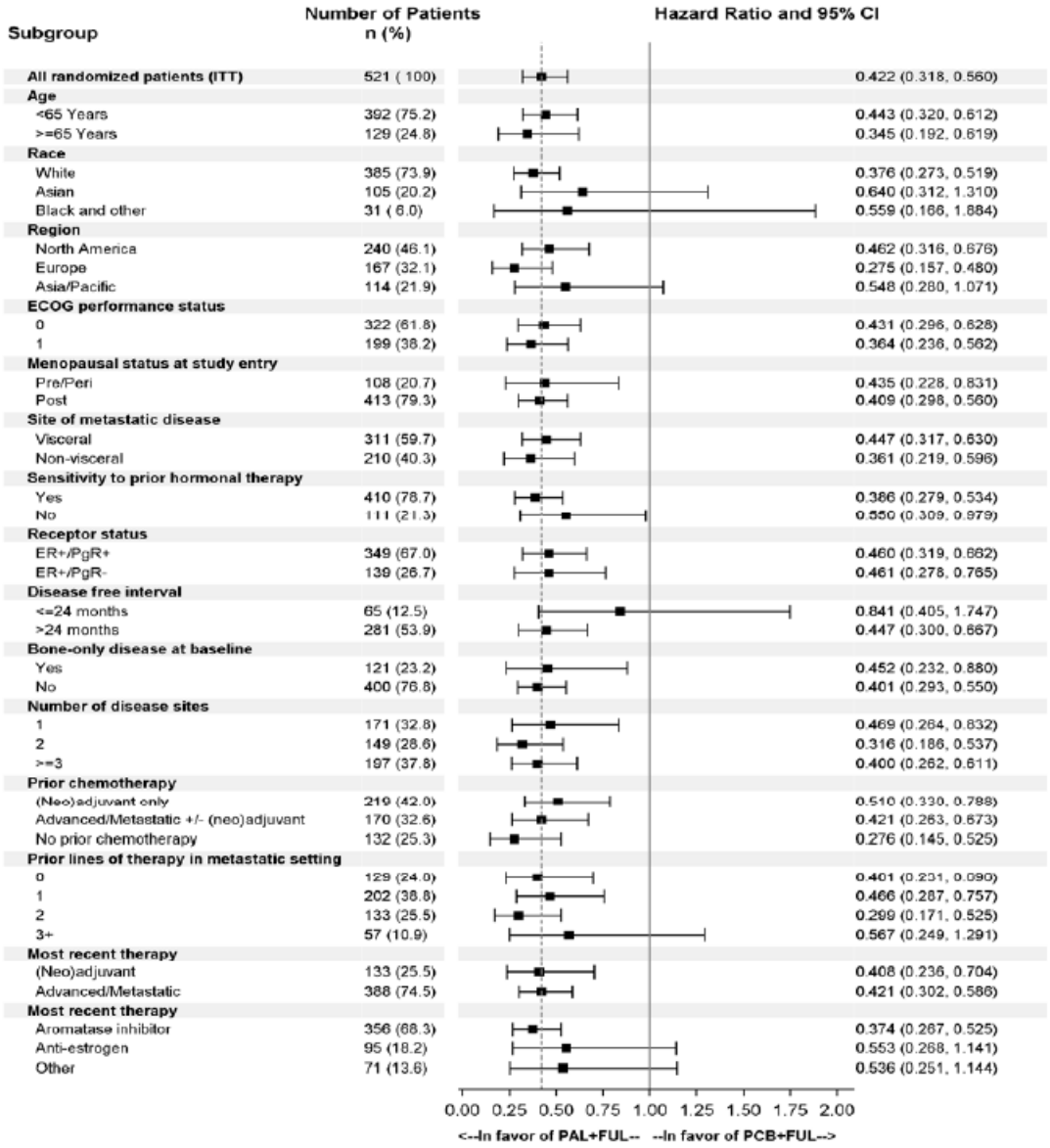
Source: FDA Statistician

Reviewer Comment: *The updated results support the results from the interim analysis for the primary efficacy endpoint. The DMC meeting for the interim analysis occurred on April 7, 2015. The DMC recommendation to stop the study early due to efficacy results was communicated to Pfizer on April 7, 2015 and the data were presented publically for the first time at ASCO on June 1, 2015. There should have been no impact of the released interim data on the updated analysis since the data cut-off (March 16, 2015) for the updated analysis was three weeks prior to the DMC meeting.*

Although exploratory, the review team chose to include the updated results in the label since they were more mature, with narrower confidence intervals, providing a better estimate regarding the efficacy of palbociclib.

Subgroup Analyses:
Several subgroups of various demographic and baseline characteristics were examined by the Applicant. The forest plots of these subgroups analyses of PFS are shown in Figure 5.

Figure 5. Forest Plot of Progression-Free Survival by Additional Baseline Characteristics, Investigator Assessment – Intent-to-Treat Population (Applicant Figure)



Source: Study 1023 CSR Figure 2

Reviewer Comment: *The treatment effect is consistent in the different subgroups. In some cases, such as race, disease-free interval (≤24 months), prior lines of therapy (+3) and most recent therapy (anti-estrogen and other), the spread of the confidence intervals is broad due to a small number of patients. No subgroup demonstrates a detriment with palbociclib plus fulvestrant treatment.*

Data Quality and Integrity – Reviewers' Assessment

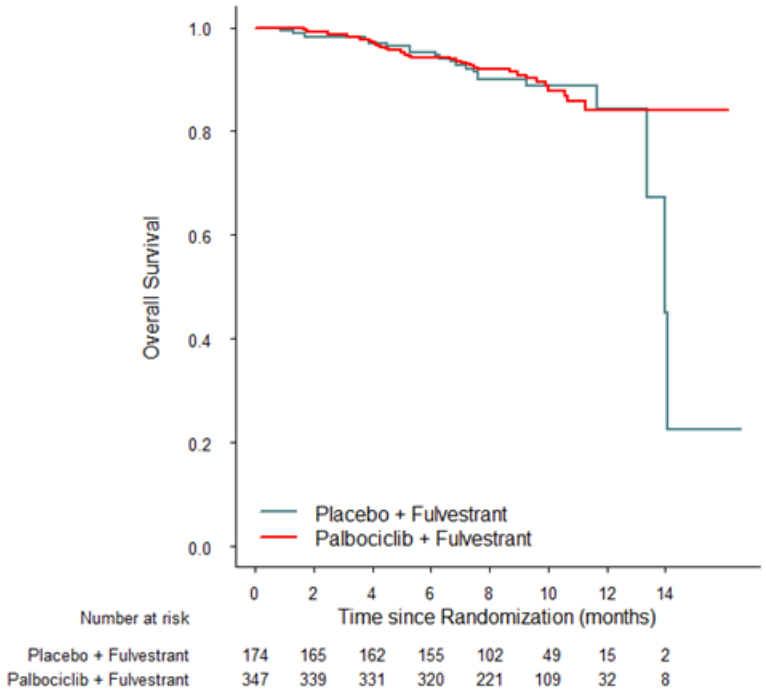
The submission contains all required components of the eCTD. The overall quality and integrity of the application appear to be acceptable. Requests for additional information from the Applicant throughout the review process were addressed in a timely fashion.

Efficacy Results – Secondary and other relevant endpoints

Key secondary endpoints included overall survival, objective response rate, clinical benefit rate, and duration of response.

Overall Survival:
At the data cut-off of March 16, 2015, there were 57 deaths among the 521 patients. The OS data was immature with only 29% of the planned 198 events. OS results are shown below in Figure 6.

Figure 6. Overall Survival in Study 1023



Source: FDA Statistician

Objective Response Rate (ORR):

At the March 2015 cut-off, as per investigator-assessment, ORR was 24.6% in the palbociclib plus fulvestrant arm compared with 10.9% in the placebo plus fulvestrant arm for patients with measurable disease at baseline. Results at the time of interim analysis and final analysis are shown in Table 19.

Clinical Benefit Response (CBR):

CBR was defined as CR or PR or SD ≥24 weeks according to the RECIST version 1.1. At the March 2015 cut-off, for patients with baseline measurable disease, the CBR rates were 66.6% in the palbociclib plus fulvestrant arm and 39.7% in the placebo plus fulvestrant arm. Results at the time of interim analysis and final analysis are shown in Table 19.

Duration of Response (DOR):
DOR was defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of disease progression or to death due to any cause, whichever occurs first. At the March 2015 cut-off, DOR was 9.3 months in the palbociclib plus fulvestrant arm and 7.6 months in the placebo plus fulvestrant arm. Results at the time of interim analysis and final analysis are shown in Table 19.

Table 19. Secondary Endpoint Results for Study 1023

	Interim Analysis (December 5, 2014 Cutoff)		**Updated/Final Analysis (March 16, 2015 Cutoff)**	
	Palbociclib plus Fulvestrant (N=347)	**Placebo plus Fulvestrant (N=174)**	**Palbociclib plus Fulvestrant (N=347)**	**Placebo plus Fulvestrant (N=174)**
ORR	10.4%	6.3%	19.0%	8.6%
ORR (measurable disease)	13.4%	8.0%	24.6%	10.9%
CBR	34.0%	19.0%	66.6%	39.7%
DOR (months)	9.3	5.7	9.3	7.6

N=number of patients; PFS=progression-free survival; CI=confidence interval; NE=not estimable; ORR=objective response rate; CBR=clinical benefit response; DOR=duration of response.

Reviewer comment: *The OS results were immature at the time of analysis. Numerically, results for ORR, CBR and DOR support the primary efficacy endpoint results.*

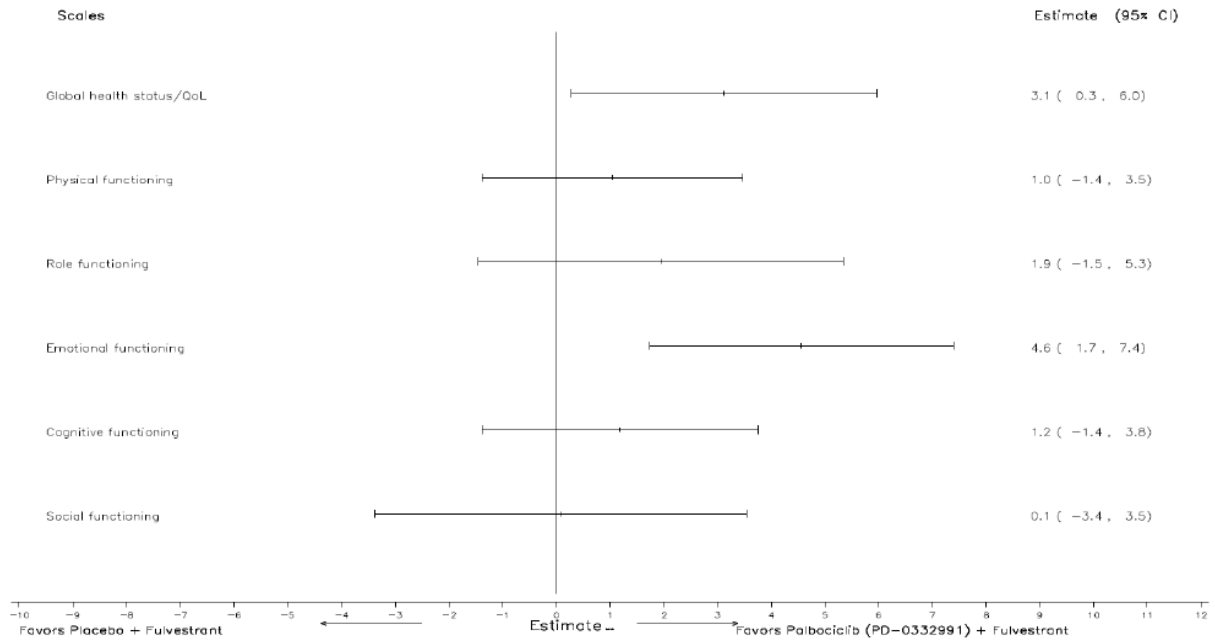
Patient Reported Outcomes (PROs):

PROs of functioning, global quality of life (QOL) and general health status were assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30, Breast Cancer Module (EORTC QLQ-BR23) and EuroQoL-5D (EQ-5D) score. In addition, a prespecified time to event analysis was assessed for pain. Time to deterioration (TTD) in pain was defined as time between baseline and first occurrence of increase of ≥10 points in pain.

Patients completed each instrument at pre-dose on Day 1 of Cycles 1-4, then on Day 1 of every other subsequent cycle starting with Cycle 6, and then at the End-of-treatment visit. Patients were to complete these instruments in the clinic (not to be taken home) and prior to having any tests and to any discussion of their progress with healthcare personnel at the site. Patients with baseline and at least one on study assessment were considered assessable change from baseline and TTD analyses.

There was an improvement in the numeric score for Global QOL (difference in change from baseline score of 3.1) and emotionally function (difference in change from baseline score of 4.6) from the EORTC QLQ-C30 when comparing palbociclib plus fulvestrant vs placebo plus fulvestrant (as shown in Figure 7).

Figure 7. Forest Plot in Overall Change From Baseline for EORTC QLQ-C30 Global Health and the QLQ-C30 Functional Scales (Applicant Figure)

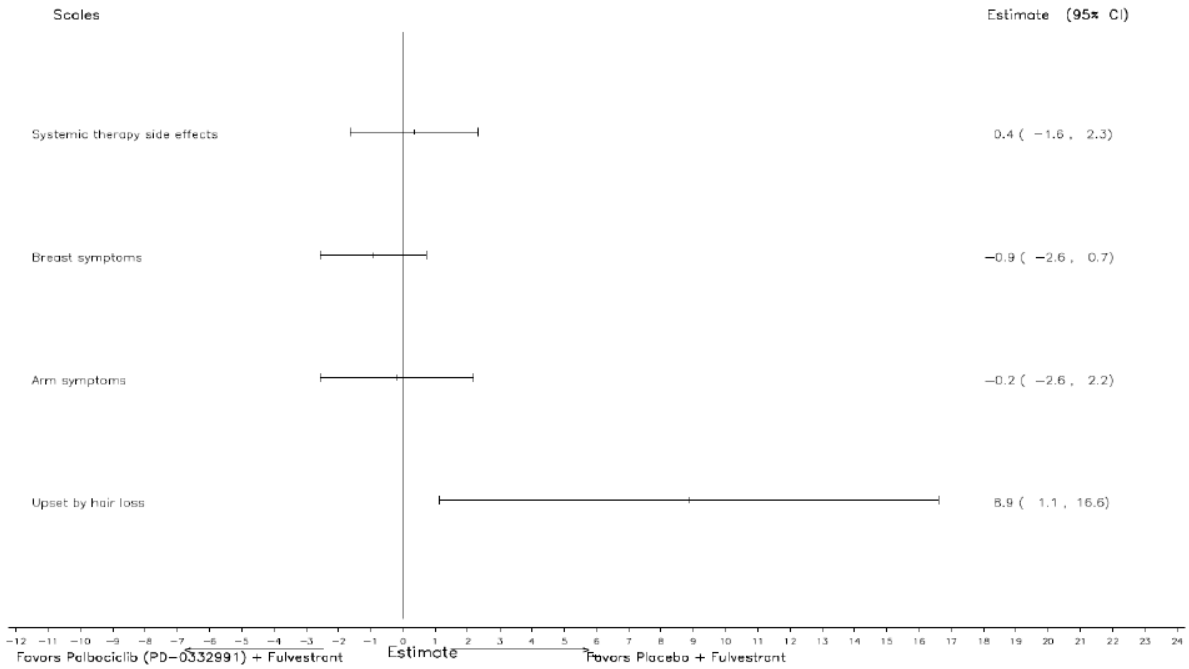


Source: Section 14.5, Figure 14.5.5.1
Abbreviations: EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, PRO: patient-reported outcome
Note - higher scores indicate better functioning, hence positive differences favor palbociclib plus fulvestrant

Source: Study 1023 CSR Figure 11

From the EORTC QLQ-BR23 questionnaire on the symptom scale, there was a difference between the two treatment arms in change from baseline score for being upset by hair loss favoring the placebo arm (as shown in Figure 8).

Figure 8. Forest Plot of QLQ-B23 Change from Baseline Scale Scores Between-treatment comparison - Symptom Scales (Applicant Figure)



Source: Section 14.5, Figure 14.5.5.4
Abbreviations: EORTC-QLQ-BR23: European Organisation for Research and Treatment of Cancer Breast Cancer Module, PRO: patient-reported outcome
Note - higher numbers indicate more severe symptoms, hence negative differences favor the palbociclib plus fulvestrant arm

Source: Study 1023 CSR Figure 14

The median TTD in pain was 8 months (95% CI 5.6, not estimable) in the palbociclib plus fulvestrant arm compared with 2.8 months (95% CI, 2.3, 5.4) in the placebo plus fulvestrant arm (results shown in Table 20).

Table 20. QLQ-C30 Time to Deterioration - Symptom Scale of Pain Increase of ≥10 Points - PRO Analysis Population (Applicant Table)

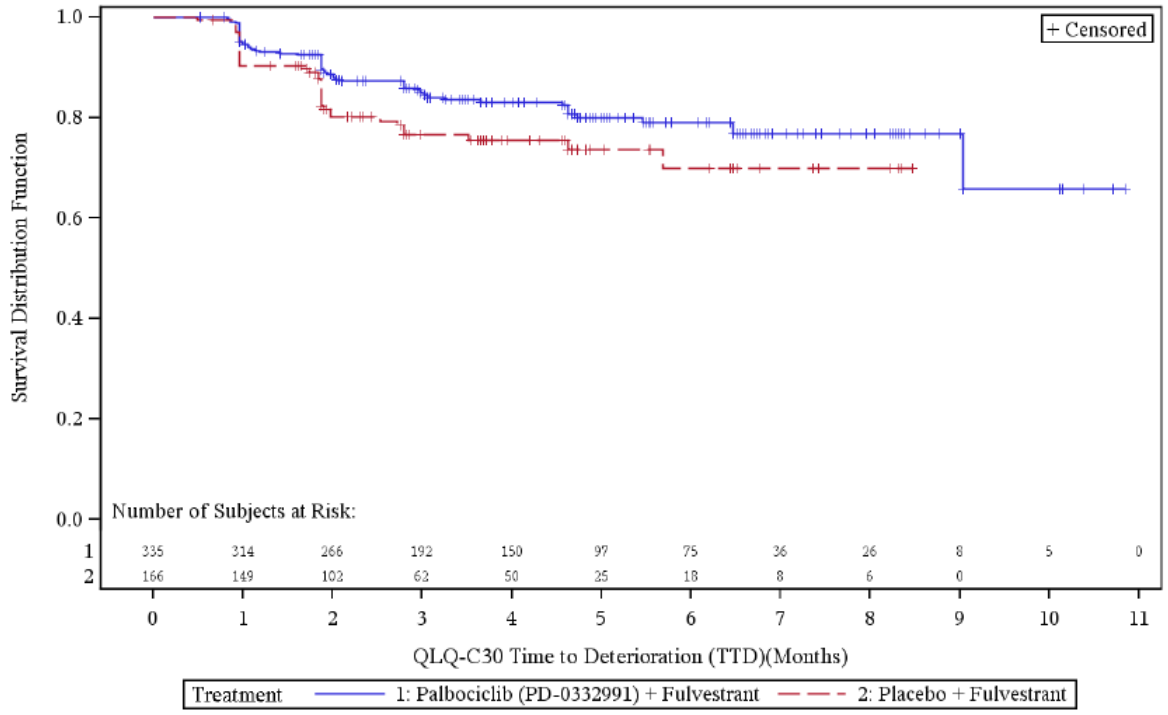
	Palbociclib plus Fulvestrant N=335	Placebo plus Fulvestrant N=166
	n (%)	n (%)
Patient had symptom scale of pain increase of ≥10 points while on study [n (%)]	131 (39.1)	83 (50.0)
Patient did not have symptom scale of pain increase of ≥10 points while on study [n (%)]	204 (60.9)	83 (50.0)
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI) [1]		
25%	1.9 [1.2,2.2]	1.0 [1.0,1.9]
50%	8.0 [5.6, NE]	2.8 [2.3,5.4]
75%	NE	NE
Unstratified analysis		
Hazard ratio [2]	0.642	
95% CI of Hazard ratio	0.487-0.846	
p-value [3]	<0.001	

Source: Study 1023 CSR Table 35

There were no notable differences between treatment arms on any of the other scales.

Since a pain increase of ≥10 points using the transformed scores on a scale of 1-100 would not be considered clinically significant, we asked the Applicant to perform two additional analyses for the pre-specified time to event analysis for pain (TTD) using a responder definition of delay in increase of pain ≥20 points and ≥30 points. Both of the additional TTD analyses delayed TTD in pain symptom with palbociclib plus fulvestrant treatment compared with placebo plus fulvestrant (HR of 0.655 [95% CI 0.435, 0.986]; p <0.0212). The results are the same by both definitions as the EORTC transformed pain scores have an incremental increase of 16.66 points. Kaplan Meier results for these additional exploratory analyses are shown in Figure 9.

Figure 9. TTD in Pain (increase in pain of >20 points and >30 points)-Applicant Figure



Source: Applicant Response to Information Request Dated December 15, 2015

In addition, the FDA statistical reviewer (Dr. Erik Bloomquist) performed several other analyses to further explore TTD for pain based on a raw 1 point, 2 point, and 3 point change from baseline (shown below Figure 10, 11, 12 and Table 21).

Figure 10. TTD for Pain 10-point change (1-point)

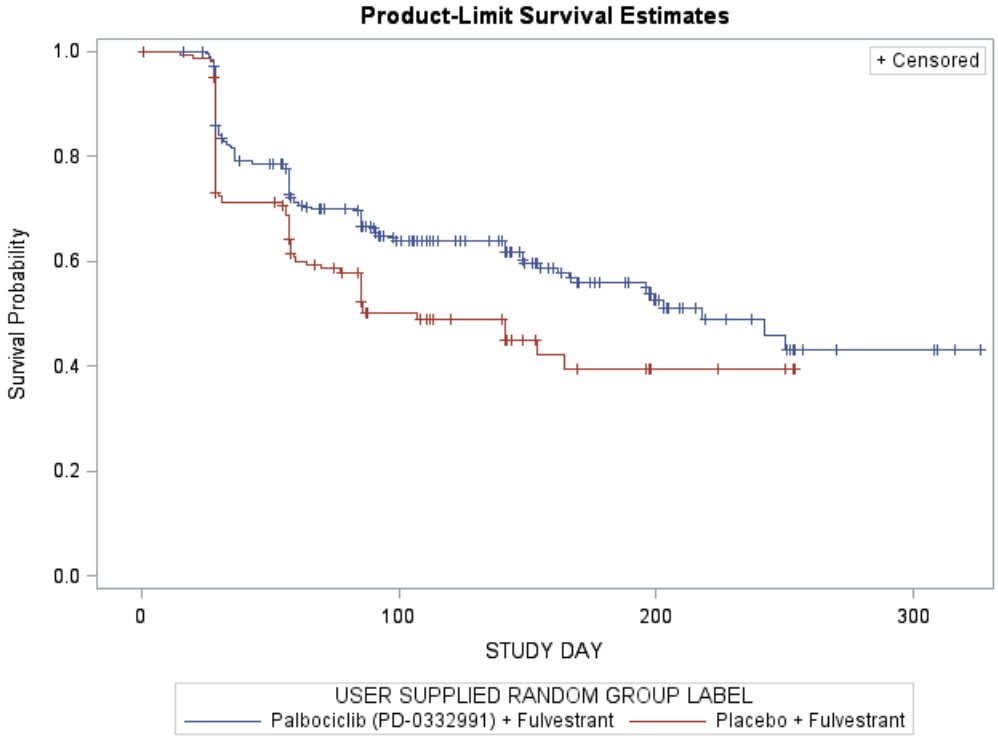


Figure 11. TTD in Pain 20-point change (2-point);

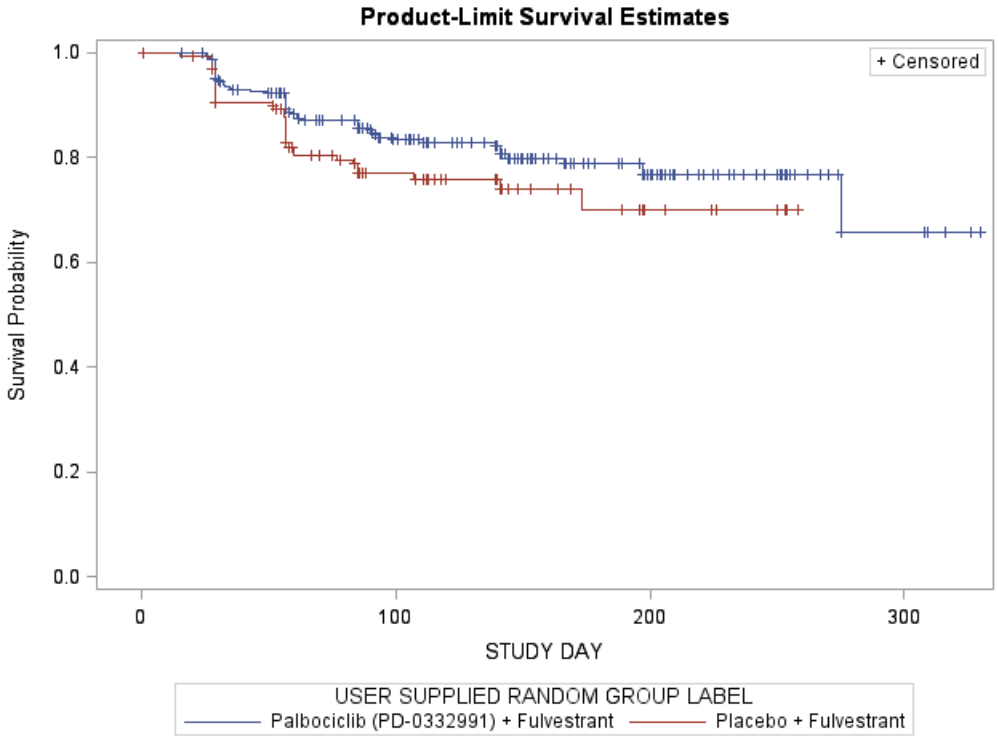


Figure 12. TTD in pain 35-point drop (3-point drop)

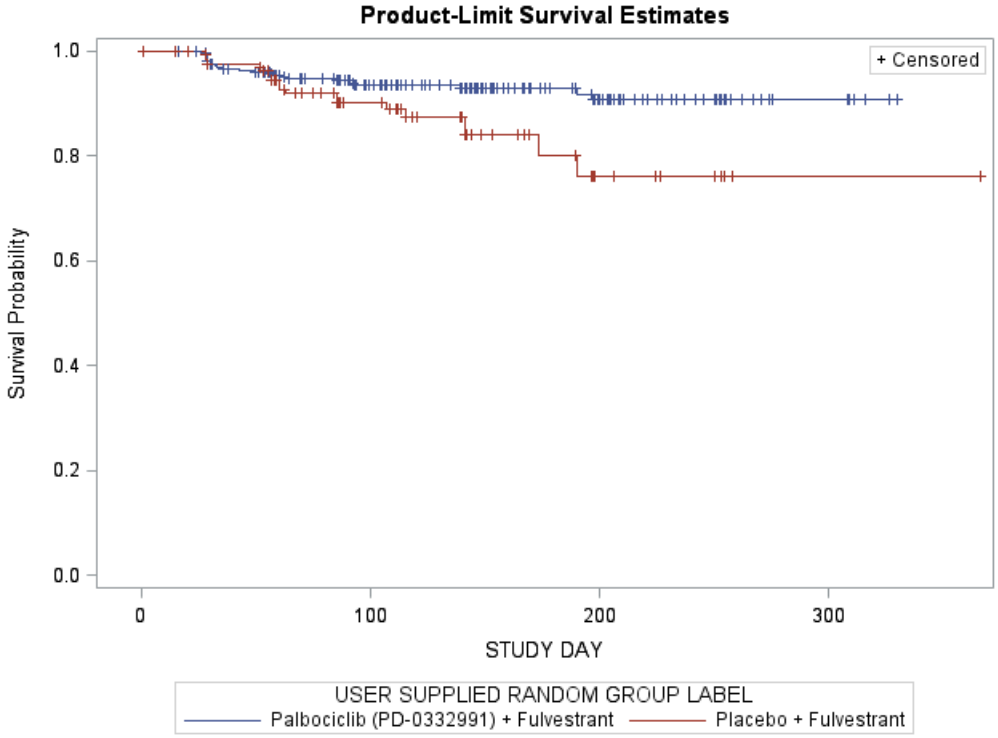


Table 21. TTD in Pain Analysis for Study 1023

Change from Baseline for TTD in Pain Analysis			
	1 point	2 point	3 point
HR	0.666	0.673	0.479
95% CI	0.506, 0.877	0.447, 1.011	0.262, 0.876
# of Events	216	99	43

Reviewer Comment: *Patient reported outcome (PRO) measurements can be quite valuable in assessing how disease symptoms and quality of life are affected by a certain therapy (11). A double-blind, randomized study as in Study 1023 is the ideal setting to investigate PROs. PROs for Study 1023 were listed as secondary endpoints in the clinical protocol but were not identified as key secondary endpoints detailed in the statistical analysis plan and no adjustments were made for multiplicity testing.*

(b) (4)

(b) (4)

Furthermore, the observed improvement in numeric score for global QOL and emotional functioning would typically not be considered clinically significant.

Although the TTD for pain was a prespecified analysis (still not identified as a key secondary endpoint with alpha allocation), it utilized questions from instruments that are broad in nature and difficult to interpret clinically. Analgesic use was captured in the case report form as part of concomitant medications but was not incorporated into the TTD for pain analyses. In addition, the prespecified definition for deterioration in pain (≥10 points) is not considered clinically significant. Yet, the additional analyses performed by the Sponsor and the FDA statistician looking at ≥20, ≥30 and ≥35 point changes may be considered clinically relevant.

Finally, the timing of the questionnaires in relation to the treatment schedule was not ideal. The questionnaires were given in clinic on day 1 of each 28 day cycle. Palbociclib is administered daily on days 1-21 followed by 7 days off treatment. Fulvestrant is given every 28 days (following the loading dose). Many questions on the EORTC QLQ-C30 and EORTC QLQ-BR23 asked the patient how they felt within the last week. For patients on the palbociclib plus fulvestrant treatment arm this would cover the week that they are off of palbociclib therapy. This may not be an issue to assess disease related symptoms. However, for treatment related symptoms the timing of the questionnaire is important. By querying about symptoms over only the past week, the true impact of palbociclib on quality of life may not be achieved. Since health-related QOL is a multi-domain concept which represents the patient's perception of illness and treatment on various aspects of life (ie, physical, psychological, social, etc), the timing of questionnaires is an important consideration in interpreting the results (10).

The clinical review team had extensive discussions with the Clinical Outcomes Assessment (COA) and Biostatistical teams regarding the analysis and interpretation of the PRO results from Study 1023. All of the TTD in pain analyses favor the palbociclib plus fulvestrant treatment arm and are supportive in reviewing the benefit-risk analysis for this application. However, for all of the reasons outlined above, the PRO results should be considered exploratory

(b) (4)

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

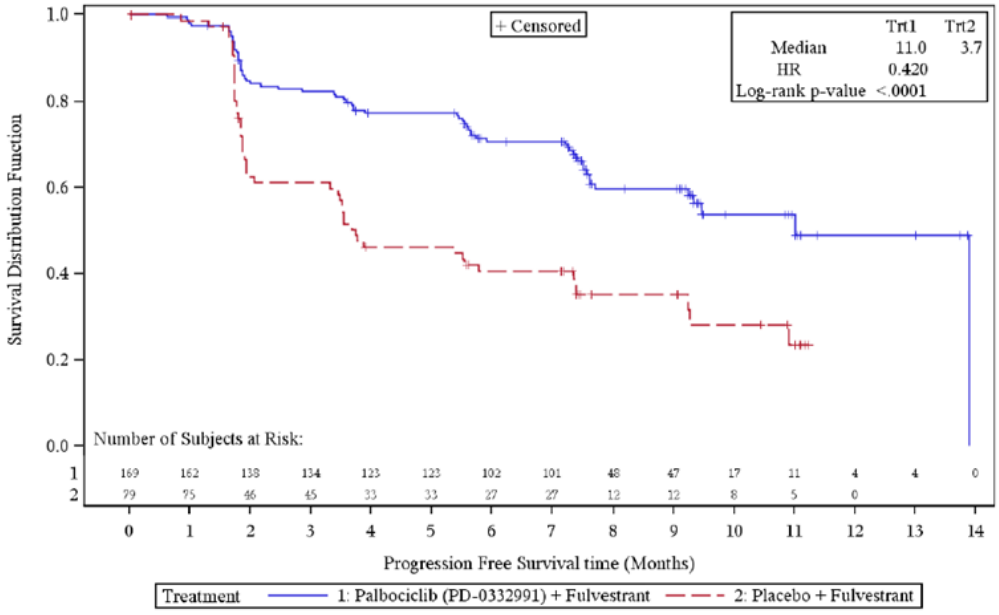
These issues are addressed throughout the efficacy review given that the primary endpoint of the trial is a time to event endpoint. The duration of response for the ORR also supports the primary endpoint results.

Additional Analyses Conducted on the Individual Trial

Biomarker Results:
Exploratory analyses evaluating the potential role of ESR1 mutations and PIK3CA mutations on PFS results were performed by the Applicant using the updated March 16, 2015 cutoff for Study 1023 data. Circulating free DNA (cfDNA) was isolated from baseline Day 1 of Cycle 1 plasma samples by using QIAamp circulating free nucleic acids purification kit (Qiagen, Venlo, Netherlands) for 396 patients in the PALOMA-3 study. ESR1 and PIK3CA mutation detection using BEAMing digital PCR assays were conducted by (b) (4) in its CLIA laboratory .

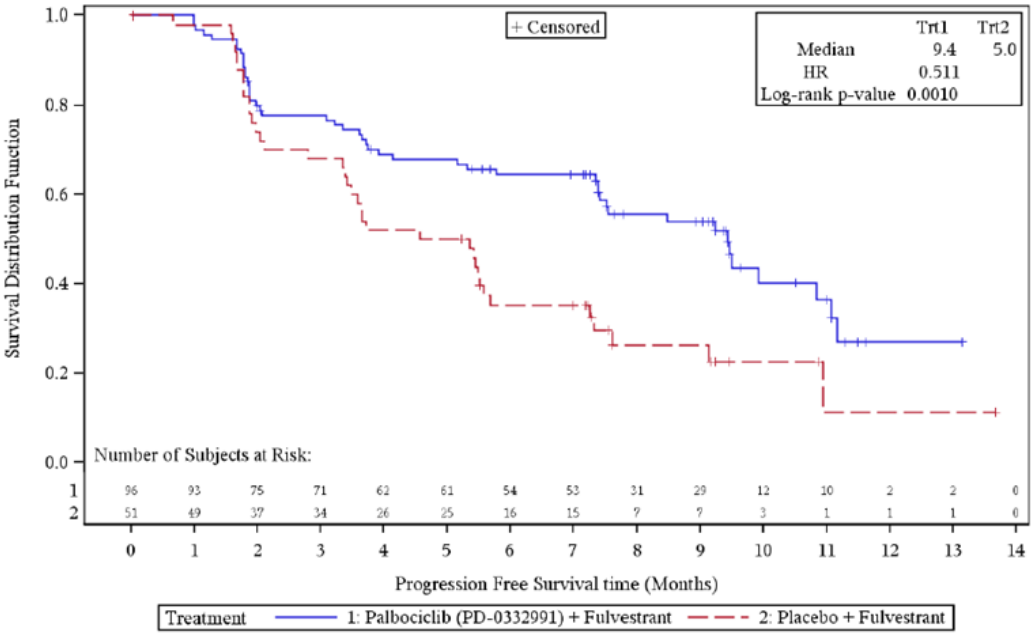
The mutations analyzed included ESR1 Exon 5 E380Q, Exon 7 S463P, Exon 8 V534E, P535H, L536R/H/P/Q, Y537N/S/C, and D538G; PIK3CA Exon 9 E542K, Exon 9 E545K, Exon 20 H1047R/L. One sample from the 396 samples tested failed the analysis. An ESR1 mutation was detected in 147 analyzed samples (37.2%). In patients with no ESR1 mutation detected, the median PFS was 11.0 months in the palbociclib plus fulvestrant group compared with 3.7 months in the control group (HR 0.42, 95% CI 0.29 – 0.61, one-sided p<0.0001; Figure 13). In patients with ESR1 mutation detected, the median PFS was 9.4 months versus 5.0 months, respectively (HR 0.51, 95% CI 0.33 – 0.79, one-sided p=0.001; Figure 14).

Figure 13. PFS of Patients with no ESR1 Mutation Detected (Applicant Figure)



Source: Applicant Response to Information Request Dated November 2, 2015

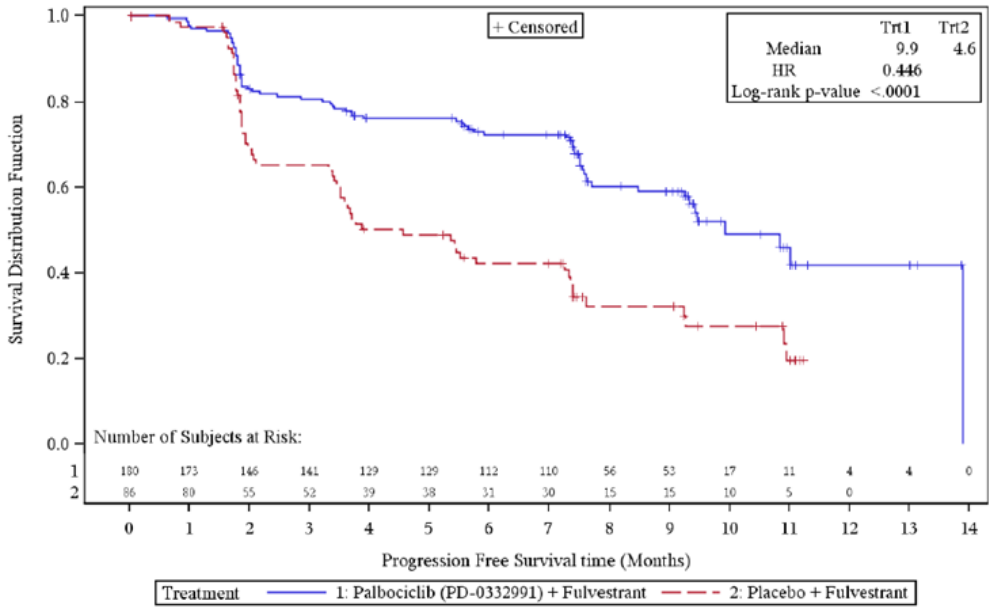
Figure 14. PFS of Patients with ESR1 Mutation Detected (Applicant Figure)



Source: Applicant Response to Information Request Dated November 2, 2015

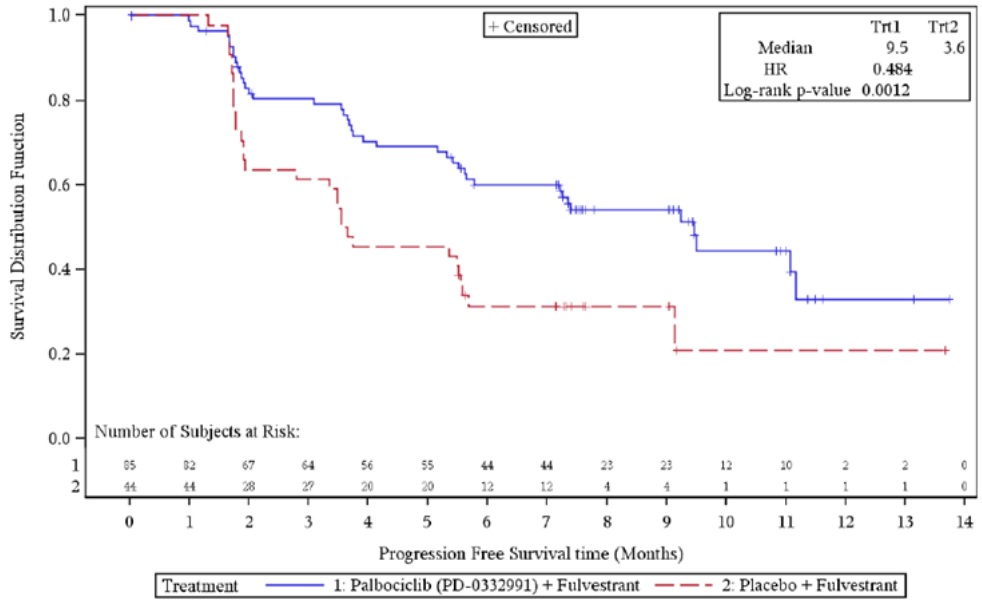
A PIK3CA mutation was detected in 129 analyzed samples (32.7%). PIK3CA H1047R/L was the most frequent mutation detected (14.4%) among the four most common mutations assessed, followed by E545K (11.6%) and E542K (9.4%). In patients with no PIK3CA mutation detected, the median PFS was 9.9 months in the palbociclib plus fulvestrant group compared with 4.6 months in the control group (HR 0.45, 95% CI 0.31 – 0.64, one-sided p<0.0001; Figure 15). In patients with PIK3CA mutation detected, the median PFS was 9.5 months versus 3.6 months, respectively (HR 0.48, 95% CI 0.30 – 0.78, one-sided p=0.001; Figure 16).

Figure 15. PFS of Patients with No PIK3CA Mutation Detected (Applicant Figure)



Source: Applicant Response to Information Request Dated November 2, 2015

Figure 16. PFS of Patients with PIK3CA Mutation Detected (Applicant Figure)



Source: Applicant Response to Information Request Dated November 2, 2015

Reviewer Comment: *Based on the exploratory analyses performed by the Applicant, ESR1 and PIK3CA mutation status do not appear to affect the efficacy results.*

The protocol specified biomarker analyses for assessment of gene copy numbers of CCND1 and CKKN2A, RNA expression of cdk4 and cdk6, and protein expression of Ki67, pRb, cyclin E, and p16 were not performed in this study and are being done on samples from Study A5481008 (PALOMA-2).

ER, PR, and HER2 Results:

Patients were enrolled in this study based on local laboratory results of ER, PR, and HER2. Tissue slides/blocks from 490 of 521 enrolled patients were sent to the central laboratory for analysis. The samples from 87 patients either had no breast tumor cells in the tissue or were not evaluable based on hematoxylin and eosin stain assessment. See Table 22

Table 22. ER, PR, and HER2 status in ITT population

	Palbociclib plus Fulvestrant N=347 N (%)	Placebo plus Fulvestrant N=174 N (%)
Results from local laboratory		
ER		
Positive	339 (97.7)	167 (96.0)
Negative	1 (0.3)	2 (1.1)
Missing	7 (2.0)	5 (2.9)
PR		
Positive	243 (70.0)	117 (67.2)
Negative	91 (26.2)	49 (28.2)
Missing	13 (3.7)	8 (4.6)
HER2		
Positive	2 (0.6)	2 (1.1)
Negative	341 (98.3)	171 (98.3)
Equivocal	3 (0.9)	1 (0.6)
Missing	1 (0.3)	0
Results from central laboratory		
ER IHC		
Positive	224 (64.6)	115 (66.1)
Negative	26 (7.5)	15 (8.6)
Missing*	97 (28.0)	44 (25.3)
PR IHC		
Positive	154 (44.4)	90 (51.7)
Negative	92 (26.5)	39 (22.4)
Missing*	101 (29.1)	45 (25.9)
HER2 IHC		
Positive	9 (2.6)	5 (2.9)
Negative	166 (47.8)	90 (51.7)
Equivocal**	72 (20.7)	34 (19.5)
Missing*	100 (28.8)	45 (25.9)

**Missing results for ER, PR, and HER2 were due to tissue sample availability, tissue samples with no tumor content or not evaluable and failed tests at the central laboratory.*
***Among the 72 HER2 IHC equivocal cases in the Palbociclib plus Fulvestrant arm, results of HER2 FISH testing was negative in 58 cases, positive in 10 cases, and failed in 4 cases. Among the 34 HER2 IHC equivocal cases in the Placebo + Fulvestrant arm, results of HER2 FISH testing was negative in 28 cases, positive in 5 cases, and failed in 1 case.*

Source: Study 1023 CSR Table 14.6.1.1.2 and Table 14.6.1.2.1

Reviewer Comment: *As with most clinical trials, patients were enrolled onto study based on local laboratory results for ER, PR and HER2. Patients were eligible for Study 1023 if they were ER-positive and/or PR-positive and HER2-negative. Based on central laboratory assessment for samples that were analyzed, 28 patients were shown to have ER- and PR-negative disease, 20 patients in the palbociclib plus fulvestrant arm and 8 patients in the placebo plus fulvestrant arm. In addition, 15 patients were confirmed to be HER2-positive (10 in the palbociclib plus fulvestrant arm and 5 patients in the placebo plus fulvestrant arm). The Applicant generated Kaplan-Meier plots (not shown) of PFS by treatment and ER status (positive or negative), PR status (positive or negative), and HER2 status (positive or negative) based on central laboratory results. Central laboratory confirmed ER- and/or PR-positive patients showed similar efficacy results compared to the ITT population.*

7 Integrated Review of Effectiveness

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

Refer to FDA Clinical Pharmacology Review from the original NDA submission.

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

Not applicable.

7.3. Integrated Assessment of Effectiveness

HR-positive/HER2-negative advanced or metastatic breast cancer is a life-threatening disease that clearly has unmet medical needs in its treatment. Although there are several endocrine and chemotherapy agents available to these patients; resistance often develops, leading to progression of disease and ultimately death. Palbociclib is a reversible inhibitor of 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 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.

In this sNDA, the Applicant relied on results from a single study, Study 1023. Study 1023 was a randomized, double-blind, placebo- controlled study in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease had progressed on prior endocrine therapy. This was a well-designed trial with an appropriate comparator arm. The primary endpoint was investigator assessed PFS. At the final analysis, the median PFS in the palbociclib plus fulvestrant arm was 9.5 months compared to 4.6 months in the placebo plus fulvestrant arm (HR=0.46; 95% CI: 0.36, 0.59; p<0.000001). Palbociclib plus fulvestrant showed a 4.9 month improvement in median PFS compared to placebo plus fulvestrant which is both clinically meaningful and statistically significant. Results of a BICR audit, subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results. OS results are immature at this time. In conclusion, based on a favorable risk-benefit profile for palbociclib in combination with fulvestrant, the reviewers recommend regular approval for the following indication "IBRANCE is a kinase inhibitor indicated in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic cancer with disease progression following prior endocrine therapy." Study 1023 used a different endocrine therapy and different population than that used in the pivotal trial (Study 1003, PALOMA-1) that granted accelerated approval to palbociclib. (b) (4) the benefit-risk profile from Study 1023 supports regular approval for the new indication listed above (b) (4)

While the added clinical benefit from the combination of palbociclib with fulvestrant was demonstrated in Study 1023, there are still some uncertainties. The clinical benefit is based on an improved PFS and it is unknown if there will be an OS benefit with this combination.

However, given the numerous therapies available to patients with MBC following progression, it may be difficult to determine an OS benefit. In addition, as of yet, there are have been no identified biomarkers to predict resistance or response to palbociclib.

8 Review of Safety

8.1. Safety Review Approach

In this sNDA, the Applicant submitted safety data from Study 1023, a Phase 3 trial of palbociclib plus fulvestrant versus fulvestrant and placebo, with the original submission. A total of 345 patients received palbociclib in Study 1023 (347 patients randomized). 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. Laboratories were collected at baseline and every 15 days during the first 2 cycles, followed by every 28 days starting at day 1 of cycle 3. Hematology labs included hemoglobin, WBC, absolute neutrophil count, platelet count. Blood chemistries included AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, blood urea nitrogen (BUN), serum creatinine, and albumin. Upon approval of Amendment 2, hemoglobin A1c was measured every 3 months to characterize whether or not palbociclib affects glucose metabolism. There were no clinical holds for safety during the development of palbociclib.

Table 9 outlines the safety studies submitted with the sNDA, as well as the data cut-offs for Initial Submission and the 90-Day Safety Update.

Table 23. Summary of Safety Populations Submitted with sNDA

Study[1]	Design	Population	N	Status	Cut-off (sNDA)	Cut-off (90-Day)
A5481003	Phase 1/2	Advanced Breast Cancer	95	Completed	1/2/2015	7/31/15
A5481008[2]	Phase 3 R	Advanced Breast Cancer	444[3]	Ongoing	1/2/2015	7/31/15
A5481010	Phase 1/2	Advanced solid tumors	50	Ongoing	Phase 1: 3/31/2015 Phase 2: 1/2/2015	7/31/15
A5481023[2]	Phase 3 R	Advanced	345	Completed	12/5/2014	7/31/15

		Breast Cancer				
A5481034	Expanded Access	Advanced Breast Cancer	93	Ongoing	1/2/2015	7/31/15

N=number of patients, R=randomized
[1] Healthy Volunteer Studies and Investigator-Initiated Research Studies are not included in this table, although the data from these studies were reviewed for this sNDA
[2] Blinded therapy
[3] Approximate, based on 2:1 randomization of 666 patients

Overall, safety data from approximately 1,015 women with advanced/metastatic breast cancer who received at least one dose of palbociclib 125mg QD on Schedule 3/1 in combination with endocrine therapy (either fulvestrant with or without goserelin or letrozole) in Pfizer-sponsored clinical trials were submitted with the initial sNDA and comprise the target population receiving the recommended dosing regimen for palbociclib treatment. Of these, 345 patients received palbociclib plus fulvestrant with or without goserelin in completed randomized, double-blind Phase 3 Study 1023. The remaining 670 of the 1015 patients received palbociclib plus letrozole of whom 95 participated in completed Study 1003; 38 participated/are participating in ongoing Study 1010 (6 patients in the completed Phase 1 Part 2 portion and 32 patients in the ongoing Phase 2 portion of the study); 93 are participating in ongoing open-label Expanded Access Protocol 1034; and approximately 444 (based on a 2:1 randomization ratio for palbociclib versus placebo [666 × 2/3 = 444]) are participating in ongoing randomized, double-blind Phase 3 Study 1008.

The 90-Day Safety Update provided cumulative safety information as of July 31st, 2015 for those studies that were included in the original sNDA as well as two ongoing Pfizer-sponsored clinical studies of palbociclib - Phase 3 study 1027 in Asian patients with advanced breast cancer and Phase I Study 1013 in subjects with hepatic impairment who were otherwise healthy.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The duration of exposure to palbociclib or placebo plus fulvestrant in Study 1023 is summarized in Table 10 below. As of July 31, 2015, 39.2% of patient in the palbociclib plus fulvestrant arm and 19.5% of patients in the placebo plus fulvestrant arm were still receiving protocol directed therapy. The median daily dose of palbociclib was 125.0 mg (range 81-131 mg). The median duration of palbociclib exposure was approximately 11 months.

Table 24. Summary of Patient Exposure to Palbociclib in Study 1023

	Palbociclib plus Fulvestrant (n= 345)		**Placebo plus Fulvestrant (n=172)**	
	Palbociclib	Fulvestrant	Placebo	Fulvestrant
Median number of	12 (1-21)	12 (1-21)	5 (1-22)	5 (1-22)

cycles (range)				
Median treatment duration in days (range)	330 (1-596)	341 (28-596)	137 (14-611)	145 (27-618)
Patients with at least 1 dose reduction (%)	128 (37.1)	NA[1]	3 (1.7)	NA
Patients with 2 dose reductions (%)	18 (5.2)	NA	0	NA
Patients with at least 1 dose interruption (%)	286 (82.9)	11 (3.2)	104 (60.5)	2 (1.2)
Patients with cycle delay (%)[2]	187 (54,2)	--	22 (12.8)	--
Mean cumulative dose in mg (SD)	22,514 (13,237)	5,502 (2,722)	17,829 (13,723)	4,064 (2,712)
Median cumulative dose in mg (range)	24,175 (125-54,500)	6,500 (500-11,500)	12,750 (1,750-57,625)	3,000 (500-11,500)
Mean relative dose intensity (SD)[3]	85.6 (15.4)	96.3 (6.8)	97.7 (4.9)	98.9 (5.7)
Median relative dose intensity (range)	89.8 (22-107)	98.4 (50-106)	99.5 (69-108)	100 (50-108)

[1] Protocol did not allow for the fulvestrant dose to be reduced, but a single dose could be skipped or dosing delayed because of fulvestrant related toxicity.
[2] Cycle delay defined as a 2-day or longer delay in the cycle start date (Cycles 1 and 2) or a 7-day or longer delay in Cycles 3 and beyond.
[3] Relative dose intensity = (actual dose intensity/intended dose intensity)*100%
Source: 90-Day Safety Update, Tables 4 and 5, page 32-33

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

Demographic information for the 345 patients in Study 1023 is included in Section 6.1.2 above. In summary, the two treatment arms were well balanced in terms of baseline characteristics. All patients in this study were women whose median age was 57 (30-88) years in the palbociclib plus fulvestrant arm and 56 (29-80) years in the placebo plus fulvestrant arm. Most patients in either treatment arm were White (72.6% in the palbociclib plus fulvestrant arm and 76.4% in the placebo plus fulvestrant arm). The two treatment arms were well balanced in terms of ECOG PS at baseline. More than half of the patients in either treatment arm had an ECOG PS of 0 at baseline. Prior treatments for patients in this study were also generally well balanced between the two treatment arms. The majority of patients in either arm had undergone prior surgery (82% in the palbociclib plus fulvestrant arm and 85% in the placebo plus fulvestrant arm); most patients in each treatment arm had received prior radiotherapy (68% and 75%, respectively); and all patients in either treatment arm had received prior systemic therapy.

8.2.3. **Adequacy of the safety database:**

The safety database from the 406 patients treated with palbociclib on Study 1023 is adequate. The age and sex of the patients is as expected for patients with breast cancer. Of note, there were no males included in Study 1023. Minorities are also underrepresented in this trial. The performance status of the patients entered on this trial is greater than the performance status of patients with breast cancer as a whole.

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. There were some inconsistencies between the AE dataset and CRFs, as further described in this review.

8.3.2. Categorization of Adverse Events

The applicant defined an adverse event as any untoward medical occurrence in a clinical investigation patient administered a product or medical device, with or without a causal relationship with the treatment or usage. An abnormal objective test finding was reported as an AE if the test result was associated with accompanying symptoms, and/or required additional diagnostic testing or medical/surgical intervention, and/or led to a change in dosing or discontinuation from the trial, significant additional concomitant drug treatment or other therapy, and/or was considered to be an AE by the investigator or the Applicant.

Reviewer Comment: *The definition of AE led to under reporting of many abnormal laboratory findings and possibly other types of abnormal subjective and objective findings in the patients.*

An SAE was defined as any untoward medical occurrence at any dose that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or results in congenital anomaly/birth defect. All AEs and SAEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 and AEs were graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0 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.

8.3.3. Routine Clinical Tests

In Study 1023, routine laboratory tests including a CBC with differential (hemoglobin, WBC, absolute neutrophil count, lymphocytes, and platelet count) and chemistry (AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, blood urea nitrogen (BUN), serum creatinine, and albumin) were collected at baseline and at each cycle. During the

first two cycles, laboratories were checked every 2 weeks. Upon approval of Amendment 1, patients underwent an ophthalmologic exam by an ophthalmologist at screening, during study treatment on Cycle 4 Day 1, on Cycle 7 Day 1, on Cycle 13 Day 1, every 12 months thereafter, and at the End of Treatment/Withdrawal Visit. Upon approval of Amendment 2, hemoglobin A1c was measured every 3 months from the date of randomization. Ocular safety assessments included the Snellen best corrected visual acuity and refraction tests, intraocular pressure measurement, slit-lamp biomicroscopy, lens grading, and ophthalmoscopy. A full physical examination including an examination of all major body systems and breasts, height (at screening only), weight, blood pressure, and pulse rate were carried out at Screening, Day 1 of every cycle, and at the End of Treatment/Withdrawal visit. A 12-Lead EKG was performed (in triplicate) at screening and also at the End of Treatment/Withdrawal Visit.

8.4. Safety Results

Deaths

Deaths in Study 1023: As of July 31st, 2015, four of 345 patients (1.2%) in the palbociclib plus fulvestrant arm and three of 172 patients (1.7%) in the placebo plus fulvestrant arm died on-study within 28 days of the last dose of palbociclib/placebo. The majority of deaths on both arms were due to disease progression. Per investigator assessment, no deaths were reported due to toxicity of palbociclib or fulvestrant. A review of the narratives of the seven patients was performed. Four patients died due to progressive disease, one patient in the palbociclib plus fulvestrant arm died from DIC presumably related to underlying malignancy or sepsis, one patient in the palbociclib plus fulvestrant arm died of neutropenic sepsis 22 days after receiving study drug, and one patient in the placebo plus fulvestrant arm died of intracerebral hemorrhage presumably related to underlying AVM or asymptomatic single CNS metastases.

Table 25. Applicant's Analysis of Deaths within 28 Days of Study Drug

	Palbociclib plus Fulvestrant (n= 345)	Placebo plus Fulvestrant (n=172)
Deaths within 28 Days	4 (1.2%)	3 (1.7%)
Progressive Disease	4	2
Study Drug Toxicity	0	0
Other	0	1[1]

[1]Intracerebral hemorrhage likely caused by AVM.
Source: 90-Day Safety Update, modified Table 14, page 50

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 provides very similar information to that above with the exception of the cause of death for subject 11661006, which is summarized below.

Subject 11661006 was a 69-year-old Caucasian woman who received palbociclib from Jul 8th, 2014 – Aug 27th, 2014. Imaging on Aug 26th, 2014 revealed progressive disease and the investigator discontinued study treatment on Sept 2nd, 2014. The end of treatment visit was conducted on Sept 4th, 2014. CBC at that time was significant for ANC of 820/uL (down from 1400 on Aug 21st), platelets 90K /µL (down from 111) and hemoglobin of 8.8 g/dL (down from 9.3). The patient presented to the ED on [redacted] (b) (6) [redacted]. She was febrile, hypotensive (BP 105/60), tachycardic (120 bpm), and blood culture was positive for E. coli. Labs were significant for neutropenia (350/µL), anemia (9.1g/dL) and thrombocytopenia (19,000/µL). Urine culture and chest x-ray were negative. The patient died on [redacted] (b) (6) [redacted]. The investigator and sponsor considered the death unrelated to blinded therapy and secondary to "Deterioration of general condition due to disease progression."

Reviewer comments: *Subject 11661006 experienced a number of toxicities within 28 days of receiving study drug which were not reported in the AE dataset including febrile neutropenia and neutropenic sepsis. The only adverse event reported during this episode was Grade 5 "Deterioration of general condition" which does not capture the full extent of adverse events that occurred within 28 days of receiving study drug. An information request was sent to the Sponsor asking for further clarification, as it appeared from the clinical information the patient experienced neutropenic sepsis. The Sponsor responded with a detailed summary of the safety report, and reported that "After review of the patient file, the Investigator updated the cause of death to Neutropenic sepsis resulting in multi-organ failure which was reported as related to disease progression. The Investigator updated the original SAE report to reflect this change." Based on the information provided, it is possible that treatment with palbociclib contributed to this patient's death.*

The additional patient deaths on study are summarized below.

Subject 10791002 was a 57-year-old Caucasian woman who received palbociclib from June 13, 2014 – July 25th, 2014. She was taken off study on July 25th secondary to progressive disease and received paclitaxel on [redacted] (b) (6) [redacted]. The following day she presented to the ED with coffee ground emesis and melenic stool. Laboratory workup revealed fulminant DIC with an INR of 12, presumably related to underlying malignancy vs. sepsis. On [redacted] (b) (6) her clinical status rapidly deteriorated with refractory shock despite pressors, worsening coagulopathy, and abdominal distention likely secondary to intraabdominal or retroperitoneal bleed. The patient died on [redacted] (b) (6) [redacted]. The Investigator and Sponsor considered the death to be unrelated to blinded therapy.

Reviewer comment: *Although we agree with the Investigator and Sponsor's Assessment of cause of death, there was no grade 5 AE in adverse event dataset in the initial application (only grade 4 DIC) even though the patient died within 28 days of receiving study drug. This error was corrected in the dataset submitted with the 90-Day Safety Update provided by the Sponsor.*

Subject 11371014 was a 36-year-old pre-menopausal Asian woman who received palbociclib from June 11th, 2014 to July 15th, 2014. CT scan on July 14th, 2014 revealed progressive disease. On [redacted] she was admitted to the hospital with liver failure and the patient died on [redacted]. The most likely cause of death was disease progression.

Subject 12891002 was a 72-year-old Caucasian woman with underlying arteriovenous malformation who received placebo from Aug 4th, 2014 to Sept 12th, 2014. On [redacted] she presented to the hospital with headache and nausea/vomiting. Head CT showed a small acute hemorrhage and CT of chest/abdomen/pelvis revealed disease progression. Workup was negative. The patient was advised to discontinue aspirin and shortly prior to discharge, she experienced another intracranial hemorrhage. Head CT revealed further extension of the bleed with acute hydrocephalus. Her clinical condition deteriorated and she died on [redacted]. ICH was reported as likely secondary to small underlying AVM or a hemorrhage secondary to a small metastatic deposit.

Subject 10011002 was a 38-year-old Caucasian woman who received palbociclib from Feb 3rd, 2014 to April 14th, 2014. Medical history was significant for bilateral malignant pleural effusions requiring pleurex catheter since May 2013. On April 15th, 2014 the patient was unable to ambulate secondary to dyspnea associated with progressive disease. She was transferred to inpatient hospice on [redacted] and died on [redacted]. The most likely cause of death was disease progression.

Subject 10511002 was a 61-year-old Caucasian woman who received placebo from June 17th, 2014 until her death [redacted]. Her medical history was significant for refractory malignant pleural effusions. She died at home from respiratory distress. The most likely cause of death was disease progression.

There was one additional death reported with the 90 day Safety update (July 31st, 2015). The patient was randomized to placebo and died of disease progression.

The FDA analysis of Deaths within 28 days of study drug in Study 1023 as of July 31st, 2015 is shown below.

Table 26. FDA Analysis of Deaths within 28 Days of Study Drug

	Palbociclib plus Fulvestrant (n= 345)	Placebo plus Fulvestrant (n=172)
Deaths within 28 Days	4 (1.2%)	3 (1.7%)
DIC	1[1]	0
Disease progression	2	2
Intracerebral hemorrhage	0	1[2]
Neutropenic sepsis	1[3]	0

[1]DIC related to underlying malignancy or sepsis
[2]Intracerebral hemorrhage likely caused by AVM or single brain metastases not visible on baseline MRI
[3]Cause of death reported by Investigator was "Deterioration of general condition" due to underlying malignancy.
Source: 90-Day Safety Update

Reviewer comment: *The majority of deaths in Study 1023 were due to disease progression. None of the AEs leading to death were considered by the Investigator or the Sponsor to be related to study treatment. However, one patient died of neutropenic sepsis within 28 days of receiving palbociclib. Based on the information provided, it is possible that treatment with palbociclib contributed to her death. A statement was added to Section 5.1 (Neutropenia under "Warnings and Precautions") of the label indicating there was one death due to neutropenic sepsis in Study 1023.*

Deaths in the Industry-Sponsored Clinical Studies

There have been a total of 26 deaths on study (after the first dose of study drug and within 28 days of the last dose of study drug) in industry-sponsored clinical studies. Thirteen of these deaths are in patients who received palbociclib and ten deaths are in patients on Study 1008 who either received palbociclib or placebo.

In the completed open-label phase 1/2 Study 1003 in post-menopausal women with ER-positive, HER2-negative advanced breast cancer receiving palbociclib in combination with letrozole or letrozole alone as first line treatment of their disease, one of 95 patients who were randomized to receive palbociclib died of disease progression.

In the ongoing double-blind, placebo-controlled Phase 3 Study 1008 in post-menopausal women with ER-positive, HER2-negative advanced breast cancer receiving blinded treatment (palbociclib or placebo) in combination with letrozole as the first-line treatment of their disease, there were ten deaths among a total of 666 patients. One patient (Subject No. 12501001) experienced two fatal SAEs - lower respiratory tract infection and pulmonary embolism, which were considered to be related to blinded treatment by the Investigator but not the Sponsor. Another patient experienced fatal SAEs of pneumonia and respiratory failure which were considered to be related to blinded treatment by both the Investigator and Sponsor. Pulmonary embolism was the only SAE associated with on-study death experienced by more than one patient (n=2). One patient experienced a fatal SAE of myocardial infarction which was not considered related to blinded treatment; another patient experienced fatal SAEs of bacterial peritonitis and general physical health deterioration which were not considered to be related to blinded treatment.

In the ongoing open-label expanded access study 1034 in postmenopausal women with HR-positive, HER2-negative advanced breast cancer receiving palbociclib in combination with letrozole, eight of a total of 238 patients died within 28 days of receiving palbociclib. Five patients died from disease progression. Additional causes of death include respiratory failure,

pancytopenia, and hypercalcemia which were considered by the Investigator and Sponsor to be related to disease progression.

Table 27. Summary of Deaths in Sponsor-Initiated Studies in Patients with Breast Cancer

Study	Population	N Deaths[1]	Total N Subjects
A5481003	Advanced Breast Cancer	1[2]	95
A5481008	Advanced Breast Cancer	10[3]	666
A5481023	Advanced Breast Cancer	7[4]	517
A5481027	Asian Advanced Breast Cancer	0	20
A5481034	Advanced Breast Cancer	8[5]	238

[1]Deaths occurred during the period from the start of treatment up to and including 28 days after the last dose
[2]Patient received palbociclib plus letrozole; there were no deaths in the letrozole alone arm
[3]Blinded therapy; patients either received palbociclib or placebo
[4]Randomized 2:1; 4 deaths in palbociclib plus fulvestrant arm and 3 deaths in placebo plus fulvestrant arm
[5]Expanded access protocol; all patients received palbociclib plus letrozole
Source: 90-Day Safety Update

Table 28. Causes of Death in Sponsor-Initiated Studies in Patients with Breast Cancer

Deaths within 28 days	
Palbociclib (n=686)[1]	
Respiratory Failure	1
Bacterial Peritonitis, Physical Health Deterioration	1
DIC	1
Disease progression	6
Pancytopenia	1
Hypercalcemia	1
Pneumonia, Respiratory failure[2]	1
Neutropenic sepsis	1
Total deaths	13 (1.9%)
Palbociclib or Placebo (n=666)[3]	
Bacterial Peritonitis, Physical Health Deterioration	1
Cardiac arrest	1
Cardiogenic shock	1
Cardiopulmonary Failure	1
Disease progression	1
Myocardial infarction	1

Pneumonia	1
Pneumonia, Respiratory Failure, Anemia	1
Pulmonary Embolism	2[4]
Total deaths	10 (1.5%)
Placebo or letrozole alone (n=249)[5]	
Disease Progression	2
Intracerebral hemorrhage	1
Total deaths	3 (1.2%)

[1] Includes patients randomized to palbociclib arm in Study 1003 and 1023, patients in Study 1027, and patients in Expanded Access Protocol 1034.
[2] Considered by the Investigator as related to palbociclib therapy; all other AEs leading to death in this section of the table were considered not related to protocol directed therapy.
[3] Includes patients from ongoing randomized Study 1008.
[4] Includes one patient with concurrent lower respiratory tract infection.
[5] Includes patients randomized to placebo plus fulvestrant in Study 1023 as well as patients randomized to letrozole alone in Study 1003.
Source: 90-Day Safety Update

Deaths in the Investigator-Initiated Research (IIR) Studies in patients with Breast Cancer

As of July 31st, 2015 a total of 3 patients died on investigator-initiated research studies with palbociclib for the treatment of breast cancer. The events with a fatal outcome were disease progression (n=2) and respiratory failure considered most likely related to disease progression (n=1). Neither the investigator nor the Sponsor considered the events to be related to protocol directed therapy.

8.4.2. 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 53 (15.4%) patients receiving palbociclib plus fulvestrant and 31 (18%) of patients receiving placebo plus fulvestrant. No SAE occurred in >2% of patients and most SAEs reported were experienced by 1 patient each. The most frequently reported SAEs in the palbociclib plus fulvestrant arm were pyrexia (1.4%), neutropenia (1.2%), and pulmonary embolism (0.9%). The most frequently reported SAEs in the fulvestrant arm were pleural effusion (1.7%), ascites (1.7%), pneumonia (1.2%), and pathological fracture (1.2%). Neutropenia and thromboembolic events will be discussed further below.

Table 29. Serious Adverse Events Occurring in >1 Patients Sorted by Descending Frequency in the Palbociclib plus Fulvestrant Arm

	Palbociclib plus Fulvestrant N=345	Placebo plus Fulvestrant N=172
Any	53 (15%)	31 (18%)
Pyrexia	5	1
Neutropenia	4	0
Pulmonary embolism	3	0
Deep vein thrombosis	2	0
Disease progression	2	0
Dyspnea	2	1
Febrile neutropenia	2	1
General physical health deterioration	2	0
Pharyngitis	2	0
Pleural effusion	2	3
Suicide attempt	2	0
Pneumonia	1	2
Ascites	0	3
Pathological Fracture	0	2

Includes data up to 28 days of last dose of study drug.
Source: 90-Day Safety Update, pages 53-54

8.4.3. 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.

Table 30. Summary of TEAEs Associated with Permanent Discontinuation from Treatment in Patients Receiving Palbociclib plus Fulvestrant

	Palbociclib plus Fulvestrant N=345
Any	19 (5.5%)
Fatigue	2
Thrombocytopenia	2
Infections	2
Anemia	1
ALT increased	1
Bone pain	1
Breast mass	1
Disease progression	1
Drug-induced liver injury	1
Dyspnea	1
Endometrial cancer	1
Erysipelas	1
General physical health deterioration	1
Liver disorder	1
Nausea	1
Neutropenia	1
Pneumonia	1
Rectal cancer	1
Seizure	1
Suicide attempt	1
Vocal cord paralysis	1
White blood cell count decreased	1

Source: 90-day Safety Update, modified Table 17, page 57

As of July 31st, 2015 a total of 128 patients (37%) in the palbociclib plus fulvestrant arm had their palbociclib dose reduced. One hundred eighteen patients (34%) had their dose reduced from 125mg QD to 100mg QD, and 41 patients (12%) had their dose reduced from 125mg QD to 100mg QD and further to 75mg QD. In addition, 13 patients (3.8%) had their palbociclib dose regimen changed from schedule 3/1 to Schedule 2/2 (2 weeks on palbociclib treatment followed by 2 weeks off treatment). In the placebo plus fulvestrant arm, only three patients (1.7%) had their placebo dose reduced.

The most common AEs associated with dose reductions in the palbociclib plus fulvestrant arm were neutropenia (25%) followed by neutrophil count decreased (7%) and WBC count decreased (3%). The only Grade 4 events associated with palbociclib dose reduction were

neutropenia and neutrophil count decreased, which occurred in 15 (4%) of patients. A summary of TEAEs associated with palbociclib/placebo dose reduction is shown in Table 17 below.

Table 31. Summary of TEAEs Associated with Dose Reduction Experienced by at Least 2 Patients in Either Treatment Arm, Sorted by Decreasing Frequency in the Palbociclib plus Fulvestrant Arm

	Palbociclib plus Fulvestrant N=345		Placebo plus Fulvestrant N=172	
	All Grades	Grade 3-4	All Grades	Grades 3-4
Any	124 (36%)	105 (30%)	3 (1.7%)	1 (0.6%)
Neutropenia	86	77	0	0
Neutrophil count decreased	24	23	0	0
WBC count decreased	9	5	1	0
Thrombocytopenia	4	1	0	0
Leukopenia	3	3	1	0
Stomatitis	2	1	0	0

Source: 90-Day Safety Update, modified Table 18, page 60.

The most common adverse events leading to a temporary discontinuation of treatment in the palbociclib plus fulvestrant arm were neutropenia (45.2%), neutrophil count decrease (14.5%), and WBC count decrease (8.1%). In the placebo plus fulvestrant arm, temporary discontinuations occurred most frequently due to pneumonia (2.3%) and influenza (1.2%). The incidence of dose delays is comparable to other studies of palbociclib.

8.4.4. Significant Adverse Events

The most common Grade 3/4 TEAEs observed following treatment with palbociclib plus fulvestrant were neutropenia and leukopenia. The rate of Grade 3/4 neutropenia was 66% (56% Grade 3, 11% Grade 4) and the rate of Grade 3/4 leukopenia was 31% (30% Grade 3, 1% Grade 4) in the palbociclib plus fulvestrant arm. The rate of Grade 3/4 neutropenia and leukopenia was 1% each in the placebo plus fulvestrant arm. (Note: The cluster term Neutropenia used herein comprises MedDRA PTs Neutropenia and Neutrophil Count Decreased, and the cluster term Leukopenia used herein comprises MedDRA PTs Leukopenia and WBC Count Decreased).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Table 18 provides a summary of commonly reported treatment-related AEs regardless of severity grade experienced by at least 5% of patients in either treatment arm of Study 1023 as of July 31st, 2015 sorted by MedDRA System Organ Class then relative frequency. Overall, 94.2% of patients in the palbociclib plus fulvestrant arm and 67.4% of patients in the placebo plus fulvestrant arm experienced at least 1 TEAE.

Table 32. Summary of Treatment Emergent AEs in Study 1023

System Organ Class Preferred Term	**Palbociclib 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[1]	47.0	2.6	0.6	30.8	2.9	0
Blood and Lymphatic System Disorders						
Febrile neutropenia	0.9	0.9	0	0.6	0	0.6
Neutropenia[2]	83.2	55.9	10.7	4.1	0.6	0
Leukopenia[3]	53.0	29.9	0.6	5.2	0.6	0.6
Anemia[4]	29.3	3.2	0	12.2	1.2	0
Thrombocytopenia[5]	22.6	1.7	0.6	0	0	0
Eye disorders						
Lacrimation increased	6.4	0	0	1.2	0	0
Vision blurred	5.8	0	0	1.2	0	0
Dry eye	3.8	0	0	1.7	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	15.7	0.9	0	8.1	0.6	0
Nervous System disorders						
Headache	26.1	0.6	0	20.9	0	0
Dysgeusia	6.7	0	0	2.9	0	0
Gastrointestinal disorders						
Nausea	33.9	0	0	27.9	1	0
Stomatitis[6]	28.4	0.6	0	13.4	0	0
Diarrhea	23.5	0	0	19.2	1.2	0
Constipation	20.0	0	0	15.7	0	0
Vomiting	18.8	0.6	0	15.1	0.6	0
Dry mouth	5.8	0	0	5.8	0	0

Skin and subcutaneous disorders						
Alopecia	18.0[7]	NA	NA	6.4[8]	NA	NA
Hot flush	17.4	0	0	17.1	0	0
Rash [9]	16.8	0.6	0	6.4	0	0
Dry Skin	6.1	0	0	1.2	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	6.7	0	0	1.7	0	0
General Disorders and administrative site conditions						
Fatigue	41.2	2.3	0	29.1	1.2	0
Pyrexia	12.8	0.3	0	5.2	0	0
Arthralgia	8.1	0	0	8.1	0	0
Asthenia	7.5	0	0	5.2	0.6	0
Injection site pain	6.1	0.3	0	5.8	0	0
Myalgia	4.9	0	0	5.2	0	0

[1] Infection includes all PTs that are part of the System Organ Class Infections and infestations.
[2] Neutropenia includes the following PTs: Neutropenia, Neutrophil count decreased.
[3] Leukopenia includes the following PTs: Leukopenia, White blood cell count decreased.
[4] Anemia includes the following PTs: Anemia, hemoglobin decreased, hematocrit decreased.
[5] Thrombocytopenia includes the following PTs: Thrombocytopenia, platelet count decreased.
[6] Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.
[7] Grade 1 events – 17%; Grade 2 events – 1%.
[8] Grade 1 events – 6%
[9] Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.
Source: AE dataset submitted with 90-Day Safety Update (ADVERS.xpt)

The most frequently reported TEAEs (i.e. ≥ 20% of patients) in the palbociclib plus fulvestrant arm were neutropenia (83%), leukopenia (53%), infections (47%), fatigue (41%), nausea (34%), anemia (29%), stomatitis (28%), headache (28%), diarrhea (24%), thrombocytopenia (23%), and constipation (20%). The most frequently reported TEAEs (i.e. ≥ 20% of patients) in the placebo plus fulvestrant arm were infections (31%), fatigue (29%), and nausea (28%). The following common TEAEs were reported substantially more frequently (i.e. ≥ 10% difference in frequency) for the palbociclib plus fulvestrant arm than for the placebo plus fulvestrant arm: neutropenia, leukopenia, anemia, thrombocytopenia, infections, fatigue, stomatitis, alopecia, and rash.

Reviewer's Comment: *In early February the Sponsor submitted results of their quality control audit of the 90-Day Safety Update. Based on this audit, the final label contains numbers slightly different from those reported in Table 32 above. These minor changes are summarized below:*

- *Incidence of Grade 3 Neutropenia in the palbociclib arm was 55% (down from 56%).*
- *Incidence of Anemia (all grades) was 13% in the placebo arm (up from 12%).*
- *Incidence of Grade 3 Anemia in the placebo arm was 2% (up from 1%).*
- *Incidence of Vision blurred (all grades) in the placebo arm was 2% (up from 1%).*

8.4.6. Laboratory Findings

Overall, abnormal hematologic laboratory abnormal were more commonly observed for patients in the palbociclib plus fulvestrant arm, compared with those in the placebo plus fulvestrant arm. Almost all patients in the palbociclib plus fulvestrant arm with hematologic laboratory tests available for evaluation had abnormal absolute neutrophil counts (96.2%) and white blood cell counts (98.5%). With the exception of abnormal absolute neutrophil count and white blood cells, most abnormal hematologic findings were Grade 1/2 severity. ANC counts of Grade 3 severity were observed for more than half of the patients (56%) in that treatment arm; in addition, Grade 4 neutrophil counts were observed for 11% of the patients receiving palbociclib plus fulvestrant.

Table 33. Summary of Abnormal Clinical Hematology Laboratory Findings by Maximum Severity Grade in Study 1023

	Palbociclib plus Fulvestrant (N=345)		Placebo plus Fulvestrant (N=172)	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
WBC decreased	99	46	26	1
Neutrophils decreased	96	67	14	1
Anemia	78	3	40	2
Platelets decreased	62	3	10	0

Source: 90-Day Safety Update, modified Table 36, page 94

Hematologic laboratory data were also reviewed in terms of shifts from Grade ≤2 at baseline to Grade ≥3 post-baseline. Overall, more shifts in clinical hematology test results were observed in the palbociclib plus fulvestrant arm than in the placebo plus fulvestrant arm, with the majority of results in the palbociclib plus fulvestrant arm shifting from Grade ≤2 at baseline to Grade 3 post-baseline. Most shifts from Grade ≤2 at baseline to Grade 4 post-baseline were observed in that treatment arm for absolute neutrophil counts (10.6%). A few shifts in neutrophil counts from Grade ≤2 at baseline to Grade 4 post-baseline were also observed for patients in the placebo plus fulvestrant arm (1.2%).

Reviewer comments: *Overall, the abnormal clinical hematology laboratory findings are generally consistent with the corresponding abnormal clinical findings reported as TEAEs.*

Abnormal clinical chemistry findings observed in this study as of July 31st, 2015 are summarized

by maximum severity grade in Table 34.

Table 34. Summary of Abnormal Clinical Chemistry Laboratory Findings by Maximum Severity Grade in Study 1023

	Palbociclib plus Fulvestrant (N=345)		Placebo plus Fulvestrant (N=172)	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
ALT	36	2	34	0
Alkaline phosphatase	33	1	40	1
AST	43	4	48	4
Bilirubin	9	1	7	2
Creatinine	94	1	83	0
Hypercalcemia	14	<1	12	0
Hyperkalemia	12	1	9	1
Hypermagnesemia	11	1	11	1
Hypernatremia	13	0	12	0
Hypoalbuminemia	21	0	21	1
Hypocalcemia	26	0	15	1
Hypokalemia	16	0	15	0
Hypomagnesemia	21	0	16	0
Hyponatremia	21	3	18	2

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase.
Source: 90-Day Safety Update

Abnormal clinical chemistry laboratory findings were also reviewed in terms of shifts from Grade ≤2 at baseline to Grade ≥3 post-baseline. Such shifts were infrequent in either treatment arm. A shift from Grade ≤2 at baseline to Grade 4 post-baseline was observed for one patient in the palbociclib plus fulvestrant arm; this patient had a shift in total bilirubin from outside of the Grading range at baseline to Grade 4 post-baseline.

Preclinical evidence suggested that ocular toxicities in patients receiving palbociclib may be due to altered glucose metabolism. In order to further explore this association, glycosylated hemoglobin levels were measured and reported after the 2nd amendment. As of July 31st, 2015 there was only one case of elevated HgbA1c, and this patient received placebo plus fulvestrant arm.

Reviewer comments:
Overall, there were comparable proportions of patients between the treatment arms with abnormal values based on the data reported. Our review of the effect of palbociclib on glucose metabolism is limited due to lack of information provided by the Sponsor. Despite the preclinical

evidence suggesting that ocular toxicities in patients receiving palbociclib may be due to altered glucose metabolism, serum glucose measurements were not recorded in this study. However, it is reassuring that there were no cases of elevated HgbA1c reported in the palbociclib arm as of July 31st, 2015.

8.4.7. Vital Signs

Overall, the mean and median blood pressure, pulse rate, and weight were well balanced between the two treatment arms at baseline. The median values for each vital sign measurement in each treatment cycle were generally comparable between the treatment arms. No clinically relevant changes from baseline in any of the vital sign measurements were observed in either treatment arm as of July 31st, 2015.

8.4.8. Electrocardiograms (ECGs)

Twelve-lead triplicate ECG recordings were performed in patients in Study 1023 at screening and at the end of treatment. Clinically relevant ECG findings observed in Study 1023 were reported as TEAEs and discussed in Sections 8.4.1 and 8.4.2.

8.4.9. QT

A QTc analysis was performed on the CTc Analysis Set as part of the original palbociclib submission. Palbociclib at 125mg QD did not substantially affect the QTc interval.

In Study 1023 one patient in the palbociclib plus fulvestrant arm experienced an SAE of Grade 3 Electrocardiogram QT prolonged that coincided with a Grade 2 SAE of pericarditis and resolved to Grade 1 within 2 days. Palbociclib therapy was temporarily discontinued in response to these events and was subsequently restarted, although at a reduced dose of 100mg QD. No additional cases of Electrocardiogram QT prolonged were reported in Study 1023 as of July 31st, 2015.

8.4.10. Immunogenicity

Not applicable

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Neutropenia

Consistent with the pharmacologic activity of palbociclib (i.e. cell cycle inhibition), myelosuppression is observed in clinical studies of palbociclib. Neutropenia reported in Study 1023 comprises the MedDRA PTs of Neutropenia and Neutrophil count decreased. The data based on clinical laboratory tests of absolute neutrophil counts will also be reported here.

The frequency of neutropenia in Study 1023 was substantially higher in the palbociclib plus fulvestrant arm (83%) compared to the placebo plus fulvestrant arm (4%). The majority of neutropenia events in the palbociclib arm were Grade 3 (56%) or Grade 4 (11%) and most were considered treatment related. In the palbociclib plus fulvestrant arm, three (0.9%) patients experienced febrile neutropenia and one (0.3%) patient experienced Grade 4 neutropenia associated with permanent discontinuation from treatment. Most cases of Grade 3/4 neutropenia were managed by dose reduction, dosing interruption, and/or treatment cycle delay. Only one case of neutropenia led to treatment discontinuation.

Based on clinical laboratory findings in Study 1023, 326/339 patients (96%) in the palbociclib plus fulvestrant had abnormal absolute neutrophil counts (ANC), including 189 (56%) with Grade 3 decreases and 36 (11%) with Grade 4 decreases. In comparison, 23/167 (14%) patients in the placebo plus fulvestrant arm had abnormal ANC of whom none had Grade 3 decreases and two (1.2%) had Grade 4 decreases.

Baseline characteristics among patients in the palbociclib plus fulvestrant arm who had or did not have abnormal absolute neutrophil counts of Grade 3/4 maximum severity were comparable as demonstrated in Table 21 below.

Table 35. Baseline Characteristics for Subjects with and without Grade 3/4 Neutropenia

	Palbociclib plus Fulvestrant (N=345)		**Placebo plus Fulvestrant (N=172)**	
	With Grade 3/4 Neutropenia (n=225)	Without Grade 3/4 Neutropenia (n=120)	With Grade 3/4 Neutropenia (n=2)	Without Grade 3/4 Neutropenia (N=170)
Subjects with prior chemo, %				
Yes	72	72	100	78
No	27	28	0	22
Age, %				
≤ 65	80	74	100	77
>65	20	26	0	24
ECOG PS, %				
0	59	60	50	67
1	41	40	50	33

Source: 90-Day Safety Update, modified Table 14.3.2.1.4.2.

The shortest time from first dose of palbociclib/placebo to onset for neutropenia of any severity grade was similar between the palbociclib plus fulvestrant arm (13 days) and the placebo plus fulvestrant arm (15 days). In the palbociclib plus fulvestrant arm, the median time from first dose of palbociclib to onset of first neutropenia episode of any severity grade was

shorter than one treatment cycle (Any grade - 15 days; Grade ≥ 2 - 15 days; Grade ≥ 3 - 16 days; Grade 4 - 19 days). In the placebo plus fulvestrant arm, the median times from first dose to onset of first neutropenia episode of any grade severity was 211 days.

The median duration of any grade neutropenia by patient (i.e. duration of all episodes combined) reported in the palbociclib plus fulvestrant arm was 179 (3-573) days across all cycles, while the median duration of Grade ≥ 3 neutropenia and Grade 4 neutropenia across all cycles was 21 (1-167) days and 10.5 (2-28) days, respectively. The duration of neutropenia by patient regardless of severity grade was longer than 1 treatment cycle in most patients (94%) who had neutropenia in the palbociclib plus fulvestrant arm. The median duration of any grade neutropenia by episode reported in the palbociclib plus fulvestrant arm was 15 (1-287) days. Overall, neutropenia persisted for longer than half of total treatment duration, as the median ratio of duration of any grade neutropenia to duration of treatment was 69.5% (2.8%-160%) for patients in the palbociclib plus fulvestrant arm. The median time to recovery (i.e. >1500 ANC) from lowest neutrophil count among patients with Grade ≥ 3 neutropenia in the palbociclib arm was 36 (3-449) days. Forty-two (12.2%) patients were treated with a colony stimulating factor (e.g. filgrastim, pegfilgrastim) for neutropenia.

Febrile neutropenia was experienced by three patients in the palbociclib plus fulvestrant arm of Study 1023 (Cycle 1 Week 3, Cycle 5 Week 4, and Cycle 5 Week 5). All three cases of febrile neutropenia were Grade 3 and considered to be related to treatment with palbociclib. One patient in the placebo plus fulvestrant arm of this study experienced febrile neutropenia of Grade 4 severity, and this event was not considered to be related to treatment.

No TEAEs of neutropenic sepsis were reported in either treatment arm of Study 1023. However, as discussed previously there was one case of treatment emergent fatal neutropenic sepsis and multi-organ failure in a patient receiving palbociclib plus fulvestrant (Subject No. 11661006). Neither the Investigator nor the Sponsor consider these events to be related to treatment.

Reviewer comment: *Although neutropenia is very common on the palbociclib arm, it is reassuring that most cases resolved within 2-3 weeks without significant complications.*

8.5.2. Infections

Overall, more patients in the palbociclib plus fulvestrant arm experienced TEAEs within the MedDRA SOC Infections and Infestations as of the July 31st, 2015 cut-off (47% vs. 34%, respectively). The TEAEs coding to PTs within the SOC Infections and Infestations experienced by at least two patients in either treatment arm of Study 1023 are summarized in Table 22 below.

Table 36. Infections Experienced by ≥ 2 Patients in Study 1023

	Palbociclib plus Fulvestrant (N=345)		Placebo plus Fulvestrant (N=172)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any	162 (47%)	11 (3%)	53 (31%)	5 (3%)
Nasopharyngitis	45	0	14	0
URI	32	2	12	0
UTI	26	0	11	1
Bronchitis	11	0	3	0
Rhinitis	10	0	2	0
Influenza	9	0	8	0
Conjunctivitis	8	1	3	0
Sinusitis	8	0	2	0
Cystitis	6	0	2	0
Oral Herpes	6	0	1	0
Pneumonia	6	1	4	1
Respiratory Tract Infection	5	0	1	0
Gastroenteritis	5	0	0	0
Pharyngitis	5	1	0	0
Tooth infection	5	0	0	0
Eye infection	4	0	0	0
Herpes Simplex	4	0	0	0
Paronychia	4	0	0	0
Candida infection	3	0	0	0
Cellulitis	3	1	0	0
Gingivitis	3	0	0	0
Gastrointestinal infection	2	0	1	1
Erysipelas	2	1	0	0
Furuncle	2	0	0	0
Herpes Zoster	2	0	1	0
Lymphangitis	2	0	0	0
Oral Candidiasis	2	0	0	0
Tooth abscess	2	0	0	0
Viral infection	2	1	1	0
Gastroenteritis viral	1	0	2	0

URI: upper respiratory tract infection; UTI: urinary tract infection
Source: AE dataset submitted with 90-Day Safety Update (ADVERS.xpt)

No TEAEs of neutropenic infection were reported by the Sponsor in either treatment arm of

Study 1023. However, 50 (14%) patients in the palbociclib plus fulvestrant arm were reported to have Grade 3/4 neutropenia overlapping with any grade TEAEs within SOC Infections and Infestations. No patients in the placebo plus fulvestrant arm were reported to have Grade 3/4 neutropenia overlapping with any grade TEAEs within SOC Infections and Infestations. Two patients in the palbociclib arm experienced a Grade 3 or 4 infection in the setting of Grade 3 neutropenia and their narratives are summarized below. There were no cases of Grade 3 or 4 infection in the setting of Grade 4 neutropenia.

Grade 4 Cellulitis in Setting of Grade 3 Neutropenia
Subject 10071003 was a 44-year-old Caucasian woman who received palbociclib from Nov 21st, 2013 – Dec 20th, 2013. She had no significant past medical history other than breast cancer. On (b) (6) she was hospitalized for cellulitis of the left arm in the setting of Grade 3 Neutropenia. Palbociclib was withdrawn temporarily and she was treated with Keflex 500mg bid. She was discharged on (b) (6) and she recovered on Jan 15th, 2014. The Investigator and Sponsor agreed there was not a reasonable possibility that the event was related to palbociclib. The patient was withdrawn from study on Jan 15th, 2014 due to progressive disease.

Grade 3 Erysipelas in Setting of Grade 3 Neutropenia Leading to Permanent Discontinuation
Subject 11581002 was a 70-year-old woman of unspecified ethnicity who received palbociclib from Mar 13th, 2014 – July 15th, 2014. On July 15th, 2014 patient experienced swelling, pain, and erythema of right lower extremity in the setting of Grade 3 Neutropenia. She was diagnosed with erysipelas and hospitalized on (b) (6). She was treated with IV benzylpenicillin and discharged on (b) (6) on an oral antibiotic regimen consisting of augmentin, phenethicillin, and rifampin. On July 29th, 2014 the erysipelas showed no improvement and antibiotic regimen was switched to ciprofloxacin. On Aug 5th, 2014, patient began to show improvement in erysipelas. Patient was subsequently withdrawn from study due to a greater than three week treatment delay. The Investigator and Sponsor agree that there is a reasonable possibility that the event was related to palbociclib.

An evaluation of neutropenia based on clinical laboratory findings overlapping with TEAEs coding to PTs within the SOC Infections and Infestations is shown in Table 23 below.

Table 37. Summary of Neutropenia (Based on Clinical Laboratory Findings) Overlapping with TEAEs within the MedDRA SOC Infections and Infestations

	Palbociclib plus Fulvestrant (N=345)	Placebo plus Fulvestrant (N=172)
Any grade neutropenia	326	18
Overlapping with any Grade TEAEs within the SOC Infections and Infestations		
Yes	132 (41%)	2 (11%)
No	194 (59%)	16 (89%)
Overlapping with Grade 3/4 TEAEs within the SOC Infections and Infestations		
Yes	8 (2.5%)	0
No	318 (97.5%)	18 (100%)
Grade 3/4 Neutropenia	225	2
Overlapping with any Grade TEAEs within the SOC Infections and Infestations		
Yes	50 (22%)	0
No	127 (78%)	2 (100%)
Overlapping with Grade 3/4 TEAEs within the SOC Infections and Infestations		
Yes	3 (1%)	0
No	222 (99%)	2 (100%)

Source: 90-Day Safety Update, modified Table 29, page 79

As shown in Table 23 above, nearly half of patients (41%) who had a laboratory finding of neutropenia in the palbociclib plus fulvestrant arm experienced a concomitant TEAE within the MedDRA SOC Infections and Infestations. A total of 8 patients (2.5%) with any severity grade neutropenia experienced a concomitant Grade 3/4 TEAE within this SOC. The majority of patients with Grade 3/4 Neutropenia (78%) in the palbociclib plus fulvestrant arm did not experience concomitant TEAEs within the SOC Infections and Infestations, with only three patients (1.3%) experiencing a concomitant Grade 3/4 TEAE with this SOC (Grade 3 Erysipelas and Grade 4 Cellulitis both described above, as well as a Grade 3 Upper respiratory tract infection).

Reviewer comment: *It is reassuring that the overall rates of Grade 3/4 infections are low and only 3 patients (<1%) experienced a Grade 3 or 4 infection in the setting of concomitant Grade 3 or 4 neutropenia.*

8.5.3. Thrombocytopenia

Thrombocytopenia was reported in 86 (25%) patients receiving palbociclib plus fulvestrant in Study 1023, while no cases of thrombocytopenia were reported in the placebo plus fulvestrant arm. As shown in Table 18, most cases were of Grade 1/2 severity. Neither Grade 3 nor Grade 4 thrombocytopenia events were associated with bleeding episodes (based on hemorrhagic terms). One patient experiencing Grade 3 thrombocytopenia was permanently discontinued from treatment, while three patients with Grade 3 thrombocytopenia and one patient with Grade 4 thrombocytopenia had their dose reduced/interrupted or had their treatment cycle delayed.

8.5.4. Eye Disorders

Eye disorders were more frequently reported in patients in the palbociclib plus fulvestrant arm (22%) than in the placebo plus fulvestrant arm (11%). As shown in Table 24 below, the most frequently reported TEAEs within the SOC Eye Disorders for the palbociclib plus placebo arm were Lacrimation increased (6.4%), Vision blurred (5.8%), Dry eye (3.8%), and Eye irritation (2.0%). The most frequently reported TEAEs within this SOC in the placebo plus fulvestrant arm were Dry eye (1.7%), Lacrimation increased (1.2%) and Vision blurred (1.2%). No grade 3/4 Eye disorders were reported for either treatment arm.

Table 38. Summary of TEAEs within the MedDRA SOC Eye Disorders Experienced by ≥ 2 Patients Sorted by Descending Frequency in the Palbociclib plus Fulvestrant Arm

	Palbociclib plus Fulvestrant (N=345)	Placebo plus Fulvestrant (N=172)
Any	77 (22%)	18 (11%)
Lacrimation increased	22	2
Vision blurred	20	2
Dry eye	13	3
Eye Irritation	7	0
Visual impairment	6	1
Diplopia	5	0
Eye Pain	3	2
Vitreous floaters	3	2
Cataract	2	0
Eye pruritus	2	0
Retinal degeneration	2	0
Visual acuity reduced	2	0

Source: AE dataset with 90-Day Safety Update (ADVERS.xpt)

Nonclinical findings in rats support the notion that cataracts/lens degeneration was associated with altered glucose metabolism (glycosuria and/or hyperglycemia) in the setting of palbociclib

exposure. A further association was found between glucose metabolism and pancreatic islet vacuolation leading to beta cell depletion and decreases in serum insulin and C-peptide. Reversibility was not established for the changes in glucose homeostasis or the effects on the pancreas and eye following a 3-month recovery period.

Hyperglycemia

As of July 31st, 2015 a total of five patients (1.4%) in the palbociclib plus fulvestrant arm and four patients (2.3%) in the placebo plus fulvestrant arm were reported to experience hyperglycemia. In each treatment arm, all but one TEAE of hyperglycemia were of Grade 1 severity. The remaining patients (one in each treatment arm) experienced Grade 3 hyperglycemia. Diabetes mellitus (grade 1) was experienced by one patient (0.3%) in the palbociclib plus fulvestrant arm and an increase in HgbA1c was experienced by 1 patient (0.6%) in the placebo plus fulvestrant arm. None of the patients who experienced cataracts in the palbociclib plus fulvestrant arm experienced any hyperglycemia-related events.

8.5.5. Venous Thromboembolic Events

As of July 31st, 2015, there were a total of 3 pulmonary embolisms reported in Study 1023, all 3 of which were in the palbociclib plus fulvestrant arm and all three were categorized as SAEs. Two of three were asymptomatic and discovered incidentally. Each event is summarized below.

Subject 11661005 is a 50-year-old Caucasian woman who began therapy with palbcociclib on June 21st, 2014. On Sept 18th, 2014 a Chest CT was performed due to persistant complaints of dyspnea. CT revealed moderate segmental and subsegmental PE with right lower lobe predominance. The patient was treated with anticoagulation and no action was taken with blinded therapy and fulvestrant in response to the event. The patient recovered from the event on Jan 27th, 2015.

Subject 10101005 is a 65-year-old Caucasian woman who began therapy with palbociclib on Apr 17th, 2014. On Aug 3rd a schedule (16-week) CT of chest/abdomen/pelvis) revealed a small pulmonary embolus. The PE was an incidental finding and the patient was asymptomatic. The patient was treated with anticoagulation and no action was taken with blinded therapy and fulvestrant in response to the event. The patient recovered from the event on Aug 5th, 2014.

Subject 12611004 is a 58-year-old woman of unspecified ethnicity who began therapy with palbociclib on Jun 4th, 2014. On July 22nd, the patient went off treatment due to symptomatic disease progression. On [redacted] (b) (6) a CT of chest/abdomen/pelvis (as part of end-of-treatment evaluation) revealed a filling defect within the right main pulmonary artery, extending to the segmental branches of the right limb. The patient was asymptomatic. She was admitted for further management and treated with anticoagulation. The patient recovered from the event on May 18, 2015.

Reviewer comment: *A similar numerical increase in rate of PE with palbociclib was also observed in Study 1003 (4.8% in palbociclib plus letrozole arm vs. 0% in letrozole alone arm) and ongoing Study 1008, including 2 deaths due to blinded treatment in the latter. Taken together, these results suggest that palbociclib may increase the risk of pulmonary embolism. The label includes pulmonary embolism under "Warnings and Precautions."*

Deep venous thrombosis was experienced by two patients in the palbociclib plus fulvestrant arm. In addition, Embolism, Subclavian vein thrombosis, and Vena cava thrombosis were experienced by 1 patient each in the palbociclib arm. In the placebo plus fulvestrant arm, Pelvic venous thrombosis was experienced by 1 patient. No other venous thromboembolic events were experienced by patients receiving placebo in Study 1023 as of the July 31st, 2015 cut-off.

8.5.6. Skin and Subcutaneous Tissue Disorders

Skin and subcutaneous tissue disorders were more frequently reported in patients in the palbociclib plus fulvestrant arm (46%) than in the placebo plus fulvestrant arm (21%). As shown in Table 25 below, the most frequently reported TEAEs within the SOC Skin and Subcutaneous Tissue Disorders for both arms were Alopecia, Rash, Pruritus, and Dry skin. Only two events in the palbociclib plus fulvestrant arm were considered Grade 3; the remaining TEAEs were Grade 1 or 2. Subject 11821001 experienced a Grade 3 rash that lasted 12 days and required a treatment interruption, and Subject 12141003 experienced Grade 3 rash maculo-papular that lasted 8 days and required a dose reduction. No Grade 3/4 Skin and subcutaneous tissue disorders were reported in the placebo plus fulvestrant arm.

Table 39. Summary of TEAEs within the MedDRA SOC Skin and Subcutaneous Tissue Disorders Experienced by ≥ 2 Patients Sorted by Descending Frequency in the Palbociclib plus Fulvestrant arm

	Palbociclib plus Fulvestrant (N=345)	Placebo plus Fulvestrant (N=172)
Any	159 (46%)	36 (21%)
Alopecia	62	11
Rash[1]	59	11
Pruritus	26	11
Dry Skin	21	2
Erythema	9	2
Night sweats	9	1
Skin lesion	6	1
Hyperhidrosis	5	2
Pain of skin	5	0
Palmar-plantar erythrodysaesthesia syndrome	5	1

Skin ulcer	4	0
Ingrowing nail	3	0
Onychoclasis	3	0

[1] Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.
Source: AE dataset with 90-Day Safety Update

8.6. Safety Analyses by Demographic Subgroups

Age
Safety data reported in Study 1023 were analyzed by age (<65 and ≥65 years old). The overall frequencies of TEAEs, SAEs, and AEs associated with permanent discontinuation were generally comparable between the two age groups within the palbociclib plus fulvestrant arm. In addition, the overall rates of dose reduction/modification and temporary discontinuation from treatment associated with TEAEs were also generally comparable between the two age groups in that treatment arm.

In the palbociclib plus fulvestrant arm of Study 1023, nausea was the only TEAE experienced substantially more frequently (i.e. >10% difference in TEAE frequency) by patients younger than 65 years of age (37.1%) than by those 65 years of age or older (24.4%). Alopecia and Dyspnea were the TEAEs experienced substantially more frequently by patients 65 years of age or older (25.6% and 23.3%, respectively) than by those younger than 65 years of age (15.4% and 10.0%, respectively). Most hematologic TEAEs were reported substantially more frequently in the palbociclib plus fulvestrant arm than in the placebo plus fulvestrant arm regardless of age group.

Sex
No analysis of palbociclib safety data with regard to patients' were performed on the data from Study 1023 since all patients in this study were women. However, palbociclib has been studied in 85 males as part of Studies 1001 (n=36; advanced solid tumor malignancy), 1002 (n=14; mantle cell lymphoma), 1004 (n=30; multiple myeloma), 1010 (Phase1, Part1 n=5; advanced solid tumor malignancy) as well as in several Investigator-Initiated Research (IIR) studies. Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients) from Studies 1001, 1002, and 1003, gender had no effect on the exposure of palbociclib. In addition, the safety profile in male patients has been consistent with the safety profile seen in palbociclib across the development program.

Race
Safety data from Study 1023 were also analyzed by Race (White, Black, Asian, and Other). Most patients participating in either treatment arm of this study were White (72.6% in the palbociclib plus fulvestrant arm and 76.4% in the placebo plus fulvestrant arm). The second largest race group in this study was Asian (21.3% in the palbociclib plus fulvestrant arm and 17.8% in the placebo plus fulvestrant arm). Because of the small number of patients whose race was Black

(N = 12 in the palbociclib plus fulvestrant arm and N = 8 in the placebo plus fulvestrant arm), no reliable observations or comparisons could be made regarding the safety profile of palbociclib plus fulvestrant in patients of that race.

A comparison of data between White and Asian patients within the palbociclib plus fulvestrant arm is summarized in Table 26. There was a higher overall Grade 3/4 TEAE frequency in Asian patients (94.5%) than in White patients (71.3%), although the overall TEAE frequency was similar between the 2 race groups (98.4% for White patients and 100% for Asian patients). These differences were not appreciated in the placebo plus fulvestrant arm.

Table 40. Summary of TEAE by Race Group Reported in the Palbociclib plus Fulvestrant Arm in Study 1023

	Palbociclib plus Fulvestrant (N=345) Number (%) of Patients	
Patient category	White (N=251)	Asian (N=73)
Any TEAE	247 (98.4)	73 (100)
Grade 3/4 TEAE	179 (71.3)	69 (94.5)
Grade 5 TEAE	2 (0.8)	1 (1.4)
Any SAE	36 (14.3)	13 (17.8)
Discontinued palbociclib due to TEAEs	12 (4.8)	3 (4.1)
Discontinued fulvestrant due to TEAEs	10 (4.0)	3 (4.1)

Source: 90-Day Safety Update, modified Table 47, page 111

8.7. 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 their disease. As of July 31st, 2015 at least 20 patients have received at least one blinded treatment. This study in ongoing in China and will provide additional safety data specific to the patient population in China.

In addition, there is an ongoing Phase I 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.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

See Pharmacology/Toxicology Review.

8.8.2. Human Reproduction and Pregnancy

See Pharmacology/Toxicology Review.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
No accidental overdoses were reported in Study 1023.

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.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Palbociclib received accelerated approval in February 2015 for the treatment of postmenopausal women with ER-positive, HER2-negative, advanced breast cancer as initial endocrine-based therapy for their metastatic disease. Overall, approximately 10,000 patients received palbociclib in the US post-marketing setting from February 2015 – July 2015 (excluding patients in clinical trials receiving drug outside of commercial channels and patients receiving drug through compassionate use mechanism). The most recent quarterly NDA paper was submitted in December 2015 and covered the period from Aug 3rd, 2015 through Nov 2nd, 2015. During that period 248 safety reports were submitted. In addition, 146 initial and 102 follow up 15 Day Alerts were submitted during this period.

Reviewer comment: *The cumulative postmarket safety data of palbociclib reviewed were generally consistent with those understood with palbociclib use for its approved indication and did not raise any new safety concerns.*

8.9.2. Expectations on Safety in the Postmarket Setting

Not applicable

8.10. Additional Safety Issues From Other Disciplines

Not applicable

8.11. 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

No advisory committee meeting was held for this sNDA.

10 Labeling Recommendations

10.1. Prescribing Information

There were several internal labeling discussions. Labeling negotiations were ongoing at the time of this review and have not been finalized. Key clinical labeling recommendations include:

1. Revise the proposed indication to add the following to the already approved 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 fulvestrant in women with disease progression following endocrine therapy".* These changes were made from the initial indication submitted by the Applicant for this sNDA for the following reasons:

(b) (4)

2. Include PFS results from the updated analysis (March 16, 2015) as it provides a more complete follow-up.

(b) (4)

[redacted]

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)

None

11.1. Safety Issue(s) that Warrant Consideration of a REMS

11.2. Conditions of Use to Address Safety Issue(s)

None.

11.3. Recommendations on REMS

None.

12 Postmarketing Requirements and Commitments

The clinical team recommends the following Postmarketing Commitment (PMC):

1. Submit the final overall survival analysis with datasets and results 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."

Rationale: The final OS results of Trial A5481023 (PALOMA-3) will be important to further understand the clinical meaningfulness of palbociclib treatment in combination with fulvestrant.

The following post-marketing requirement was included in the previous accelerated approval for palbociclib.

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.

The following post-marketing commitment was included in the previous accelerated approval for palbociclib.

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

13 Appendices

13.1. References

1. Siegel R., Miller K., Jemal A. Cancer Statistics, 2016. Cancer J Clin ; 66 7-30. (2016)
2. SEER Cancer Statistics Database: Breast Cancer http://seer.cancer.gov/statfacts/html/breast.html (2016)
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4. Singh JC, Jhaveri K, Esteva FJ. HER2-positive advanced breast cancer: optimizing patient outcomes and opportunities for drug development. British J of Cancer; 111, 1888-1898. (2014)
5. Burstein HJ. The distinctive nature of HER2-positive breast cancer. N Engl J Med; (353), 1652-54. (2005)
6. Beaver J., Amiri-Kordestani L., Chen R., et al. FDA Approval: Palbociclib for the Treatment of Postmenopausal Patients with Estrogen Receptor-Positive, HER2-Negative Metastatic Breast Cancer. Clin Cancer Res; 21, 4760-6. (2015)
7. Vidula N., Rugo HS. Cyclin-Dependent Kinase 4/6 Inhibitors for the Treatment of Breast Cancer: A Review of Preclinical and Clinical Data. Clin Breast Cancer; 16, 8-17. (2016)
8. Law ME., Corsino PE, Narayan S, et al. Cyclin-Dependent Kinase Inhibitors as Anticancer Therapeutics. Mol Pharmacol; 88(5), 846-52. (2015)
9. Wright GL, Blum J, et al. PD01-01: Randomized Phase II Trial of Fulvestrant with or without Dasatinib in Postmenopausal Patients with Hormone Receptor-Positive Metastatic Breast Cancer Previously Treated with an Aromatase Inhibitor. Cancer Res; 71 (24 Suppl): Abstract. (2011)
10. FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm193282.pdf
11. Basch E, Snyder C, McNiff K, et al. Patient-Reported Outcome Performance Measures in Oncology. J Oncol Practice; 10, 209-211. (2014)

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study A5481023 (PALOMA-3)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1232		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 3 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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

/s/

SUPARNA B WEDAM
02/11/2016

AMANDA J WALKER
02/11/2016

LALEH AMIRI KORDESTANI
02/11/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 207103	Applicant: Pfizer	Stamp Date: 10/15/2015
Drug Name: Ibrance® (palbociclib)	NDA Type: Supplement	505(b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?				
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms: Location in submission:			X	
EFFICACY					
16.	Do there appear to be the requisite number of adequate and	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1 A5481023 Indication: In combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced/metastatic breast cancer who have received prior therapy Pivotal Study #2 Indication:				
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?	X			
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary[2] used for	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	mapping investigator verbatim terms to preferred terms?				
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?			X	
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			

(verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

SUPARNA B WEDAM
11/10/2015

AMANDA J WALKER
11/10/2015

LALEH AMIRI KORDESTANI
11/10/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207103Orig1s002

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-002**

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Supplement	Efficacy Supplement	15-Oct-2015	15-Oct-2015	15-Oct-2015	29-Apr-2016	02-Feb-2016

3. **Proposed Changes**: It is an efficacy supplement. It seeks approval for (b) (4) 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 (b) (4)

4. **Review #:**1

5. **Clinical Review Division**: DOP1

6. **Name and Address of Applicant**:

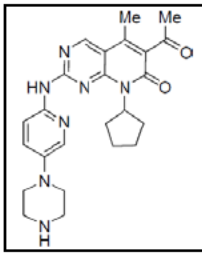
Pfizer, Inc.

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**:

	**USAN:** palbociclib **Chemical name:** pyrido[2,3-*d*]pyrimidin-7(8*H*)-one, 6-acetyl-8-cyclopentyl-5-methyl-2-[[5-(1-piperazinyl)-2-pyridinyl]amino]- **Molecular formula:** $C_{24}H_{29}N_7O_2$ **MW:** 447.54 g/mole

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 approval for (b) (4)

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 (b) applicable for action on an NDA resulting in an increase in use but the estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 part per billion. The calculated Expected Introduction Concentration (EIC) is provided in the attachment. The applicant claims that to the best of its knowledge no extraordinary circumstances exist. The claim for claims 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:
Reviewer's name, Xiao Hong Chen, Branch 2, Division of New Drug Products I, Office of New Drug Products, Office of Pharmaceutical Quality (OPQ)

Xiaohong Chen -A

Digitally signed by Xiaohong Chen -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiaohong Chen -A, 0.9.2342.19200300.100.1.1=1300133168
Date: 2016.02.02 09:26:37 -05'00'

Attachment

Projected Total Usage at Peak Market: 2000 kg/yr
Basis for Expected Introduction Concentration (EIC) Into The External Aquatic environment:

Expected Introduction Concentration (EIC)

$EIC_{aquatic}$ = 4.5 x 10-5 mg/ L calculated as follows:

$EIC_{aquatic}$ (ppm) = A X B X C X D

Where

A= kg/yr usage (2000 kg/year)
B= 1/ liters per day entering POTW*
C = years/ 365 days
D =1 X 106 mg/kg (conversion factor)
* 1.22 X 1011 liters per day entering POTW

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207103Orig1s002

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	207103/S-02
Supporting document/s:	1
Applicant's letter date:	October 14, 2015
CDER stamp date:	October 15, 2015
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, DABT (acting)
	(Geoffrey Kim, MD)
Project Manager:	Amy Tilley

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 20103/S-02 are owned by Pfizer Inc. or are data for Pfizer Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 207103/S-02 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-02.

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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. Palbociclib in combination with letrozole was approved 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 (b) (4) Results from a Phase 3 trial (PALOMA-3) assessing the safety and efficacy of palbociclib plus fulvestrant or placebo plus fulvestrant in women with HR-positive, HER2-negative advanced breast cancer regardless of their menopausal status was submitted with this application to support the approval of the proposed indication.

The proposed label in this application also included changes of nonclinical information. A male fertility assessment in rats and other nonclinical studies were submitted to support the changes in the proposed label. In addition, hematological toxicities, especially neutropenia, have been identified as dose-limiting for palbociclib in clinical trials. Microscopic bone marrow hypocellularity has been identified in nonclinical studies with palbociclib. To aid in understanding the mechanism by which the hematological toxicity occurs, and to further differentiate it from myelotoxicity caused by cytotoxic chemotherapeutic agents, an in vitro system using human bone marrow mononuclear cells was utilized to evaluate the cellular mechanism and reversibility of bone marrow suppression induced by palbociclib, and the study results were submitted with this application.

1.2 Brief Discussion of Nonclinical Findings

Nonclinical studies including 27-week repeat-dose study in rats, 39-week repeat-dose study in dogs and fertility study in male rats were submitted in this application. Refer to the pharmacology/toxicology review of NDA 207103 (1/17/2015) for the result of the 27-week rat toxicology study.

In the 39-week repeat-dose toxicity study in dogs, no severe toxicities were observed in animals treated with PD332991 at doses up to 3 mg/kg. The bone marrow, lymphoid tissues, and male reproductive organs were the target organs associated with primary palbociclib-related toxicities. Decreases in cellularity in the bone marrow and lymphoid tissues in the spleen were associated with the hematological changes. Male reproductive organ effects included degeneration of seminiferous tubules in the testes and hypospermia and increased intratubular cellular debris in the epididymis. The toxicities in the male reproductive system were observed in dogs at ≥ 0.2 mg/kg, with 0.05 times the human exposures at the recommended dose. Partial to complete reversibility of findings in the hematolymphopoietic and male reproductive systems was

demonstrated following a 12-week recovery period. The altered glucose metabolism and related effects on the pancreas, eye, teeth, kidney, and adipose tissue observed in rats were not observed in dogs at dose levels up to 3 mg/kg for treatment duration up to 39 weeks. The altered glucose metabolism and related effects may be species specific, or the plasma exposure of PD332991 in dogs at the HD was not high enough to induce these toxicities, as the plasma exposure in HD dogs was 2310 ng.h/mL, while the lowest AUC at which kidney toxicity associated with altered glucose occurred in the 27-week rat study was 6000 ng.h/mL.

The adverse effects of palbociclib on the male reproductive system were observed in rats and dogs in the repeat-dose toxicology studies. The effects of palbociclib on fertility were further evaluated in male rats administered doses up to 100 mg/kg/day for a total of 15 weeks with the same dosing regimen used in patients. Treated males were paired with untreated females for 5 days during the last 2 weeks of the dosing period. Seminiferous tubule degeneration in the testis and increases in cellular debris and hypospermia in the epididymides were identified at ≥ 30 mg/kg/day. These effects correlated with macroscopic changes in the testis and lower male reproductive organ weights, sperm motility, cauda epididymal sperm density and testicular spermatid density at 100 mg/kg. There were no effects on mating or embryonic survival at any dose level. Fertility index was lower (89%) when untreated females were mated with treated males at 100 mg/kg, compared to 100% in treated males at control or lower dose groups. The NOAEL for male reproductive toxicity in this study was 10 mg/kg/day with a mean plasma concentration of 360 ng/mL at 4 hours postdose on study day 12, and estimated AUC of 3600 ng.h/mL (based on the TK data from 15-week rat general toxicology study), which was about 1.9 fold of the clinically relevant exposures.

A study on the mechanism of bone marrow toxicity was evaluated in vitro. Treatment of human bone marrow mononuclear cells (hBMNCs) with palbociclib at concentrations up to 1 μM caused a concentration-dependent increase of cells in G1 phase, and decrease in S and G2/M phases, consistent with G1 cell cycle arrest. This was characterized by a fully reversible, concentration-dependent inhibition of proliferation without apoptosis, cellular senescence, or DNA damage. Treatment of hBMNCs with cytotoxic chemotherapeutic agents caused increases in DNA damage and apoptosis that resulted in concentration-dependent inhibition of proliferation with minimal recovery after a 4-day treatment-free period. In MCF-7 breast cancer cells, palbociclib and cytotoxic chemotherapy agents similarly caused a concentration-dependent inhibition of cell proliferation, minimal induction of apoptosis and significant concentration-dependent increase in cellular senescence. The hBMNC response to palbociclib did not change when combined with fulvestrant, as shown by comparable effects of palbociclib alone on cell viability, lack of cellular senescence, and full recovery of proliferation. By contrast, MCF-7 breast cancer cells treated with palbociclib and fulvestrant showed additive reductions in cell viability and increases in cellular senescence. Partial regrowth of MCF-7 cells was observed following a 5-day treatment-free period; however, minimal to no recovery occurred while cells continued treatment with fulvestrant alone during the 5-day period.

1.3 Recommendations

1.3.1 Approvability

Recommending approval. The nonclinical studies adequately support the safety of oral palbociclib in women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

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 review for NDA 207103 (1/17/2015).

Since the male fertility index was decreased compared to concurrent control and there were corroborating effects on the male reproductive organs in repeat-dose toxicity studies, this finding was included in the product label despite the fact that this was within the historical control range for fertility index of 78.3-100% provided by the Applicant.

The Applicant proposed to change the duration of contraception use following the last dose of palbociclib in females of reproductive potential from 2 to 3 weeks. This was based on the aneugenic mechanism of genotoxicity of palbociclib. The window of sensitivity for an aneugen spans periovulation to approximately 24 hours after the end of ovulation when the unfertilized oocyte is destroyed (Marchetti et al. 2015). On a molecular level, the sensitive stage of oocyte maturation is the transition between end of meiosis I and beginning of meiosis II, which corresponds to approximately 14 days (The Developing Human: Clinically Oriented Embryology, 10th edition). Thus, 21 days of contraception post treatment was proposed to allow for clearance (5 half-lives or approximately 7 days) and account for the sensitive stage of oocyte development. This proposed change was acceptable.

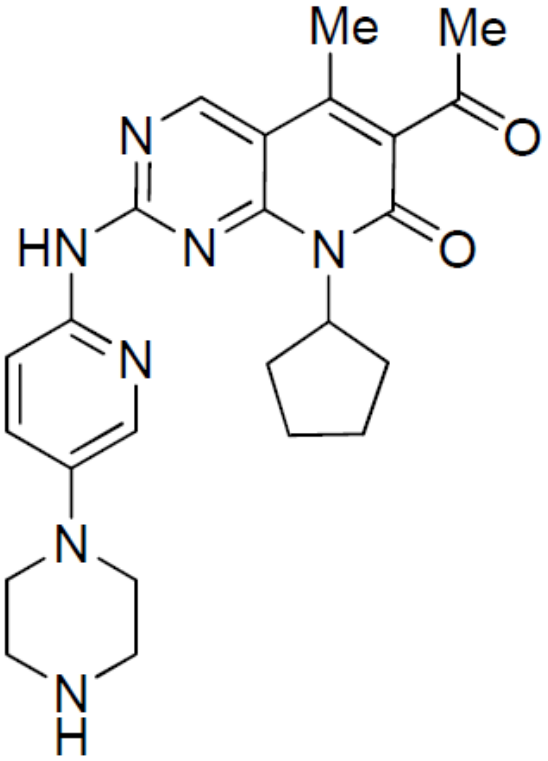
Contraception use in males with female partners of reproductive potential for 3 months after the last dose of palbociclib was added to the label based on two periods of spermatogenesis.

The term “teratogenic” was removed from the risk summary in section 8.1 upon the Applicant’s request. This was based on a re-evaluation of the findings in the embryo-fetal developmental toxicity studies in rats and rabbits. The skeletal variations observed in the presence of maternal toxicity are thought to be related to maternal toxicity and may be secondary effects. In addition, those findings are expected to resolve later in development and are not likely to lead to permanent effects in the offspring. Refer to the pharmacology/toxicology review of NDA 207103 (1/17/2015) for details about the findings in these studies.

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 (b) (4)

Route of administration: oral

APPEARS THIS WAY ON ORIGINAL

2 Studies Submitted

Studies Reviewed

Pharmacology

	Title	Study no.	Folder/file name
1*	Mechanistic investigation of bone marrow suppression associated with palbociclib	14LJ125	M4.2.3.7

*submitted in "other toxicology studies"

Toxicology studies

Repeat dose

	Title	Study no.	Folder/file name
1**	27-week oral gavage chronic toxicity and toxicokinetic study with PD-0332991 in rats with a 12-week recovery phase	8282224	M4.2.3.2
2	39-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study with PD-0332991 in Dogs with a 12-Week Recovery Phase	8282225	M4.2.3.2

**Reviewed under NDA 207103 (the nonclinical review 1/17/2015)

Reproductive and development toxicity

	Title	Study no.	Folder/file name
1	A Fertility and Early Embryonic Development Study of PD-0332991 by Oral Gavage in Male Rats	20057548	M4.2.3.5

Studies submitted, but not reviewed

Pharmacology

	Title	Study no.	Folder/file name
1	Palbociclib (PD-0332991) biochemical potency evaluation toward CDK4/6 and expanded human kinome selectivity analysis	133827	M4.2.1.1

Pharmacokinetics

	Title	Study no.	Folder/fil name
1	Partial Validation of a Method for the Determination of PD-0332991 in Dog Plasma (K2-EDTA) by Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)	1400244	M4.2.2.2

4 Pharmacology

4.1 Primary Pharmacology

Title: Mechanistic investigation of bone marrow suppression associated with palbociclib

Study Number: 14LJ125

Test facility**:** Pfizer Worldwide Research & Development
Drug Safety Research & Development
10777 Science Center Drive
San Diego, CA USA

Final approval date: May 26, 2015

Method: An in vitro bone marrow toxicity assay was utilized to evaluate the cellular mechanism and the reversibility of bone marrow suppression induced by palbociclib as a single agent or in combination with anti-estrogens. In addition, the differential effects of palbociclib and antiestrogens on bone marrow cells and breast cancer cells, as well as their effects versus cytotoxic chemotherapy agents on bone marrow cells were investigated.

The cell cultures used in the study include human bone marrow mononuclear cells (a heterogeneous population that includes hematopoietic lineage cells such as lymphocytes, monocytes, stem cells and progenitor cells), human bone marrow hematopoietic stem cells (CD34+), and MCF7 breast cancer cells. The types of in vitro assays and the detail method used for each assay are described in the result section with the study result of each assay.

Results: The following tables and figures were copied from the Applicant's submission.

The effects of palbociclib on human bone marrow mononuclear cells

In Vitro Cell Cycle Analysis - The cell cycle analysis was conducted using propidium iodide (PI) DNA staining dye. Human bone marrow mononuclear cells were fixed with 70% ethanol overnight at -20ºC, followed by washing with PBS and ribonuclease digestion at 37 ºC for 30 minutes. Cells were stained with 50 µg/ml PI and the percentage of cells in each cell cycle phase was quantitated at 10,000 events per sample in triplicates using flow cytometry.

Table 1 Cell cycle analysis in human bone marrow mononuclear cells treated with palbociclib for 4 days

	Dead Cell	G1 Phase	S Phase	G2/M Phase
Vehicle	6.25% (± 0.59%)	53.96% (± 2.33%)	27.93% (± 0.98%)	11.75% (± 1.91%)
Palbociclib 0.1uM	4.32% (± 0.84%)	60.98% (± 3.32%)	20.61% (± 0.84%)	13.19% (± 1.72%)
Palbociclib 0.3uM	4.66% (± 0.14%)	67.4% (± 2.04%)	16.10% (± 1.49%)	7.04% (± 0.39%)
Palbociclib 1uM	4.68% (± 1.17%)	79.23% (± 1.17%)	9.99% (± 2.59%)	4.55% (± 0.73%)

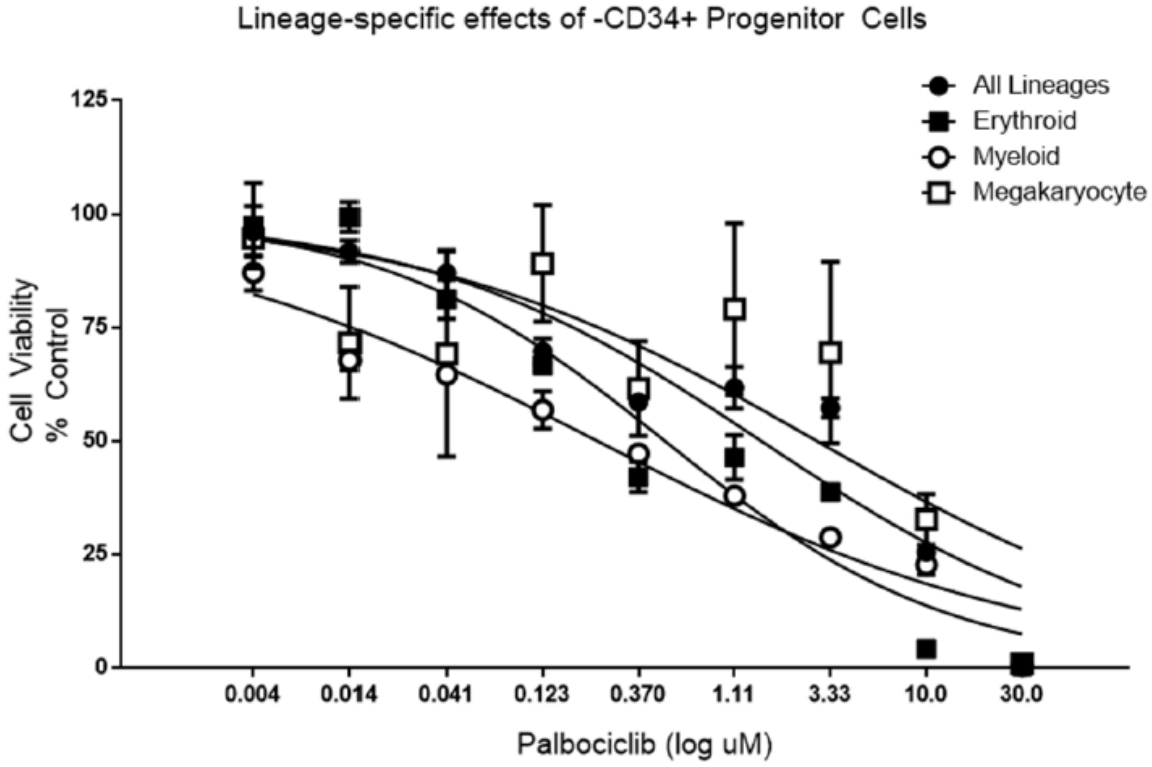
Summary: treatment of human bone marrow mononuclear cells with palbociclib caused a dose-dependent increase in G1 phase, and decrease in S and G2/M phases, with no change in percent of dead cells.

Evaluation of lineage-specific effects of palbociclib in human bone marrow CD34+ hematopoietic stem cells

In vitro testing of lineage specific effects - The human bone marrow hematopoietic stem cells (CD34+) were stimulated with the following cytokines for four days to induce lineage-specific differentiation:

SCF, EPO, and IL-3 for erythroid lineage
SCF, G-CSF, GM-CSF, IL-3 and Flt3 ligand for myeloid lineage
SCF, TPO and IL-3 for megakyrocyte lineage
SCF, EPO, G-CSF, GM-CSF, TPO, IL-3 and Flt3 ligand for all lineages
Cells were subjected to palbociclib treatment for 5 days and cytotoxicity was measured.

Figure 1 Assessment of lineage-specific effects of palbociclib treatment in human bone marrow Hematopoietic stem cells



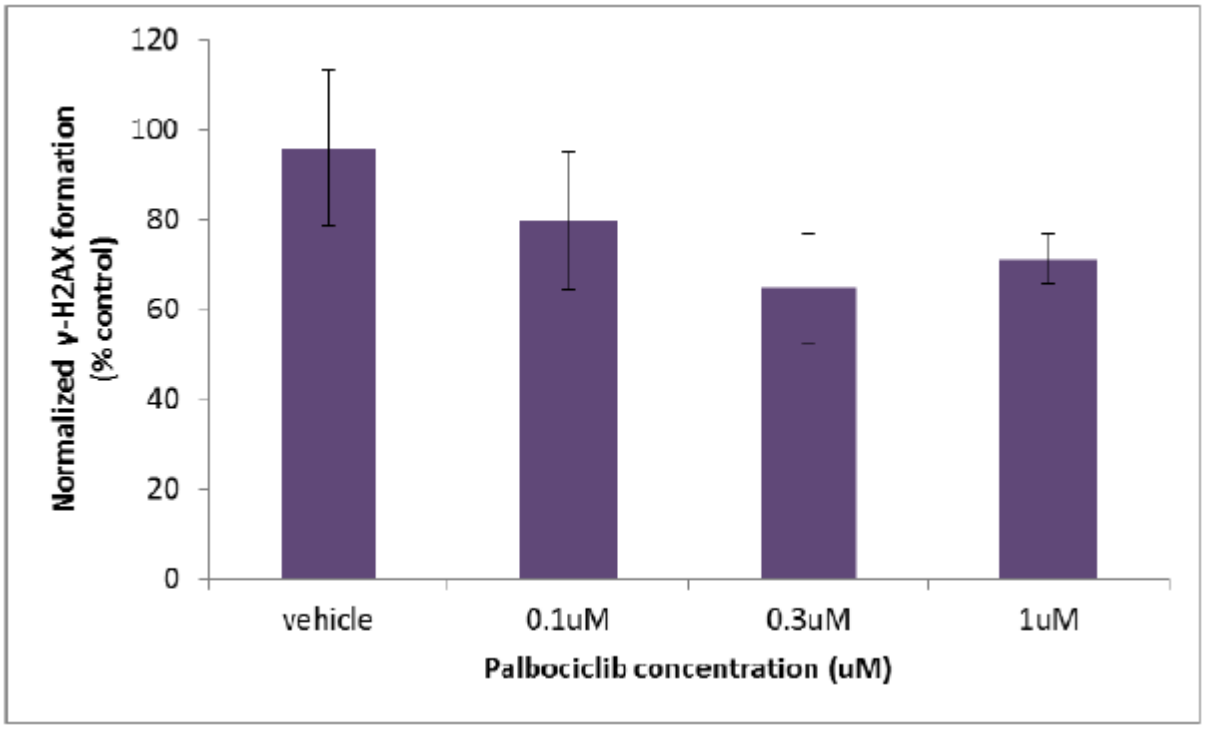
Summary: No individual lineage appears more sensitive to the anti-proliferative effects of palbociclib than the others.

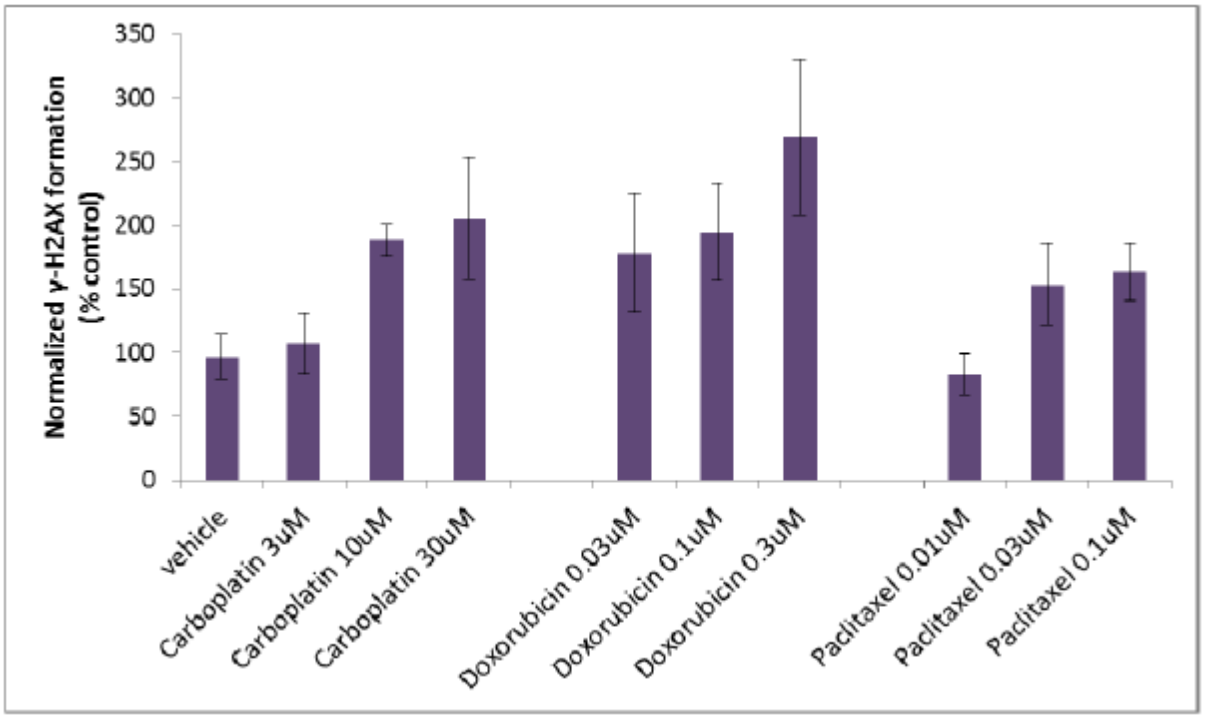
Cellular mechanism comparison in human bone marrow mononuclear cells: palbociclib vs. cytotoxic chemotherapeutic agents

The effects on DNA damage

In Vitro DNA Damage Assay - Following treatment, cells were washed with cold PBS followed by fixation and permeabilization at 4 ºC for 2 hours. DNA damage response was determined by quantification of the γ-H2AX (pS139) phosphorylation using flow cytometry (BD Biosciences).

Figure 2 Effects of palbociclib and cytotoxic chemotherapeutic agents on DNA damage response in human bone marrow mononuclear cells





Summary: Palbociclib at concentrations up to 1 μM caused no induction of DNA-damage response, while the cytotoxic chemotherapeutic agents, carboplatin, paclitaxel and doxorubicin, caused concentration-dependent induction of DNA-damage response after 48 hours of exposure.

Anti-proliferative, apoptotic and cellular senescence effects

In Vitro Proliferation Assay - The effect on cell proliferation was determined by measuring DNA synthesis using the ClickiT® plus EdU flow cytometry assay kit.

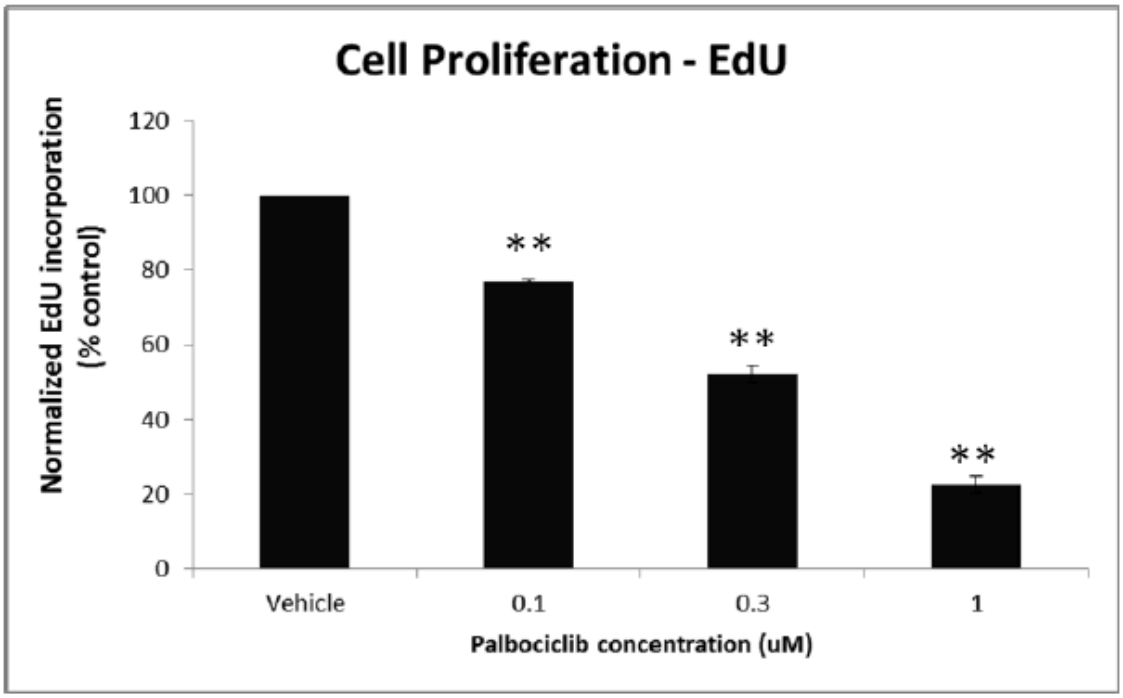
In Vitro Apoptosis Assay - Following compound incubation, cells were collected, washed, and stained with FITC Annexin V and propidium iodide. Samples were analyzed by flow cytometery and the percent of cells stained positive for Annexin V was calculated with 10,000 events per sample, in triplicates.

Caspase 3/7 activation assay - Following compound treatment for 1, 3, or 5 days, 25 ul of solubilized caspase 3/7 substrate was added to each well of the 384-well plate containing 50 ul of cell suspension, and allowed to incubate at room temperature for 30 minutes. The bioluminescence was measured using a Safire2 microplate reader.

In Vitro Cellular Senescence Assay - Cellular senescence was measured using the quantitative cellular senescence assay kit (CBA-232) and detected by flow cytometry at excitation of 485 nm and emission of 520 nM or using the 96-well cellular senescence assay kit and detected in a TECAN multi-plate reader at excitation 360 nm and emission 465 nm.

Figure 3 Evaluation of anti-proliferative, apoptotic and cellular senescence effects of palbociclib in human bone marrow mononuclear cells

A



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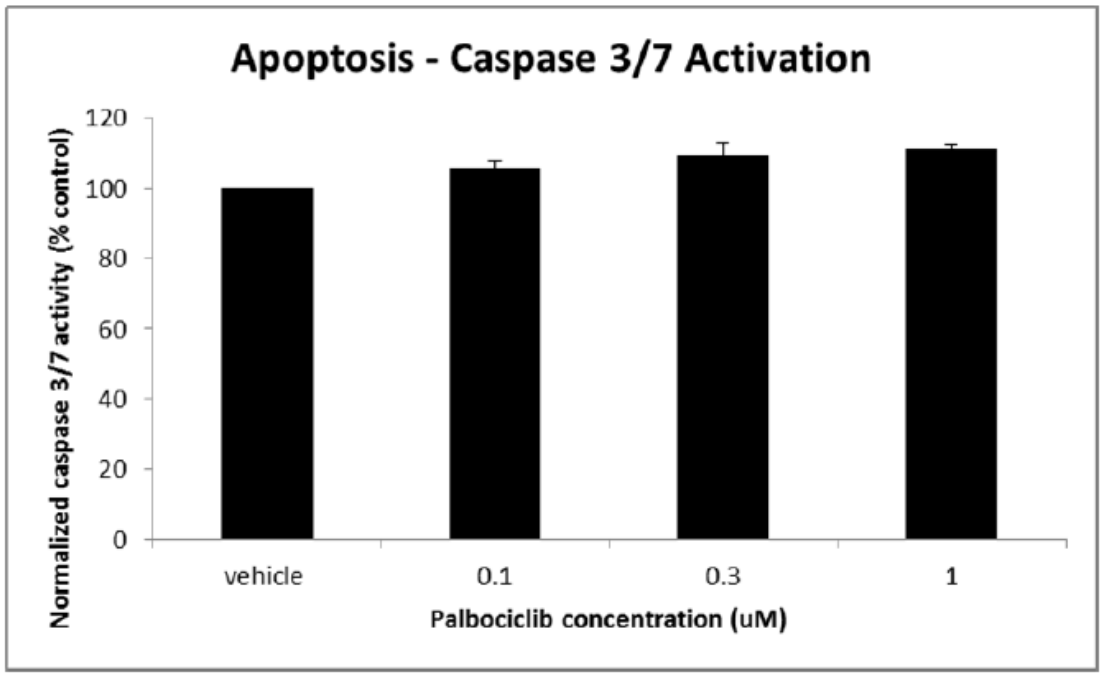

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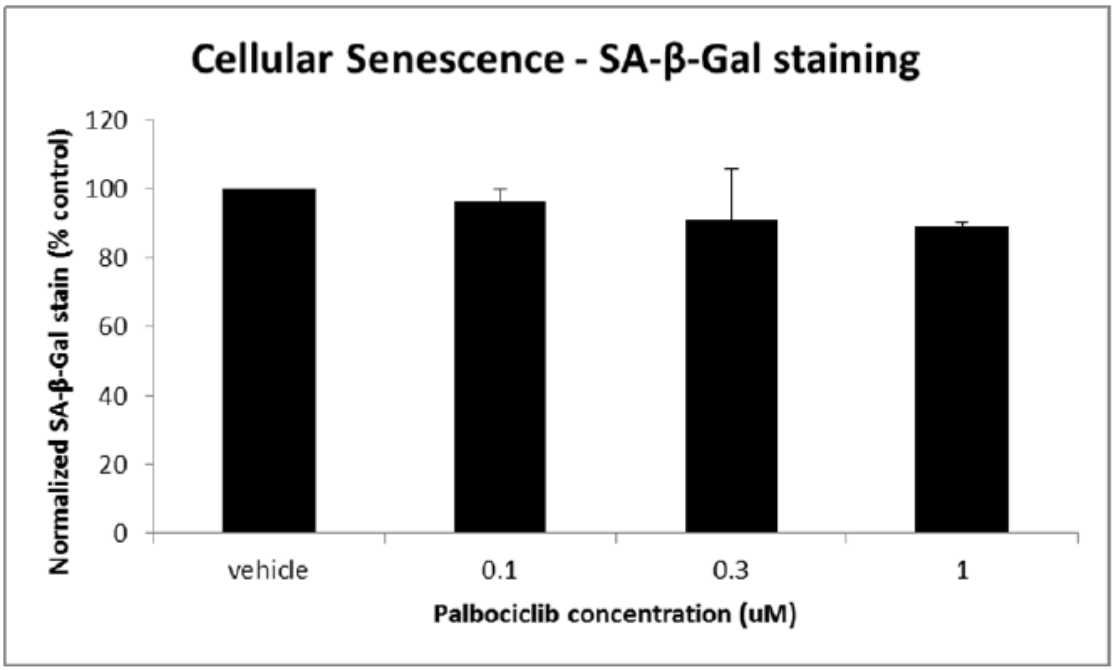
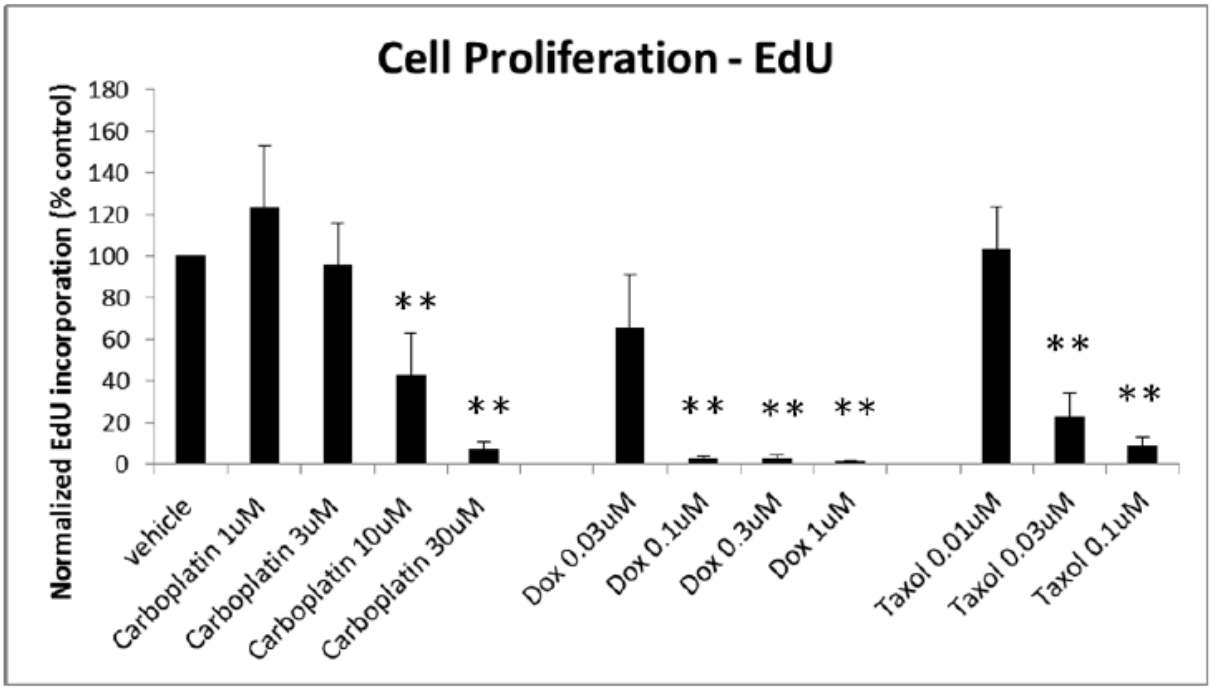


Summary: Treatment of human bone marrow mononuclear cells with palbociclib caused dose-dependent inhibition of proliferation as measured by EdU incorporation. Palbociclib treatment at concentrations up to 1 μM caused no significant induction of apoptosis or cellular senescence, as measured by caspase 3/7 activity and SA-β-gal staining, respectively.

Figure 4 Evaluation of anti-proliferative, apoptotic and cellular senescence effects of cytotoxic chemotherapies in human bone marrow mononuclear cells

A



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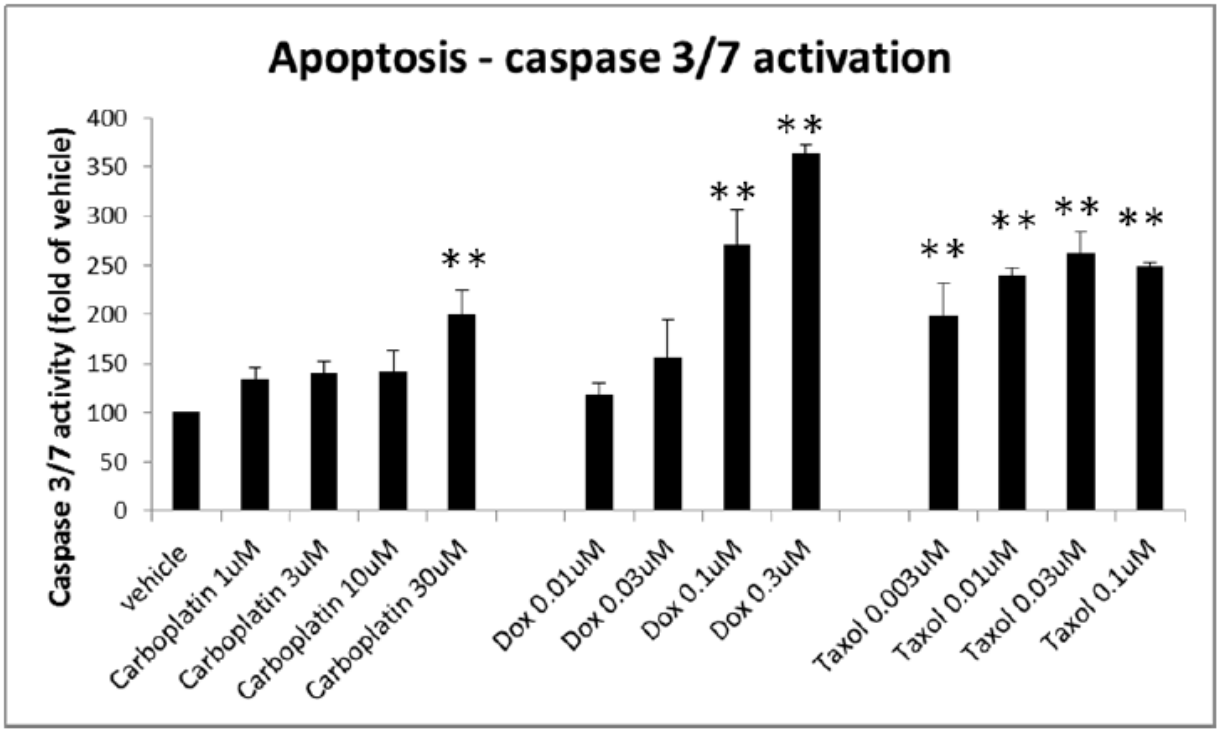

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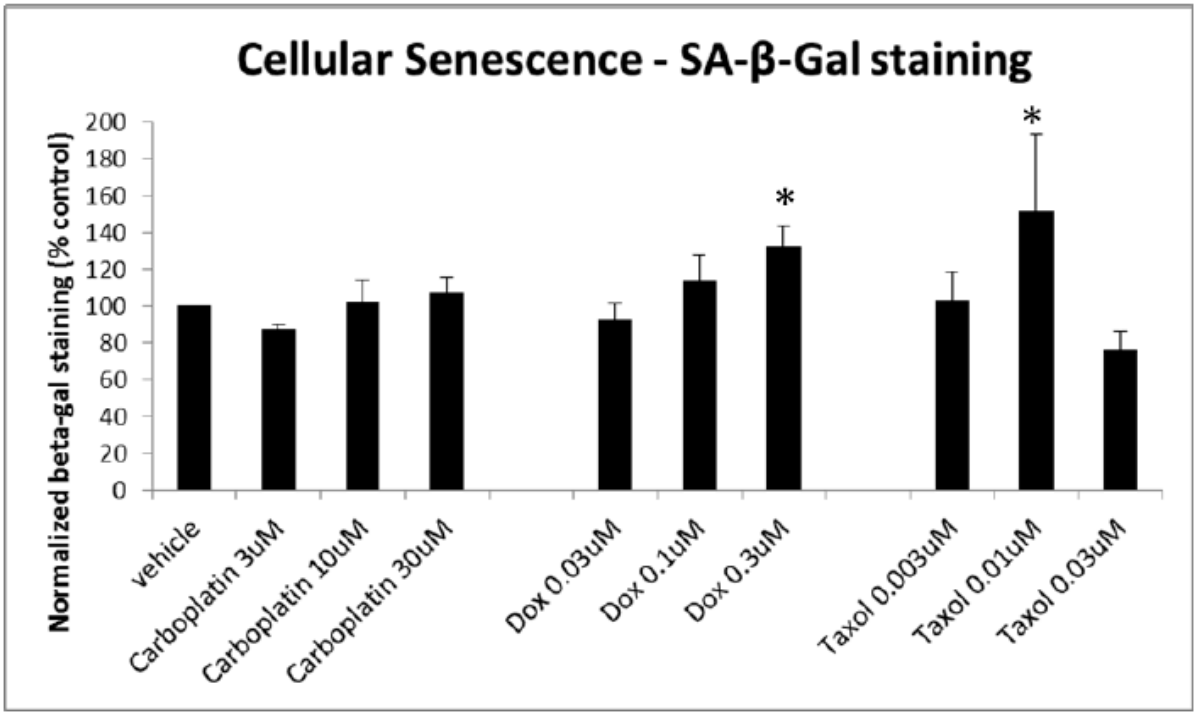


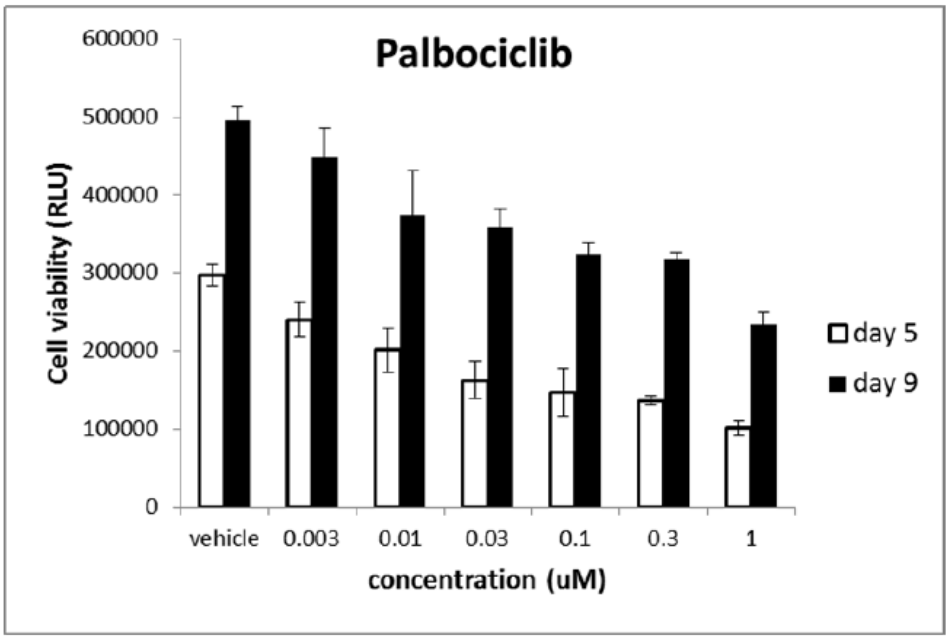
Summary: the cytotoxic chemotherapeutic agents carboplatin, paclitaxel and doxorubicin, caused dose-dependent inhibition of cell proliferation, and increases in caspase 3/7 activities. In addition, paclitaxel caused minimal induction of cellular senescence in the bone marrow mononuclear cells at 0.01 μM, although it did not display a dose-dependent effect.

Reversibility

In Vitro Assay to Assess Reversibility- Bone marrow mononuclear cells or MCF7 cells were incubated with palbociclib as single agent for 5 days, or in combination with fulvestrant for 7 days. At the end of treatment, cell viability was assessed in the dosing plate using the Cell Titer Glo® kit (Promega), while cells in the parallel plate were washed and cultured for an additional 4 (single agent treatment) or 5 days to assess reversibility of the treatment effect.

Figure 5 Assessment of the reversibility of the effects of palbociclib and cytotoxic chemotherapies in human bone marrow mononuclear cells

A



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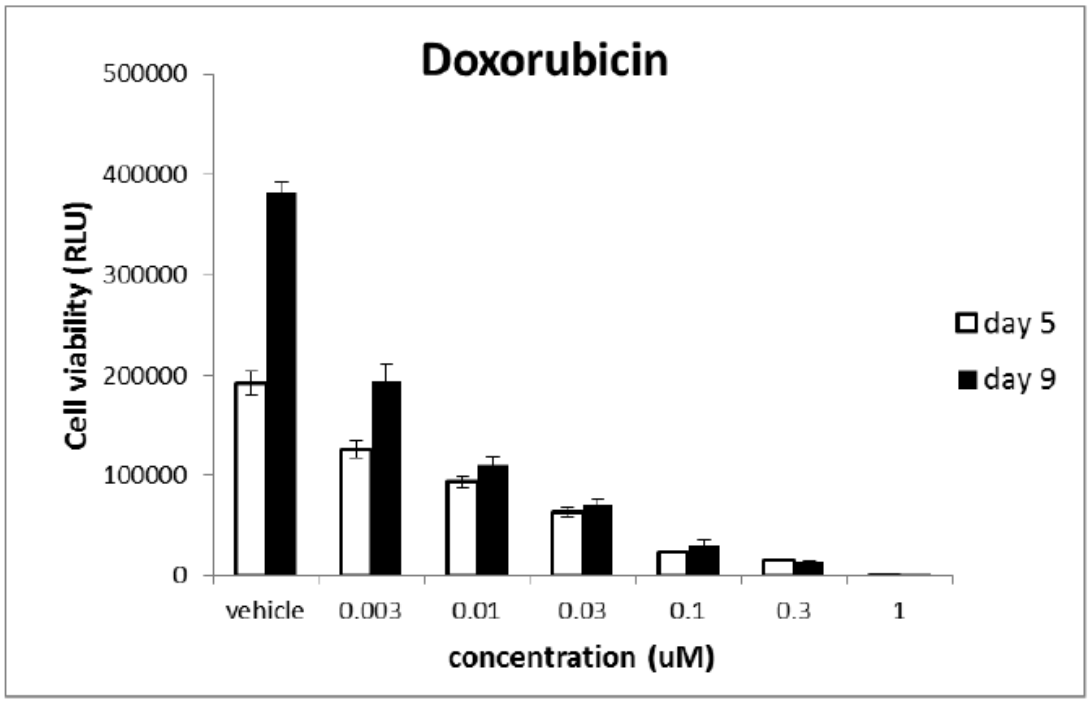

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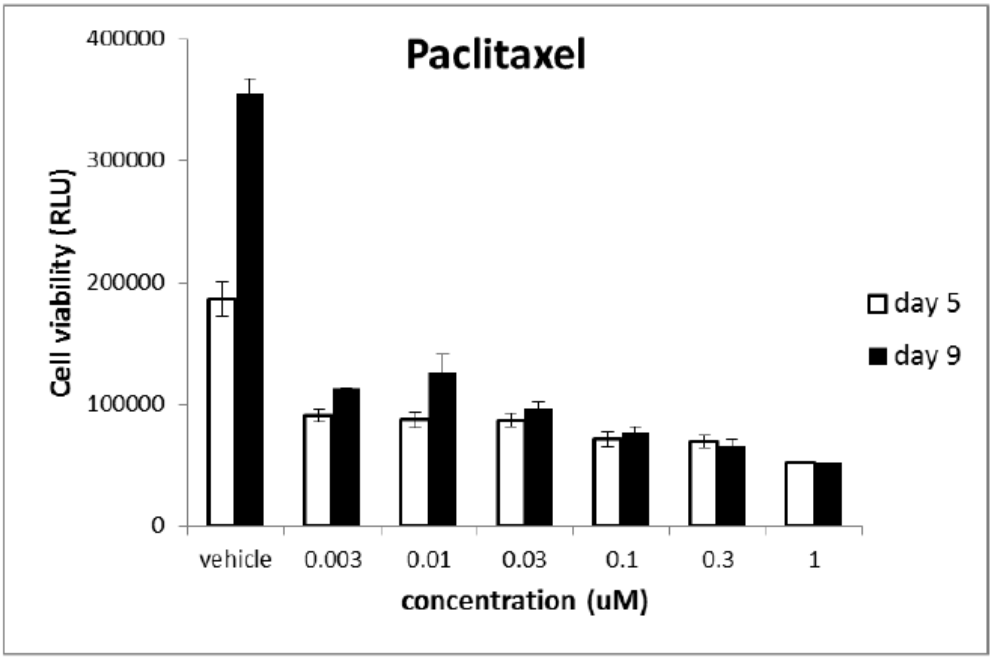

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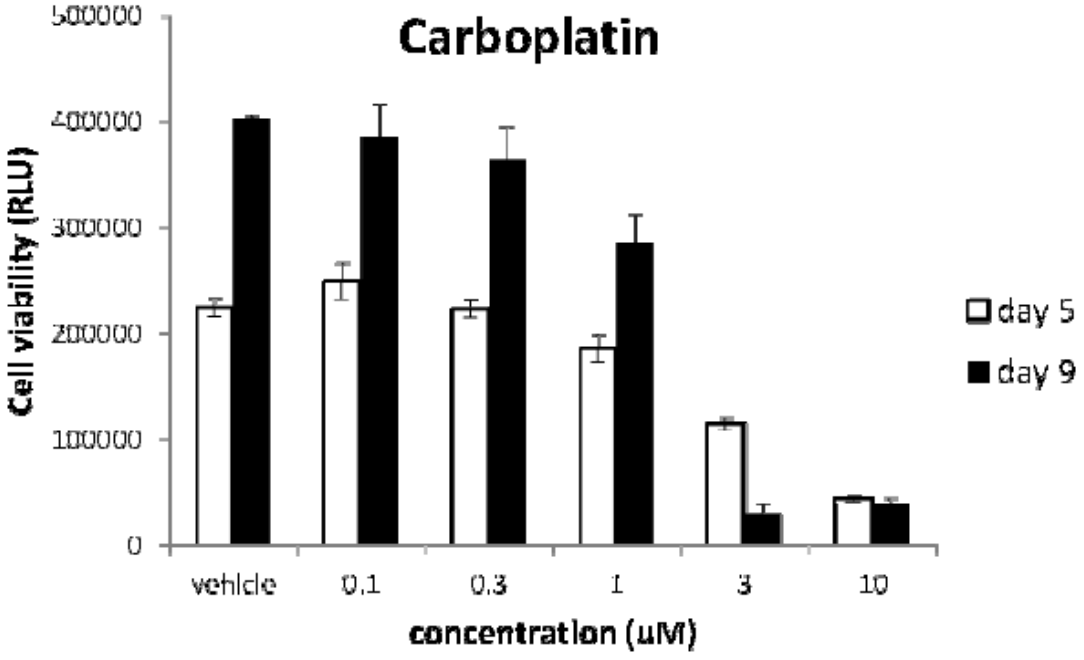
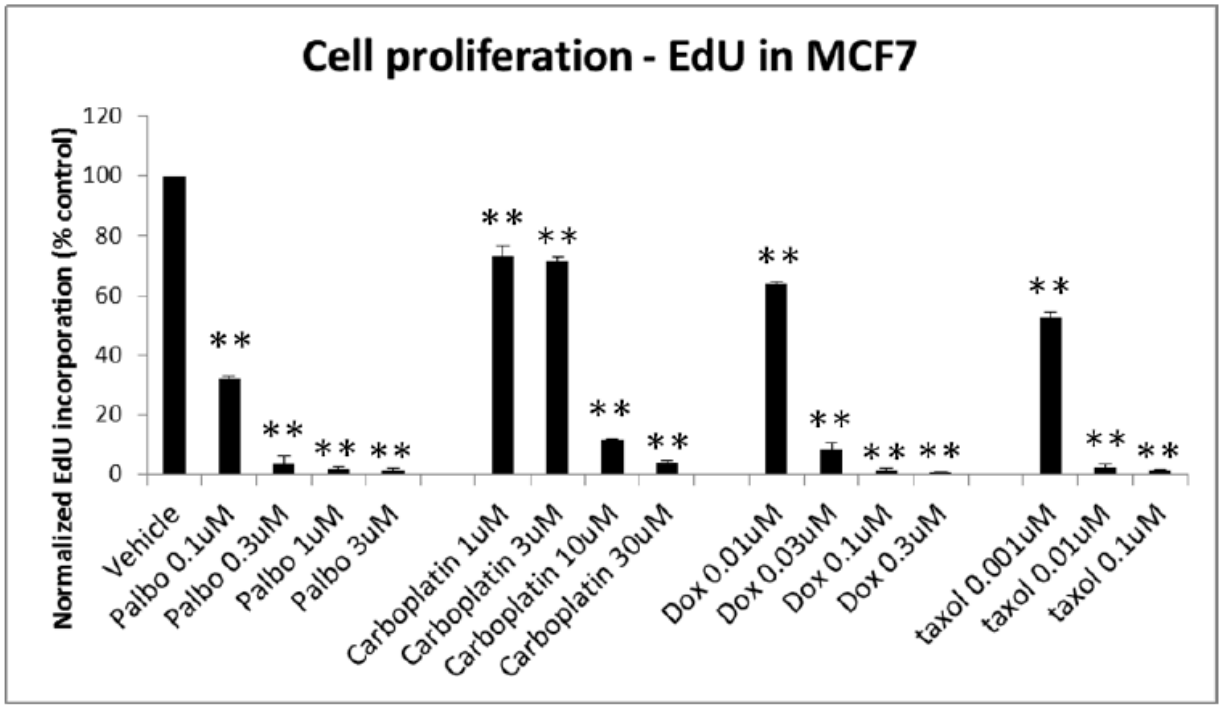


Summary: Human bone marrow mononuclear cells treated with up to 1 μM of palbociclib showed similar viability at the end of the 4-day recovery period in fresh media as the vehicle control, indicative of reversibility of cell cycle arrest. In contrast, bone marrow mononuclear cells treated with paclitaxel, doxorubicin or carboplatin showed minimal recovery over the same period for the test concentrations indicated.

Cellular mechanism comparison in MCF7 breast cancer cells: palbociclib vs. cytotoxic chemotherapeutic agents

Figure 6 Evaluation of anti-proliferative, apoptotic and cellular senescence effects of palbociclib and cytotoxic chemotherapies in MCF7 breast cancer cells

A



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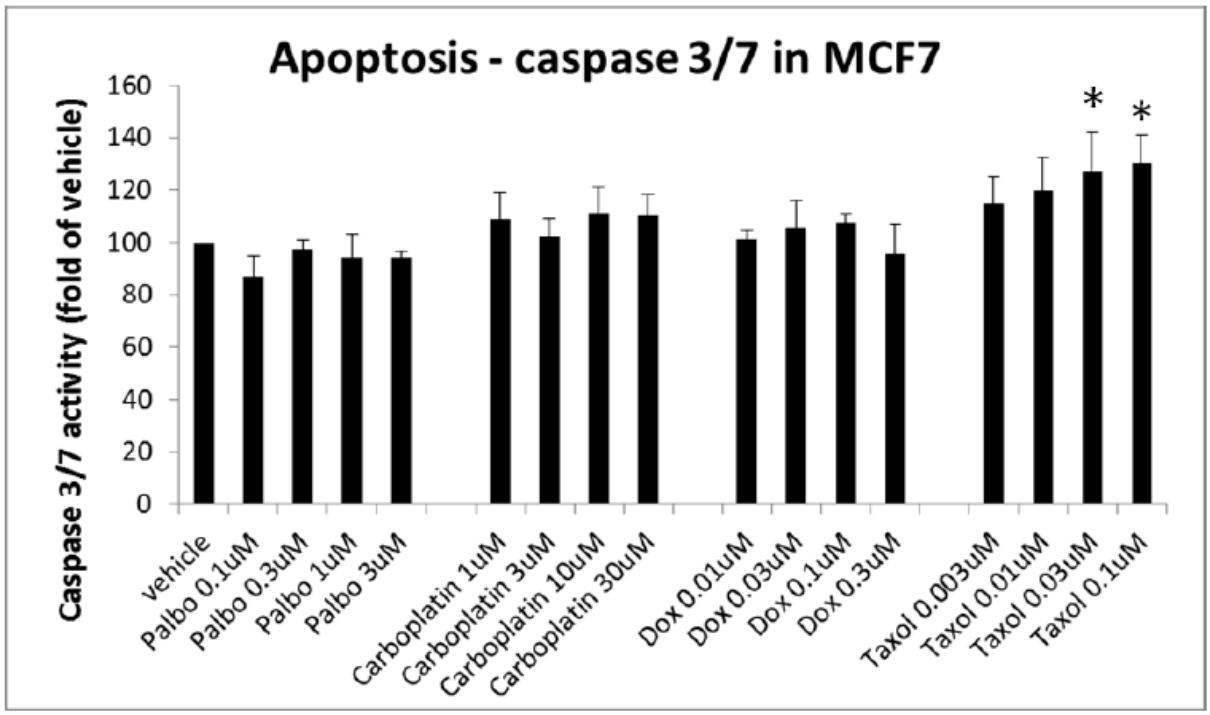
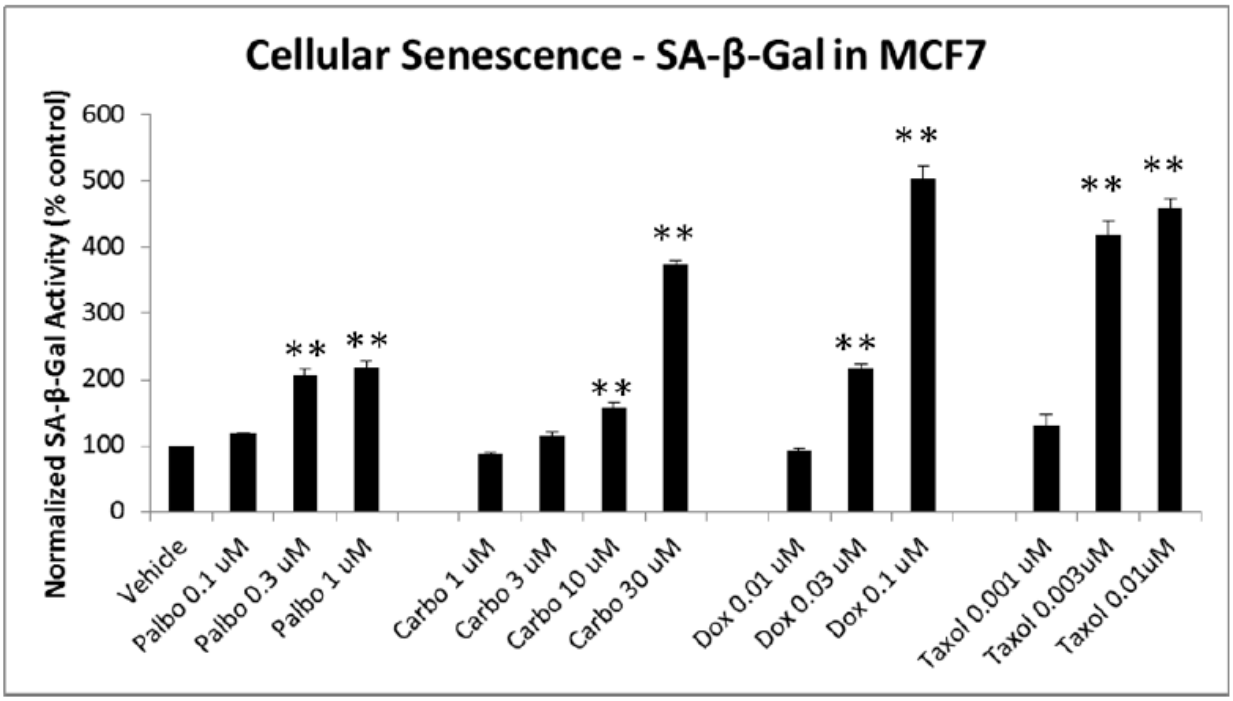


C



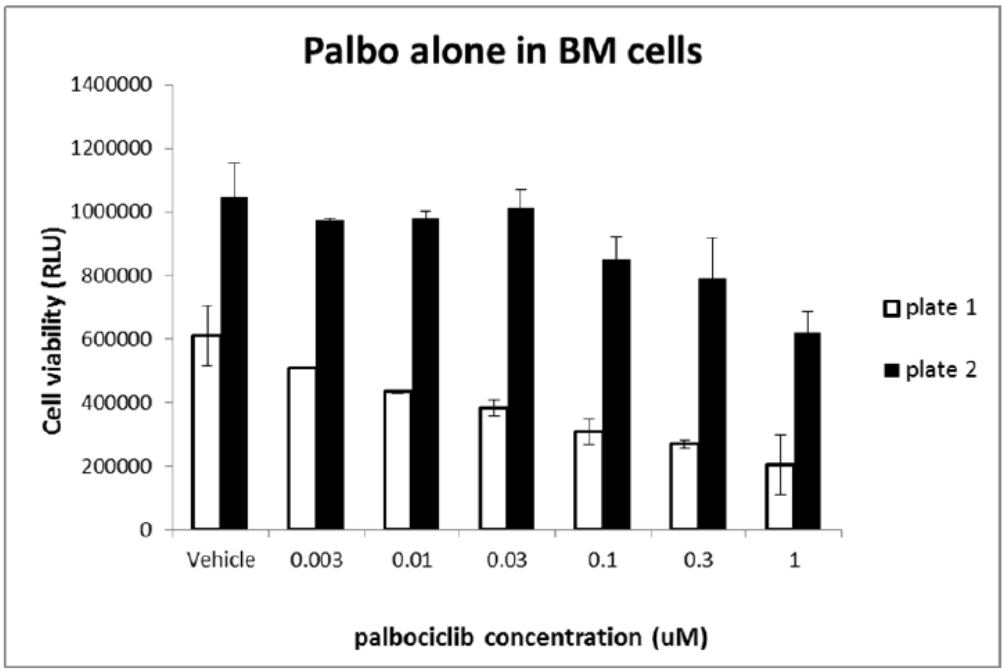
Summary: Palbociclib and chemotherapy treatments of MCF7 cells induced dose-dependent inhibition of cell proliferation and resulted in significant dose-dependent induction of cellular senescence, but minimal induction of apoptosis.

Combination treatment of palbociclib and fulvestrant, and reversibility of effects in bone marrow mononuclear cells or MCF7 cells

In Vitro Bone Marrow Viability Assay - Following 7 days of compound treatment, cell viability was assessed via ATP content in plate 1, while media was changed to test article-free media in plate 2 or media containing fulvestrant in plate 3. Following an additional five days of culture, relative cell viability was measured via ATP content from plate 2 and 3. Data represent mean relative luminescence. Error bars represent standard deviation of triplicate measurements.

Figure 7 Assessment of the reversibility of Palbociclib alone or in combination with fulvestrant in human bone marrow mononuclear cells and MCF7 breast cancer cells

A



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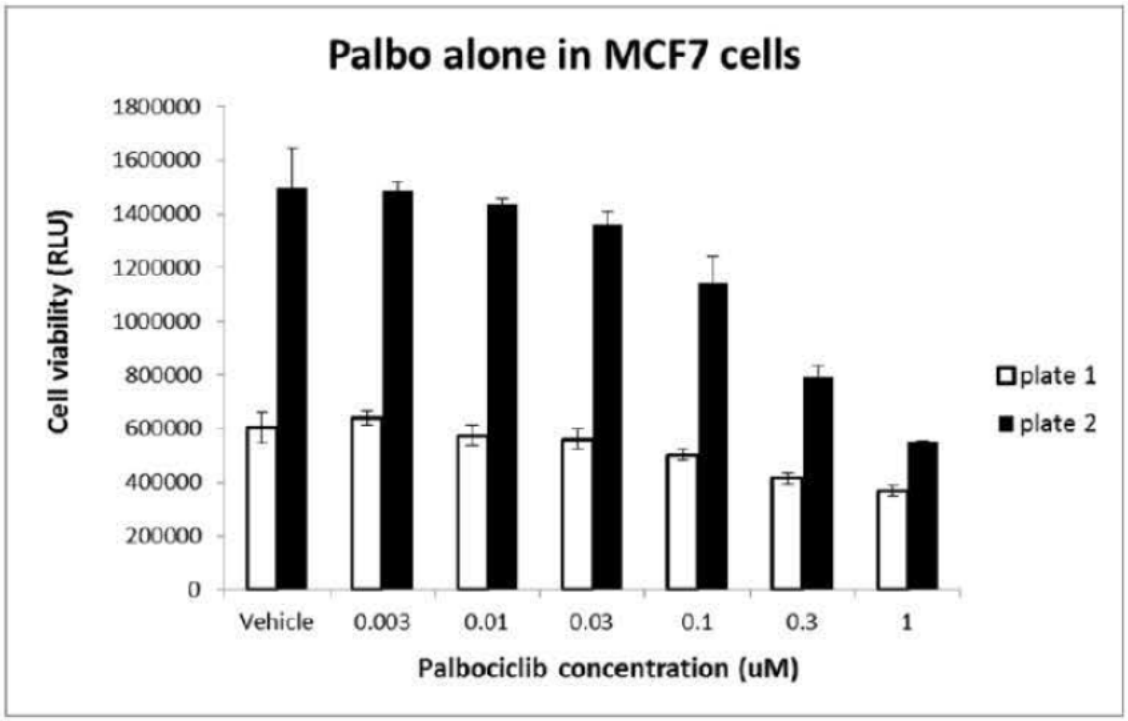
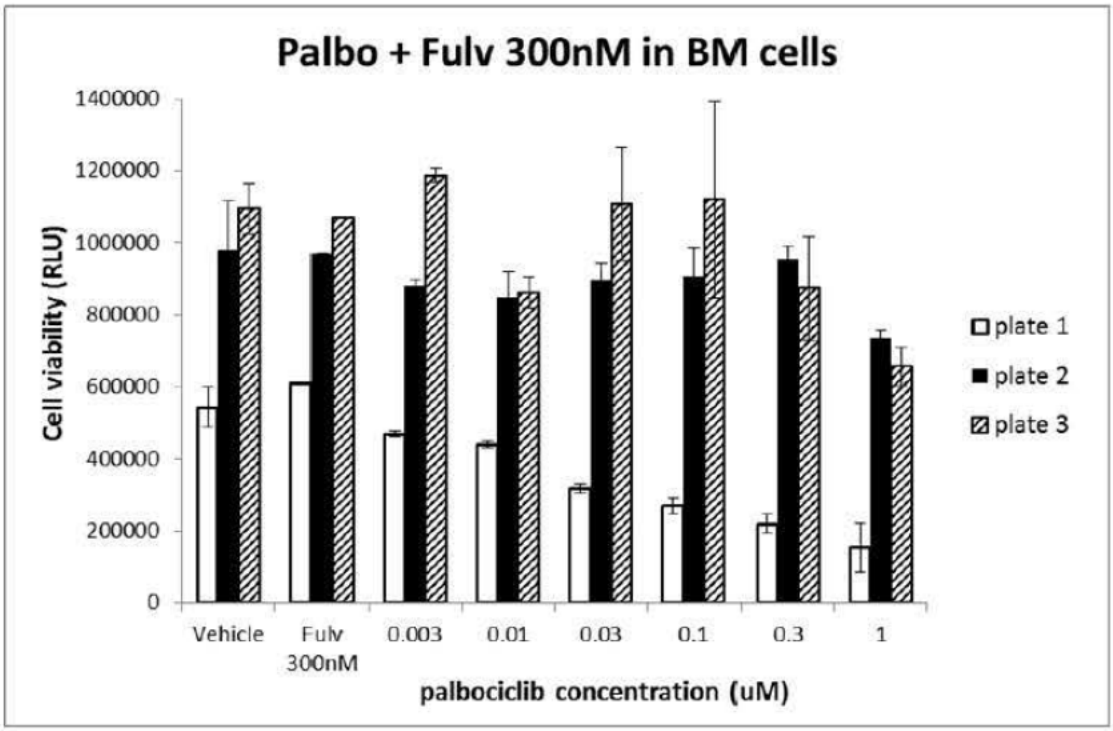
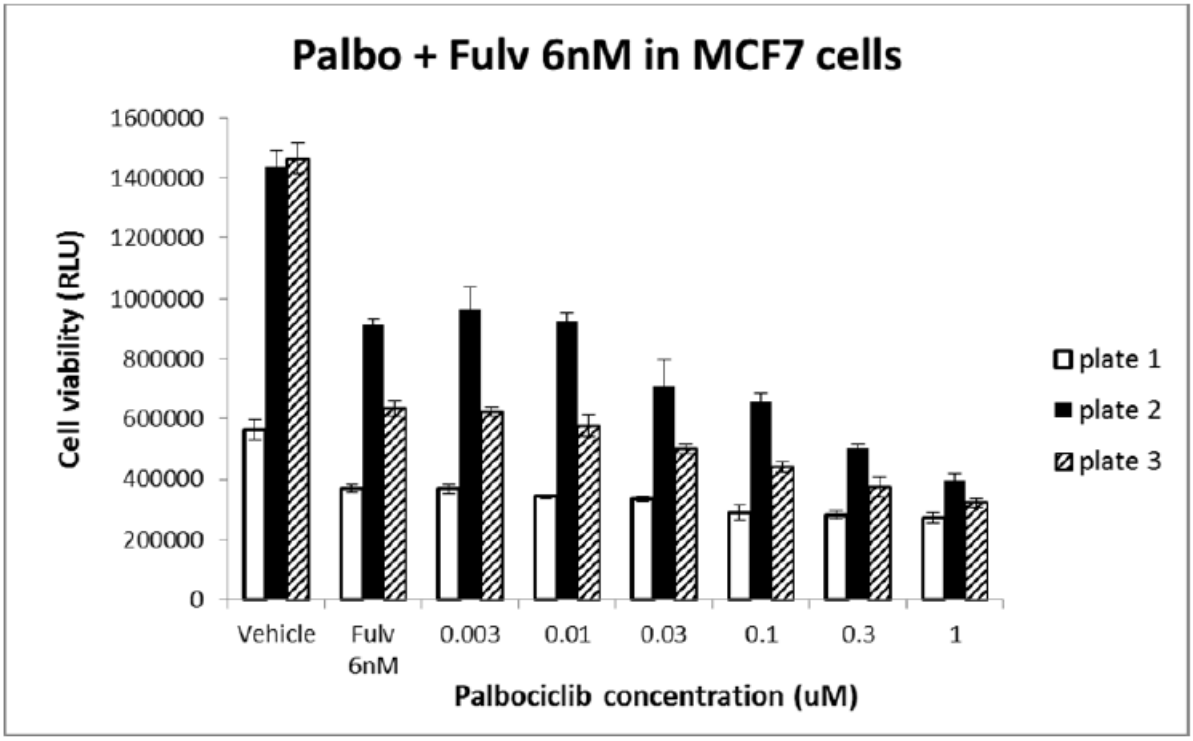

Palbo alone in MCF7 cells
Cell viability (RLU)
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
Vehicle
0.003
0.01
0.03
0.1
0.3
1
Palbociclib concentration (uM)
plate 1
plate 2

C


Palbo + Fulv 300nM in BM cells
Cell viability (RLU)
1400000
1200000
1000000
800000
600000
400000
200000
0
Vehicle
Fulv 300nM
0.003
0.01
0.03
0.1
0.3
1
palbociclib concentration (uM)
plate 1
plate 2
plate 3

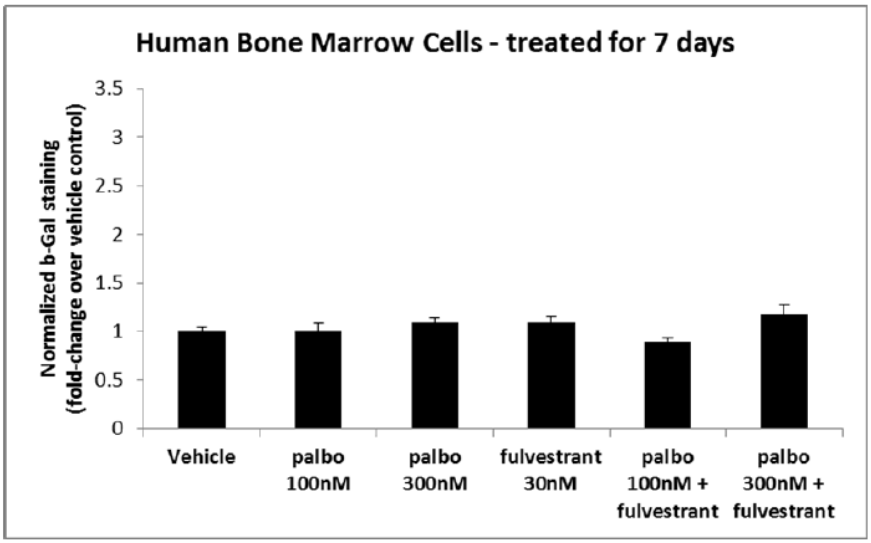
D



Summary: Combining palbociclib (up to 1μM) and the anti-estrogenic compound fulvestrant at 300 nM did not alter the inhibitory effect of palbociclib on the viability of bone marrow mononuclear cells. By contrast, inhibition of tumor cell growth was additive in MCF7 cells following treatment with palbociclib and fulvestrant. In MCF7 cells treated with palbociclib alone, cell viability recovered by the end of the 5-day treatment-free recovery period, although the magnitude of cell regrowth was less than that in bone marrow cells. When MCF7 cells were treated with the combination of palbociclib and fulvestrant, only partial viability recovery was observed following the 5-day treatment-free recovery period, and minimal recovery was observed when fulvestrant (6 nM) remained present during the recovery phase.

Figure 8 Evaluation of cellular senescence effect of palbociclib, fulvestrant alone or in combination in human bone marrow mononuclear cells and MCF7 breast cancer cells.

A



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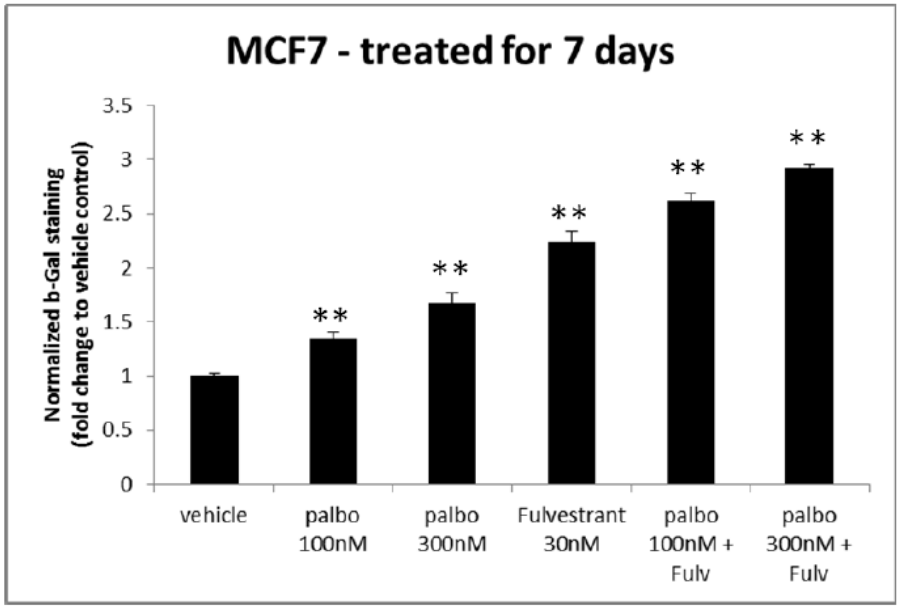

Summary: No significant increase in SA-β-gal activity was observed following treatment of human bone marrow cells with palbociclib (100 - 300 nM) or fulvestrant (30nM) alone, or these agents in combination. By contrast, treatment of MCF7 cells with palbociclib or fulvestrant caused significant increases in SA-β-gal activity over vehicle control, and the combination of these two agents produced a larger increase in SA-B-gal activity than that achieved by either single agent alone.

6 General Toxicology

Study title: 39-week oral gavage chronic toxicity and toxicokinetic study with PD-0332991 in dogs with a 12-week recovery phase

Study no.: 8282225
Study report location: M4.2.3.2, page 1-1677
Conducting laboratory and location: (b) (4) [redacted]
Date of study initiation: May 16, 2013
GLP compliance: Yes
QA statement: yes (X) no ( )
Drug, batch #, and % purity: PD-0332991
Lot#: E010014102
Purity: 98.9%

Key study findings:

- Once daily oral administration of PD-0332991 did not cause severe toxicity in dogs at doses up to 3.0 mg/kg/day;
- Target organ effects were observed in the hematolymphoid tissue, testes, and epididymides;
- All PD-0332991 effects had partially or completely reversed by the end of the recovery period.

METHODS:

Doses:	0.2, 0.6, 3.0 mg/kg* * Doses for this study were based on findings from a 15-week oral dose study.
Frequency of dosing:	Once daily for 3 weeks followed by a 1-week off for a total dosing phase of 39 weeks followed by a 12-week recovery period
Route of administration	Oral gavage.
Dose volume	2 mL/kg
Formulation/Vehicle	0.5% (w/v) methylcellulose (4000 cps) prepared in reverse osmosis water
Species/strain:	Beagle dog
Age	approximately 13 months old
Weight	Male: 7.1 - 9.4 kg; Female: 6.0 - 8.4 kg
Number/sex/group	4/sex/group (main); 2/sex/group (recovery, control and HD groups)
Satellite groups	none
Unique study design	None
Deviation from study protocol	None

OBSERVATIONS AND TIMES:

Mortality	twice daily
Health Monitoring	once daily
Detailed physical examinations	once weekly
Body weights	once weekly
Food consumption	Daily
Ophthalmoscopy	once during the predose phase and on Days 204 and 272 of the dosing phase.
EKG	once during the predose phase, and 4 to 5 hours postdose during Weeks 27 and 39 of the dosing phase.
Hematology and coagulation	Twice during the predose phase; on Days 22, 29, 106, 113, 190, 197, and 274 of the dosing phase; and on Days 50 and 85 of the recovery phase.
Serum chemistry	Twice during the predose phase; on Days 22, 29, 106, 113, 190, 197, and 274 of the dosing phase; and on Days 50 and 85 of the recovery phase.
Urinalysis	once during the predose phase, on Day 274 of the dosing phase, and on Day 85 of the recovery phase
Gross pathology:	All animals at necropsy, On Day 274 of the dosing phase, and on Day 85 of the recovery phase
Organ weights:	All animals at necropsy, On Day 274 of the dosing phase, and on Day 85 of the recovery phase
Histopathology:	All animals at necropsy, On Day 274 of the dosing phase, and on Day 85 of the recovery phase Adequate Battery: yes (x), no ( ) Peer review: yes (x), no ( )
Toxicokinetics:	1, 2, 4, 7, 12, and 24 postdose on Days 1, 49, 99 (Week 15), and 267 (Week 39) - on Day 1 and in the final week of dosing Cycles 2, 4 and 10.

RESULTS:

Mortality: none
Clinical signs**:** unremarkable
Bodyweight**:** unremarkable
Food consumption: unremarkable
Ophthalmoscopy: unremarkable
EKG: unremarkable

Hematology:

Table 2 Summary of Hematology

	Percent Change From Vehicle Control					
Gender	Male			Female		
Doses (mg/kg)	0.2	0.6	3	0.2	0.6	3
Day 22						
RBC	-6		-11			
Hemoglobin	-7	-4	-10			
RDW		9	21			14
Reticulocytes	-27	-12	-60			-34
Platelets			-24	-16	-9	-26
Fibrinogen		35	15		8	12
WBC	-12	-10	-53		-22	-45
NEUT	-16	-22	-61	-6	-18	-43
Lymphocytes			-32		-31	-43
Monocytes			-62			-56
Eosinophils		-28	-68	-49	-51	-77
Basophils	-29	-14	-86			-40
Day 29						
RBC		-4	-10			
Hemoglobin	-4	-7	-10			
RDW		7	24			14
Reticulocytes	-14	12	-11		-10	-16
Platelets			-24	-11	-9	-29
Fibrinogen		17		21	17	23
WBC			-23		-5	-13
NEUT		-8	-35			-11
Lymphocytes					-17	-14
Eosinophils		-32	-57		-39	-45
Basophils	-13		-33			
Day 106						
RBC	-6	-6	-19	-6	-10	-15
Hemoglobin	-6	-6	-12		-5	-7
MCV			12		6	10
RDW			15		8	14
Reticulocytes	-28	-21	-51			-13
Platelets			-23	-8	-10	-15
Fibrinogen			25	14		27
WBC	-23	-23	-57	-13	-41	-51
NEUT	-29	-39	-66	-22	-40	-49
Lymphocytes			-34		-42	-48

	Percent Change From Vehicle Control					
Gender	Male			Female		
Doses (mg/kg)	0.2	0.6	3	0.2	0.6	3
Monocytes			-68		-24	-61
Eosinophils	-24	-16	-76	-22	-68	-73
Basophils	-39	-23	-85			-62
Day 113						
RBC	-7	-5	-17	-7	-8	-10
Hemoglobin	-6	-4	-8			
MCV			12			10
RDW			14			10
Reticulocytes	-19		-19	42	56	62
Platelets		-6	-32	-13	-16	-16
MCH	6	8	12		7	11
MCV			15	5	5	18
Reticulocytes	-11	-43	-45	-12	-37	-47
Platelets			-32			-31
Fibrinogen				7		35
WBC	-16		-32		-12	
NEUT	-22	-14	-46	-7	-9	
Lymphocytes					-17	-7
Eosinophils			-63		-52	-58
Basophils	-25		-31			
Day 190						
RBC	-5	-6	-17		-5	-7
Hemoglobin	-4	-4	-9			
MCV			11			8
RDW			19			8
Reticulocytes	-34	-34	-58	25		-43
Platelets		-7	-32	-16	-21	-36
Fibrinogen						16
WBC	-28	-34	-65		-39	-60
NEUT	-33	-42	-75	-8	-39	-65
Lymphocytes	-19	-19	-39		-39	-50
Monocytes	-26	-26	-77			-69
Eosinophils		-36	-84	-39	-66	-85
Basophils	-50	-50	-87	33	-33	-56
Day 197						
RBC			-16			
Hemoglobin			-7			
MCV			12		6	9
RDW			18			8
Reticulocytes	-21		-17	46	21	
Platelets		-10	-31	-14	-21	-32

	Percent Change From Vehicle Control					
Gender	Male			Female		
Doses (mg/kg)	0.2	0.6	3	0.2	0.6	3
Fibrinogen						22
WBC	-13	-5	-43		-15	-30
NEUT	-16	-19	-58		-15	-34
Lymphocytes					-12	-17
Monocytes			-22	66		-43
Eosinophils			-75	-38	-67	-85
Basophils			-45	83	33	17
Day 274						
RBC	-7		-19		-12	-19
Hemoglobin		-5	-11		-6	-11
MCV			12		6	11
RDW			23			15
Reticulocytes	-26	-28	-38	-15		-22
Platelets		-11	-40	-7	-6	-6
Fibrinogen						80
WBC	-33	-34	-71		-34	-58
NEUT	-28	-45	-79		-39	-63
Lymphocytes	-11	-7	-46		-26	-45
Monocytes	-14	-29	-83			
Eosinophils	-19	-37	-87	-44	-64	-32
Basophils	-17	-17	-83	20	-20	-40
Recovery Day 50						
RBC			-15	-6	-12	-7
Hemoglobin	12		-10			
Reticulocytes	-32	-51	-47	-48	-30	-50
Lymphocytes	-27		-14			-18
Eosinophils			106	-37	-37	-40
Fibrinogen	38	17	14	7	-25	4
Recovery Day 85						
Erythrocyrtes			-14	-7	-4	-6
Hemoglobin			-12			
Reticulocytes	-14	-33	-30	-27	-43	-55
Lymphocytes	-32		-14			-38
Eosinophils			136	-24	-45	-7
Fibrinogen	47	17	54	21		33

Blank cells: unremarkable
Values underlined: P≤ 0.05

Summary: Dose-related decreases in red blood cell parameters, decreases in leukocytes including neutrophil, counts, lymphocyte counts, monocyte counts and eosinophil counts, and decreases in platelets were observed at the end of each dosing period in both sexes. The magnitudes of decreases were similar in each dosing cycle.

The changes in leukocytes and platelets exhibited reversibility during the recovery phase, the changes in erythrocytes, hemoglobin, and reticulocytes did not recover by the end of the recovery period.

Clinical Chemistry: unremarkable

Urinalysis: unremarkable

Gross Pathology**:** unremarkable

Organ Weights:

Table 3 Summery of Organ Weight

	Percentage deviation from control (n=10)							
	Absolute Organ Weight				Absolute Organ Weight			
Study	Main			Recovery	Main			Recovery
Dose Group (mg/kg)	0.2	0.6	3	3	0.2	0.6	3	3
No. Animal/group	4	4	4	2	4	4	4	2
Male								
Testes	-2	-22	-39		-14	-26	<u>-45</u>	
Spleen	44	5	-14		31	2	-22	
Female								
Spleen	9	14	-23		13	29	-13	

Blank cells: unremarkable
Values underlined: P≤ 0.05

Histopathology

Main (Day 274)

Table 4 Summary Incidence and Severity of Selected PD-0332991-Related Microscopic Findings - Hemolymphatic System - Terminal Necropsy

Gender	Male				Female			
Dose (mg/kg)	0	0.2	0.6	3	0	0.2	0.6	3
No. animals examined	4	4	4	4	4	4	4	4
Marrow, Sternum								
Hypocellularity, hematopoietic								
-mild								1
-moderate								1
Gut-Associated Lymphoid Tissue								
Decreased Cellularity, Lymphoid								
-minimal							2	
-mild				2				2
Mesenteric Lymph Node								
Decreased cellularity, lymphoid								
-minimal								1
-Mild				3			3	2
Spleen								
Decreased cellularity, lymphoid								
-Minimal								1
-Mild				1			3	2

Table 5 Summary Incidence and Severity of Selected PD-0332991-Related Microscopic Findings - Male Reproductive System

Dose (mg/kg)	0	0.2	0.6	3
No. animals examined	4	4	4	4
Testes				
Degeneration of seminiferous tubules				
-minimal		1		
-mild		2	2	
-moderate		1	2	
-mark				2
-severe				2
Epididymides				
Cellular debris, intraductal -minimal		3		
-mild		1	3	1
-moderate			1	
Hypospermia -mild		1	3	
-moderate			1	
-severe				4

Recovery (recovery day 85)

Gender	Male			
Dose (mg/kg)	0	0.2	0.6	3
No. animals examined	2	2	2	2
Testes Degeneration of seminiferous tubules -mild			1	1
Epididymides Cellular debris, intraductal -minimal			1	

Blank cells: unremarkable

Summary: Treatment related changes involved in the testes, epididymides in males, and bone marrow, lymph nodes, and spleen in males and females. The observed changes were reversible.

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Toxicokinetics:

Table 6 Summary of Toxicokinetic Parameters in dogs (PD-0332991)

Study day	Dose level (mg/kg/dose)	Gender	C_{max} (ng/mL)	Dose Normalized C_{max}	AUC_{0-24} (ng.h/mL)	Dose Normalized AUC_{0-24}	T_{max} (h)
Day 1	0.2	M	2.5	12.5	39.7	198.5	7
		F	1.9	9.5	31.2	162.5	7
	0.6	M	10.3	17.2	154	256.7	5.5
		F	8.0	13.3	122	203.3	12
	3	M	33.8	11.3	484	161.3	12
		F	47.6	15.9	606	202	4.5
Day 49	0.2	M	7.3	36.5	123	615	4
		F	5.1	25.5	84.4	422	4
	0.6	M	18.8	31.3	335	558.3	4
		F	24.7	41.2	416	693.3	4
	3	M	98.8	32.9	1640	546.7	7
		F	55.2	18.4	942	314	2
Week 15 (Day 99)	0.2	M	5.7	28.5	97.5	487.5	5.5
		F	4.2	21	70.8	354	7
	0.6	M	11.5	19.2	189	315	7
		F	13.7	22.8	247	411.7	4
	3	M	83.8	27.9	1530	510	4
		F	58.3	19.4	975	325	4
Week 39 (Day 267)	0.2	M	6.0	30	96.6	483	4
		F	5.4	27	83.3	416.5	3
	0.6	M	11.3	18.8	193	321.7	7
		F	21.6	36	349	581.7	4
	3	M	138	46	2580	860	2
		F	119	39.7	2050	683.3	3

Conclusion:

- On Days 1 and 49, and in weeks 15 and 39, plasma exposures (C_{max} and mean AUC_{0-24}) were generally increased proportionally to the dose increases from 0.2 mg/kg to 3 mg/kg;
- There were no apparent gender difference;
- The exposure of PD-0332991 on Days 49 increased up 3 fold when compared to Day 1, indicating accumulation following repeated dosing from Day 1 to Day 49;
- The exposure of PD-0332991 in Week 15 generally slightly lower (less than 2 fold) when compared to Day 49, indicating increasing of clearance/metabolism after Day 49;
- The exposure of PD-0332991 after Week 15 generally remained similar, indicating no apparent changes in absorption/ clearance/metabolism with repeated cycles after Week 15;
- T_{max} ranged from 4 to 12 hours in male dogs, and 2 to 12 hours in female dogs.

Note: Blood samples collections took place on Day 1 and in the final week of dosing Cycles 2, 4 and 10.

6 Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title:	A Fertility and Early Embryonic Development Study of PD-0332991 by Oral Gavage in Male Rats
Study no.:	20057548
Study report location:	(b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 5, 2014
GLP compliance:	Yes
QA statement:	yes
Drug, lot #, and % purity:	PD-0332991, lot# E010014102 98.6%

Key Study Findings

- PD-0332991 at 100 mg/kg/day caused lower body weights, body weight gain, food consumption;
- PD-0332991 at ≥ 30 mg/kg/day caused lower epididymal and testicular weights, and reduced testicular spermatid density, epididymal sperm density, and sperm motility;
- Fertility index was lower (89%) when untreated females were mated with treated males at 100 mg/kg;
- The no-observed-adverse-effect level (NOAEL) was 10 mg/kg/day with corresponding plasma concentration at 360 ng/mL.

Methods

Doses:	0, 10, 30, and 100 mg/kg * Doses were selected based on previous 15-week and 6-month general toxicity studies.
Frequency of dosing:	Once daily x 21 days, 28 days/cycle for a total of 4 cycles (84 doses)
Dose volume:	10 mL/kg
Route of administration:	oral gavage
Formulation/Vehicle:	0.5% (w/v) Methylcellulose in Reverse Osmosis Deionized Water
Species/Strain:	Crl:CD(SD) male rats
Number/Sex/Group:	20/group
Age:	Male: 71 days, Female: 66 days
Weight:	Males: 286 - 346 g; females: 228 - 282 g
Satellite groups:	none
Study design:	PD-0332991 was administered once daily with a schedule of 3 week on, 1 week for 15 week. During the last 2 weeks of the dose period, treated males were paired with untreated females for a period of 5 days. All surviving males were euthanized on Study Day (DS) 107 through 110, after the completion of the mating period.
Deviation from study protocol:	none

Experimental Design

Group No.	Test Material	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg)	Assigned Rat Numbers	
					Males	Females
1	Control Article	0 (Control)	0	10	1201-1220	2101-2120
2	PD-0332991	10	1	10	1221-1240	2121-2140
3	PD-0332991	30	3	10	1241-1260	2141-2160
4	PD-0332991	100	10	10	1261-1280	2161-2180

Observations and Results

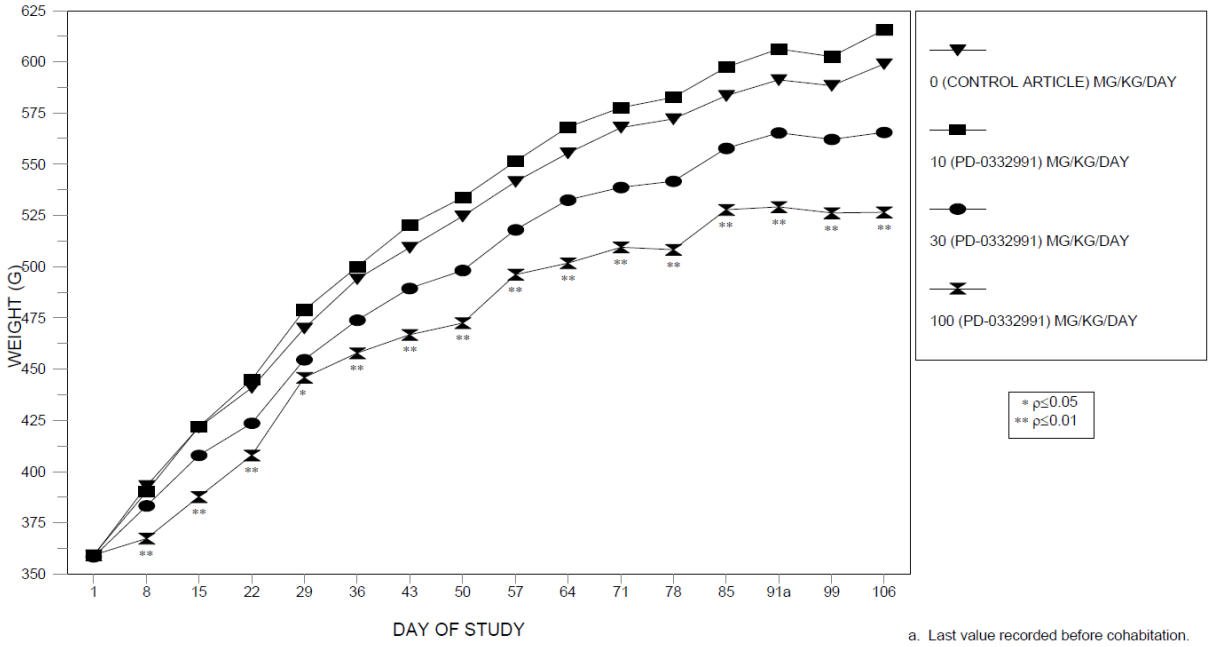
OBSERVATIONS AND TIMES:

<table>
<tr><td>Mortality</td><td>at least twice daily (AM and PM)</td></tr>
<tr><td>Clinical observations</td><td>Male: at least once weekly during the pretreatment period, daily during the dose period (including non-dosing days) and on the day of scheduled euthanasia.
Female: at least once weekly during the acclimation period and daily beginning on GD 0 continued through the day of scheduled euthanasia.</td></tr>
<tr><td>Body weights</td><td>Male: at least weekly during the pretreatment period, daily during the dose period (including non-dosing days) and on the day of scheduled euthanasia.
Female on the day after arrival, at least weekly during acclimation, and on GD 0, 3, 7, 10, and 14</td></tr>
<tr><td>Food consumption</td><td>Male: at least twice weekly during the dose period through the week prior to scheduled euthanasia.
Females: on GDs 0, 3, 7, 10, and 14.</td></tr>
<tr><td>Estrous Cycle Evaluations</td><td>Estrous smears will be collected once daily from two weeks prior to cohabitation until spermatozoa are observed in a smear of the vaginal contents and/or a copulatory plug is observed in situ during the cohabitation period.</td></tr>
<tr><td>Cohabitation</td><td>
<table>
<tr><th>Period</th><th>Day of Study</th><th>Duration of Cohabitation</th><th>Number of Rats (if possible)</th></tr>
<tr><td>End of Dosing[a]</td><td>Beginning Study Week 14</td><td>14 days</td><td>20 rats/sex/group</td></tr>
</table>
[a] The last 14 days of the male dose period.
</td></tr>
<tr><td>Mating</td><td>Treated males were assigned to cohabitation with an untreated female, one treated male per one untreated female, by consecutive order. Females with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug observed in situ were considered to be at GD 0 and assigned to individual housing.</td></tr>
<tr><td>Gross pathology:</td><td>All animals, males during Study Week 16 (DS 107 through DS 110), females on GD 14.
See the details in the tables below (copied from the Applicant’s submission).
Terminal Procedures for Treated Male Rats</td></tr>
</table>

	<table><tr><th rowspan="2">Group No.</th><th rowspan="2">No. of Treated Male Rats</th><th rowspan="2">Scheduled Euthanasia Day</th><th colspan="4">Necropsy Procedures</th><th rowspan="2">Histology</th><th rowspan="2">Histopathology</th></tr><tr><th>Sperm Analysis</th><th>Necropsy</th><th>Tissue Collection</th><th>Organ Weights</th></tr><tr><td>1</td><td>20</td><td rowspan="4">Week 16 of Study (DS 107 through DS 110)</td><td rowspan="4">X</td><td rowspan="4">X</td><td rowspan="4">X[a]</td><td rowspan="4">X[a]</td><td>X[a]</td><td>Epididymides, testes, prostate, seminal vesicles, and any gross lesions</td></tr><tr><td>2</td><td>20</td><td>X[a]</td><td>Epididymides, testes, prostate, seminal vesicles, and any gross lesions</td></tr><tr><td>3</td><td>20</td><td>X[a]</td><td>Epididymides, testes, prostate, seminal vesicles, and any gross lesions</td></tr><tr><td>4</td><td>20</td><td>X[a]</td><td>Epididymides, testes, prostate, seminal vesicles, and any gross lesions</td></tr><tr><td colspan="3">Unscheduled Deaths[b]</td><td>-</td><td>X</td><td>X</td><td>X[a]</td><td>X[a]</td><td>Epididymides, testes, prostate, seminal vesicles, and any gross lesions</td></tr></table> Terminal Procedures for Untreated Female Rats <table><tr><th rowspan="2">Group No.</th><th rowspan="2">No. of Untreated Female Rats</th><th rowspan="2">Scheduled Euthanasia Day</th><th colspan="4">Necropsy Procedures</th><th rowspan="2">Histology</th><th rowspan="2">Histopathology</th></tr><tr><th>Ovarian/ Uterine Examination</th><th>Necropsy</th><th>Tissue Collection</th><th>Organ Weights</th></tr><tr><td>1</td><td>20</td><td rowspan="4">GD 14</td><td rowspan="4">X</td><td rowspan="4">X</td><td rowspan="4">X[a]</td><td rowspan="4">-</td><td>-</td><td>-</td></tr><tr><td>2</td><td>20</td><td>-</td><td>-</td></tr><tr><td>3</td><td>20</td><td>-</td><td>-</td></tr><tr><td>4</td><td>20</td><td>-</td><td>-</td></tr><tr><td colspan="3">Unscheduled Deaths</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr></table> GD = Gestation Day; X = procedure conducted; - = not applicable.
Organ weights:	All males during Study Week 16 (DS 107 through DS 110) for epididymides, epididymis left cauda, prostate gland, seminal vesicles (with coagulating gland), and testis. See other details in the above tables copied from the Applicant's submission.
Histopathology:	All males during Study Week 16 (DS 107 through DS 110). See other details in the above tables copied from the Applicant's submission.
Others	sperm motility, sperm concentration, spermatid head count
Toxicokinetics:	at 1, 2, 4, 7, 12, and 24 hrs following the 12th dose (Day 12)

Results
Mortality: none
Note: three unscheduled deaths were considered due to a gavage accident
Clinical Signs: unremarkable
Body Weight:

Figure 9 Body weight changes in treated male rats



a. Last value recorded before cohabitation.

(copied from the Applicant's submission, the data were verified by the reviewer.)
Summary: Dose-dependent decreases in mean body weights were observed in treated rats at 30 and 100 mg/kg (↑up to 12% at 100 mg/kg).

Food consumption: At 100 mg/kg/day, mean absolute food consumption was statistically significantly lower (↓ up to 8%) compared to controls. These effects corresponded to lower body weights.
Estrous Cycling, Mating: unremarkable

Gross Pathology:

Table 7 Summary of Gross Pathology Findings – Terminal Euthanasia

	Male			
Dose (mg/kg)	0	10	30	100
No. Animals Examined	19	20	20	18
Testis				
Small, bilateral				12
Flaccid, bilateral				11
Prostate				
Yellow				3
Fore- and Hind paws				
Yellow, bilateral				2
Ears				
Yellow, bilateral				2

Organ Weights: Lower absolute (0.68 to 0.82x controls) and relative to body weights (0.77 to 0.93x controls) of the epididymides (left, right, and cauda) and testes (left, right, and left without the tunica albuginea) were observed at 100 mg/kg/day.

Histopathology:

Table 8 Summary of Microscopic Findings – Terminal Euthanasia

		Male			
Dose (mg/kg)		0	10	30	100
No. Animals Examined		19	20	20	18
Testis					
Degeneration, seminiferous tubules	-Minimal				3
	-mild				3
	-moderate			2	10
	-marked				1
Epididymis (right)					
Debris, cellular, lumen	-Minimal				3
	-mild			2	5
	-moderate				7
Hypospermia	-Minimal				3
	-mild			2	6
	-moderate				3
	-marked				1
Epididymis (left)					
Debris, cellular, lumen	-Minimal				3
	-mild			2	5
	-moderate				7
Hypospermia	-Minimal				3
	-mild			2	6
	-moderate				3
	-marked				1

Sperm Evaluation

Table 9 Sperm evaluation

Dose (mg/kg)	0	10	30	100
No. Animals Examined	19	20	20	18
Vas deferens sperm motility Motile percent	92.7	89.9	90.5	73.6**
Cauda epididymal sperm density Sperm density d	1052	922	989	764**
Testicular spermatid density Spermatid density e	108	123	103	56**

** Significantly different from the control group value ($p \leq 0.01$).

Untreated Female Rats: There were no PD-0332991-related effects on any ovarian or uterine parameters, the litter means for corpora lutea, implantations, the percentage of preimplantation loss, viable and nonviable embryos, and the percentage of postimplantation loss. No dam had a litter consisting of only nonviable embryos. No placentae examined had any detectable abnormalities.

Fertility: Fertility index was 88.9% when untreated females were mated with treated males at 100 mg/kg, fertility index was 100% when untreated females were mated with treated males at control, 10, and 30 kg/day dose groups.

Toxicokinetics: PD-0332991 was detected in plasma samples from all PD-0332991-dosed animals at 4 hours after dose administration on DS 12. The mean concentration of PD-0332991 on Day 12 was 360, 874, and 2413 ng/mL in the 10, 30, and 100 mg/kg/day dose groups, respectively.
Reviewer comment: T_{max} was approximately 4 hours based on the TK data from the conducted 15-week rat general toxicology study. The plasma concentration of PD-0332991 at 4 hours post dosing on Day 12 in this study was similar to the C_{max} observed on Day 49 in 15-week rat study (see the table below). The following table was copied from the pharmacology/toxicology review for NDA 207103. The yellow highlighted numbers were used for comparison.

Table 10 Summary of toxicokinetic parameters in rats (PD-0332991)

- 15 week rat toxicology study

Study day	Dose level (mg/kg/dose)	Gender	C_{max} (ng/mL)	Dose normalized C_{max}	AUC_{0-24} (ng.h/mL)	Dose Normalized AUC_{0-24}	t_{max} (h)
1	10	M	270	27	2920	292	4
	50	F	265	5	1400	28	2
	30	M	1270	42	18000	600	4
	100	F	356	4	3280	33	3
	100	M	2110	21	35300	353	9
	200	F	704	4	6450	32	2
49	10	M	385	39	3600	360	4
	50	F	349	7	1430	29	1
	30	M	1140	38	15100	503	3
	100	F	268	3	1850	19	1
	100	M	2270	22	43700	437	6
	200	F	639	3	5640	28	1
105	10	M	367	37	3770	377	4
	50	F	247	5	1710	34	2
	30	M	1260	42	18300	610	3
	100	F	308	3	2820	28	3
	100	M	2260	23	41600	416	3
	200	F	586	3	7050	35	4

12 Integrated Summary and Safety Evaluation

Table 11 TOXICOLOGY TABULATED SUMMARY

Repeat Dose Toxicity Studies			
Title	**27-week**** GLP		**39-week** GLP
Species	Rat		Dog
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		0.2, 0.6, 3
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		-
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		-
Body weight	Male: ↓ up to 38% dose dependent	Female: ↓ up to 14% 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	Females: -	-

	at 100 mg/kg			
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: ↓ WBC (↓up to 53%) ↓RBC (↓up to 19%) ↓RETIC(↓up to 50%) ↓platelet (↓up to 40%) Dose dependent Reversible	Female: ↓ WBC (↓up to 60%) ↓RBC (↓up to 19%) ↓RETIC(↓up to 43%) ↓platelet (↓up to 36%) Dose dependent reversible
Clinical chemistry	Male: 100 mg/kg ↑GLU, UN, ↑AST, ALT, ALP Not recovery after 12 weeks	Female: -	-	
Urinalysis	-		-	
Organ weight	Male: ↓ spleen, thymus, testes, epididymis ↑ Adrenal reversible	Female: -	Male: ↓ spleen, testes Reversible	Female: ↓ spleen reversible
Gross Pathology	100 mg/kg: foot, tooth, adrenal, lung, GI, spleen, kidney, male reproductive system. reversible	Female: -	-	
Histopathology	Male: Hypocellularity in bone marrow, spleen, lymph nodes, thymus; Degeneration in kidney and chronic progressive nephropathy;	Female: Hypocellularity in bone marrow, lymph nodes; Islets cells vacuolar Change in pancreas; lens degeneration in eyes.	Male: Decreased lymphoid cellularity in spleen and lymph nodes; Degeneration in testes, Hypospermia in epididymides.	Female: Hypocellularity in bone marrow; Decreased lymphoid cellularity in spleen and lymph nodes;

	Degeneration in tooth; Islets cells vacuolar change in pancreas; Vacuolation in liver; Lens degeneration in eyes Degeneration in testes, Epididymides; Adipose atrophy in skin. Changes in eye and kidney did not recover, others reversible	Reversible	reversible	Reversible
Review comment	<u>Toxicities only seen in rats</u> Pancreatic islet cell vacuolation; Eye lens degeneration; degeneration of tooth ameloblasts; Renal tubuloepithelial cell vacuolation correlated with increased serum glucose levels and glucosuria <u>Exposure (AUC) at HD compared to human exposure at the therapeutic dose</u> Males: 16x Females: 7x <u>Exposure (AUC) with male reproductive toxicity compared to human exposure at the therapeutic dose</u> 11x		<u>Exposure (AUC) at HD compared to human exposure at the therapeutic dose</u> 1.2x <u>Exposure (AUC) male reproductive toxicity compared to human exposure at the therapeutic dose</u> 0.02x	
Fertility and Early Embryonic Development				
0, 10, 30, and 100 mg/kg in rats • Lower epididymal and testicular weights, and reduced testicular spermatid density, epididymal sperm density, and sperm motility at ≥ 30 mg/kg/day; • Fertility index was lower (89%) when untreated females were mated with treated males at 100 mg/kg;				

- NOAEL was 10 mg/kg/day with corresponding plasma concentration of 360 ng/mL (4 hours postdosing on SD12) and AUC of 3600 ng.h/mL (estimated, based on the data from the 15-week rat general toxicology study), approximately 1.9 fold of human exposure at the therapeutic dose.

**Reviewed under NDA 207103 (the nonclinical review 1/17/2015)

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Primary Pharmacology

The in vitro assay results demonstrated that palbociclib-induced bone marrow suppression manifested through cell cycle arrest without apoptosis; by contrast, chemotherapeutic agents, including paclitaxel, doxorubicin, and carboplatin, primarily caused apoptotic cell death in bone marrow. Following palbociclib treatment withdrawal in vitro, bone marrow cells resumed proliferation in the presence or absence of anti-estrogen (fulvestrant); while breast cancer cells (MCF-7) remained arrested in presence of fulvestrant. Bone marrow cells did not resume proliferation following chemotherapy treatment withdrawal within the timeframe of the in vitro study. Bone marrow cells did not enter senescence following treatment with palbociclib, anti-estrogen, or a combination of both agents. MCF-7 cells, on the other hand, became senescent following palbociclib or anti-estrogen treatment, and this effect was greater in presence of both agents.

In summary, the study results suggested that the mechanism of palbociclib-induced bone marrow suppression was different from that induced by cytotoxic chemotherapeutic agents.

Toxicology

General toxicology:

Palbociclib was assessed in 39-week toxicology study in dog. Repeat-dose toxicology studies were conducted with daily administration for 21 days followed by 7-day non dosing period. No new toxicities were identified in the 39-week study compared to the 15-week study in dogs.

No unscheduled deaths occurred, and no test article-related clinical observations, ophthalmic observations or effects on body weight, food consumption, or ECGs were noted during the dosing or recovery phases. Effects on hematopoiesis including decreases in leukocyte and absolute reticulocyte counts were noted during 3 weeks of dosing in each cycle followed by partial or complete recovery during the week without dosing. PD-0332991-related decreases in red blood cell and platelet counts and increases in mean corpuscular volume, mean corpuscular hemoglobin, red cell distribution width, and mean platelet volume exhibited little or no evidence of reversibility in the week without dosing. All PD-0332991-related hematology effects exhibited reversibility or reversible tread during the 12-week recovery phase. Bone marrow hypocellularity (hematopoietic) and/or decreased lymphoid cellularity were present in the gut-associated lymphoid tissue (GALT), mesenteric lymph node, spleen, in males given 3.0 mg/kg/day and females given >0.6 mg/kg/day. In the male reproductive system, degeneration of the seminiferous tubules was present in the testes of males in all dosed groups. Following the 12-week recovery phase, PD-0332991-related microscopic findings were limited to the testes and epididymides, where mild degeneration of the seminiferous tubules (testis) with or without intratubular cellular debris (epididymis) was present in one male given 0.6 mg/kg/day and one male given 3.0 mg/kg/day.

Reproductive toxicology:

Palbociclib was administered to Sprague-Dawley rats at doses up to 100 mg/kg/day in males. Male rats were administered palbociclib once daily during a 15-week period in a scheduled dosing regimen of 3 weeks of consecutive daily dosing followed by a 1-week non-dosing period (a total of 4 cycles). Treated males were paired with untreated females for 5 days during the last 2 weeks of the dosing period. Testicular and epididymal effects (minimal to marked seminiferous tubule degeneration in the testis, and minimal to moderate or marked increases in cellular debris and hypospermia in the epididymides) were identified at ≥ 30 mg/kg/day. These effects correlated with macroscopic changes in the testis, and lower male reproductive organ weights, sperm motility, cauda epididymal sperm density and testicular spermatid density at 100 mg/kg/day. There were no effects on mating and embryonic survival at any dose level. Fertility index was lower (89%) when untreated females were mated with treated males at 100 mg/kg, compared to 100% in treated males at control or lower dose groups. The NOAEL was 10 mg/kg/day with mean plasma concentration of 360 ng/mL at 4 hours postdose on SD12.

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/s/

WEI CHEN
02/08/2016

TODD R PALMBY
02/08/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 207103/SD-193 **Applicant:** Pfizer **Stamp Date:** October 15, 2015

Drug Name: Ibrance (palbociclib) **NDA Type:**

prior approval supplement 2 (efficacy)

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	n/a		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	x		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			n/a
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	*x		* Issues generally identified during review
11	Has the applicant addressed any abuse potential issues in the submission?			n/a
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			n/a

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____yes____

If the NDA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

WEI CHEN
11/10/2015

TODD R PALMBY
11/10/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207103Orig1s002

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 207103
Supplement #:	2
Drug Name:	Ibrance (palbociclib)
Indication(s):	Metastatic breast cancer
Applicant:	Pfizer
Date(s):	Submission date: 10/15/2015
Review Priority:	Priority
Biometrics Division:	5
Statistical Reviewer:	Erik Bloomquist, PhD
Concurring Reviewers:	Shenghui Tang, PhD
	Rajeshwari Sridhara, PhD
Medical Division:	OHOP/DOP1
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	Laleh Amiri-Kordestani, MD
	Geoff Kim, MD
Project Manager:	Amy Tiley

Keywords: Survival Analysis, Interim Analysis, Progression Free Survival, Audit, Patient Reported Outcomes

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1 EXECUTIVE SUMMARY

This supplemental NDA submission is to add a 2nd line indication for the previous accelerated approval of palbociclib. The sponsor has submitted the results of the study Paloma-3, a large, double-blind placebo controlled trial of palbociclib + fulvestrant vs. placebo + fulvestrant in metastatic breast cancer patients who have progressed on at least one prior hormonal therapy. Patients (N=521) were randomized 2:1 to the treatment arm (N=347) using the stratification factors of visceral metastases, sensitivity to prior hormonal therapy, and menopausal status. Treatment with palbociclib was given orally for 21 days followed by 1 week off of therapy.

The primary endpoint of Paloma-3 was investigator-assessed progression-free survival (PFS). The study had one planned interim analysis of PFS when 143 events had occurred (60% of the final planned events). The study was stopped for efficacy at the time of the interim analysis. The hazard ratio for PFS was 0.42 (95% CI: 0.32, 0.56, p-value < 0.0001).

After the interim analysis, the sponsor continued to follow-up all enrolled subjects for an additional four months. Using this additional follow-up information for PFS, the hazard ratio for PFS was 0.46 (95% CI: 0.36, 0.59), p-value < 0.0001. Also based upon the updated follow-up data, the estimated median time to progression for the treatment arm was 9.5 months (95% CI: 9.2, 11.0), and the estimated median time to progression for the control arm is 4.6 months (95% CI: 3.5, 5.6). A 40% blinded independent central review audit of the PFS results supported the results of the primary analysis.

Based on the data from Paloma-3, the combination of palbociclib + fulvestrant showed a statistically significant improvement in PFS when compared to fulvestrant alone. Whether the data and analyses provided in this submission showed an overall favorable benefit/risk profile in supporting a traditional approval is deferred to the clinical review team.

2 INTRODUCTION

Pfizer has submitted this NDA supplement for Ibrance (palbociclib) in the 2nd line metastatic HR+, Her2- breast cancer setting. Currently, palbociclib is approved in the front-line HR+, Her2-, metastatic breast cancer setting in combination with letrozole. [redacted] (b) (4) Pfizer has used to results of Paloma-3 to support their NDA supplement.

2.1 Overview

Palbociclib is a cyclin-dependent kinases (CDK) inhibitor. Palbociclib stops cellular proliferation by prohibiting progression of the cell cycle from G1 into the S phase. Palbociclib is taken in capsule form orally with food. A recommended starting dose of Palbocicib is a 125mg capsule once daily with food for 21-days followed by 7 days off treatment.

In February 2015, FDA granted palbociclib accelerated approval for the treatment of HR+ metastatic breast cancer in combination with the hormonal agent letrozole. This approval was given in the front-line metastatic setting and was the original approval for palbociclib. A randomized Phase 2 study, Paloma-1, was used as a pivotal study to support the accelerated approval. The sponsor has an ongoing phase 3 study (Paloma-2) to confirm the results found in Paloma-1. The results of Paloma-2 are expected in the first-half of 2016.

For this current NDA supplement, Pfizer is asking [redacted] (b) (4) Pfizer is using the results of Paloma-3 to support their NDA supplement. Paloma-3 was a double-blind, phase 3 study of fulvestrant plus palbociclib/placebo in the 2nd line metastatic breast cancer setting. The study used investigator-assessed progression free survival (PFS) using RECIST v1.1 as the primary endpoint. A 40% random blinded independent central review (BICR) audit was conducted to confirm whether bias existed in the primary investigator PFS endpoint.

Table 1: List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
Paloma-3	3	Until disease progression or toxicity	OS until study end	347 Ibrance + Fulvestrant 174 Placebo + Fulvestrant	2nd line ER+, Her2-, mBC

2.2 Data Sources

The sponsor submitted data for PALOMA-3 electronically using the SDTM and AdAM format. The sponsor also submitted their SAS analysis programs. The submission can be accessed at the following location: \\CDSESUB1\evsprod\NDA207103\207103.enx.

3 STATISTICAL EVALUATION

This section focuses the efficacy results on PALOMA-3. Section 3.2 and its subheadings focus on the primary endpoint of PFS and associated audit. Section 3.3 and its subheadings focus on the patient reported outcomes reported in the trial.

3.1 Data and Analysis Quality

The data submitted for the primary PFS outcome and the data submitted for the PRO outcome were of good quality and sufficient for review purposes.

3.2 Paloma-3 Efficacy Results

Paloma-3 was a randomized, phase 3 double-blind study of fulvestrant plus palbociclib/placebo in HR+ metastatic breast cancer patients who had progressed on at least one prior hormonal therapy. The study randomized patients 2 to 1 to the palbociclib + fulvestrant arm and stratified the randomization based upon the presence of visceral metastases, documented sensitivity to prior hormonal therapy, and menopausal status (pre/peri-menopausal vs. post-menopausal). The study was conducted at 144 sites in 17 different counties, 56 of the sites were within the USA.

Palbociclib was taken at 125mg orally for 21 days with food followed by 7 days off treatment. Patients in the control arm took a matching placebo on the same schedule. Fulvestrant at 500mg was taken intramuscularly on days 1 and 15 of the first cycle, and day 1 of every subsequent cycle. Tumor assessment by CT/MRI occurred every 8 weeks the first year, and then every 12 weeks. Patient reported outcomes (PRO) data, based upon questionnaires, was taken on day 1 of cycle 1,2,3,4, and then every other cycle, i.e. 6, 8, 10. More information on the PRO data and the questionnaires can be found in Section 3.3.

3.2.1 Sample Size and Interim Analysis

Paloma-3 used investigator-assessed PFS as the primary endpoint for their study. The study was designed to detect a 3.4 month difference in median PFS (6.0 months vs 9.4 months) with a hazard ratio of 0.64. The study was planned to enroll 417 subjects and have the final PFS analysis when 238 events had occurred in both arms. The study had a planned interim analysis for PFS when 143 events (60% of the total) had occurred. The interim analysis adopted a Haybittle-Peto boundary with an alpha allocation of 0.00135. Note that an O'Brien-Fleming boundary for would set an alpha allocation closer to 0.004. The sponsor used a one-sided alpha of 0.025 for the primary analysis.

Overall survival was a key secondary endpoint. The final analysis of OS will occur when 198 deaths have occurred. An interim analysis for OS will occur when 97 events have occurred; the sponsor has pre-specified an O'Brien-Fleming boundary for the OS interim analysis.

The final cutoff date for the interim analysis was Dec 5, 2014. The sponsor has provided follow-up data for PFS until March 16, 2015. According to the sponsor, no crossover occurred between the two analyses.

3.2.2 Statistical Methodologies

For the primary analysis of PFS, the sponsor relied upon a stratified log-rank test. All three stratification factors used during randomization were used for the analysis. To assess whether the BICR audit provided support for the primary analysis, the sponsor used the NCI methodology developed by Dodd and collaborators (Dodd LE et al. An audit strategy for progression free survival. *Biometrics*, 67, 1092-1099, 2011). The sponsor also relied upon the PhRMA methodology developed by Amit and collaborators (Amit O et al. Blinded independent central review of progression in cancer clinical trials: results from a meta-analysis. *Eur J Cancer*, 47, 1772-1778, 2011).

To further assess whether the BICR audit provided support, I used a multiple imputation approach to estimate the BICR hazard ratio. The method is similar to the NCI method. Appendix 1 outlines the multiple imputation methodology I used.

3.2.3 Patient Demographic and Baseline Characteristics

Patient demographics and baseline characteristics can be found in Table 2 (page 9). The two arms appeared to be well balanced on demographic and baseline characteristics. There was approximately 20% pre/peri-menopausal patients enrolled on the trial. Also, the trial included a sizable fraction of patients with at least 3 or more lines of systemic therapy (45%-50%).

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Table 2: Paloma-3 Demographics and Baseline Characteristics

	Palbociclib + Fulvestrant N=347	Placebo + Fulvestrant N=174
Age (years)		
Median (range)	57.0 (30 to 88)	56.0 (29 to 80)
≥ 65 (%)	86 (24.8%)	43 (24.7%)
Race		
White	252 (72.6%)	133 (76.4%)
Asian	74 (21.3%)	31 (17.8%)
Other	21 (6%)	10 (5.7%)
ECOG		
0	207 (59.7%)	115 (66.1%)
1	140 (40.3%)	59 (33.9%)
Visceral Metastases		
Yes	206 (59.4%)	105 (60.3%)
Post-Meno Status		
Yes	276 (79.5%)	138 (79.3%)
Prior Systemic Thrpy		
1	71 (20.5%)	39 (22.4%)
2	106 (30.5%)	56 (32.2%)
3 or more	170 (49.0%)	79 (45.0%)

Source: CSR Section 11, Reviewers Analysis

3.2.4 Primary Efficacy Results

Primary efficacy results for PFS are provided in Table 3 (page 10). The trial reached the pre-specified stopping boundary for efficacy at the planned interim analysis (planned at 60% of total events, conducted at 81% total events) with an estimated hazard ratio of 0.42 (95% CI: 0.32, 0.56) (estimated using a stratified cox proportional hazard model). The median progression-free interval for the control group was 3.8 months (95% CI: 3.5, 5.5) and the median progression-free interval for the treatment group was 9.2 months (95% CI: 7.5, NR).

With an additional 3 months of follow-up and 64 more progression events (the March 16, 2015 cutoff), the trial demonstrated a hazard ratio of 0.46 (95% CI: 0.36, 0.59). The analysis conducted at the March 16, 2015 cutoff exceeded the number of events necessary for the planned final analysis of PFS by 21 events. The median progression-free interval for the treatment group was 9.5 months (95% CI: 9.2, 11.0) and the median progression free interval for the control group was 4.6 months (95% CI: 3.5, 5.6). Kaplan-Meier plots of PFS are provided in Figure 1 (page 11) for the interim analysis and
Figure 2 (page 12) for the final PFS analysis.

Reviewers Comment:_ Although the control group appears to underperform at the time of the interim analysis, the difference at the March 16, 2015 cutoff was 4.9 months. Also, the high percentage of pre/peri-menopausal patients and the high percentage with 3 or more lines of systemic therapy may help to explain lower than expected median PFS in the control group.

The objective response rate (ORR) in the treatment arm was 10.4%, and the control arm ORR was 6.3%. The median duration of response (DoR) in the treatment arm was 9.3 months (95% CI = (4.0, Not Estimable)), and DoR in the control arm was 5.7 months (95% CI = (3.7 – 5.7)).

Table 3: Paloma-3 Primary PFS Results

	Interim Analysis (Dec 5, 2015 cutoff)		**Updated Analysis (March 16, 2015 cutoff)**	
	Palbociclib + Fulvestrant N=347	**Placebo + Fulvestrant N=174**	**Palbociclib + Fulvestrant N=347**	**Placebo + Fulvestrant N=174**
Number of events	102 (29.4%)	93 (53.4%)	145 (41.8%)	114 (65.5%)
Censored	245 (70.6%)	81 (46.6%)	202 (58.2%)	60 (34.5%)
In-follow up	227 (65.4%)	70 (40.2%)	177 (51.0%)	48 (27.6%)
Median PFS (months)	9.2	3.8	9.5	4.6
95 CI	(7.5, NR)	(3.5, 5.5%)	(9.2, 11.0)	(3.5, 5.6)
Hazard Ratio	0.42		0.46	
95 CI	(0.32 – 0.56)		(0.36 – 0.59)	
p-value	<0.0001		<0.0001	

Source: Reviewers Analysis

Several sensitivity analyses were done to assess the robustness of the PFS results. Using an un-stratified log rank test, the hazard ratio was estimated to be 0.42 (95% CI: 0.36, 0.59). An additional analysis considering the start of anti-cancer therapy, lost to follow-up, consent withdraw, or medication error without an adverse event as progressive disease events was conducted. This sensitivity analysis estimated a hazard ratio equal to 0.438 (95% CI: 0.34, 0.58). A final sensitivity analysis considered documented progression events in between two follow-up visits as occurring at the earlier of the two visits. This final sensitivity analysis estimated a hazard ratio equal to 0.40 (95% CI: 0.30, 0.53).

Reviewers Comment: The primary PFS results are statistically significant. Moreover, the sponsor used a more stringent boundary at the interim analysis than an O'Brien-Fleming stopping rule. Several sensitivity analyses also support the primary PFS results. It is recommended to use the updated PFS results (March 16, 2015) cutoff for labeling purposes.

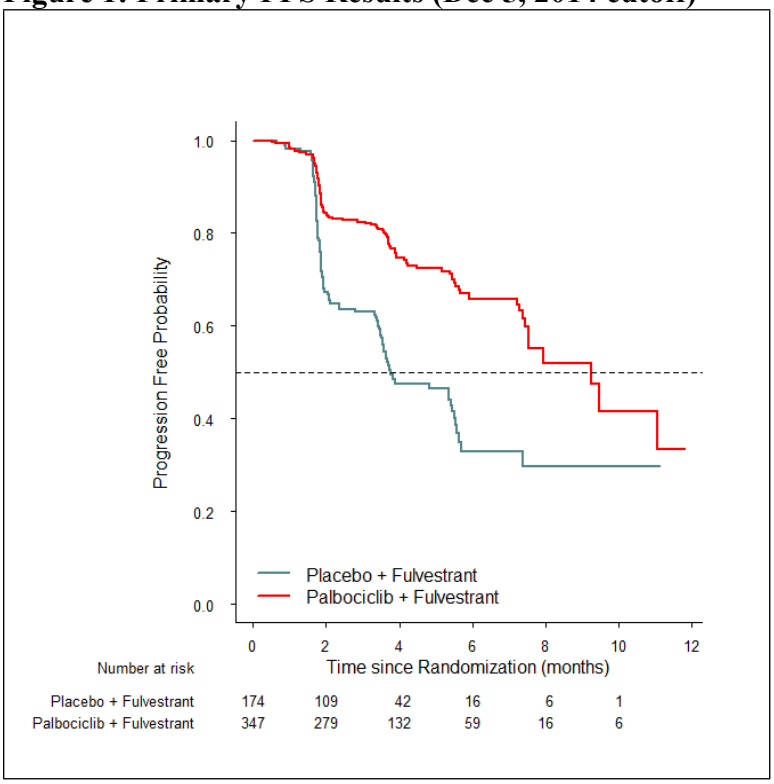
3.2.5 Overall Survival Results

At the March 16, 2015 cutoff, the overall survival (OS) results were not mature with only 57 total death events between the two arms. Based upon the currently available information for OS, the estimated HR = 0.811 and the 95% CI= (0.473, 1.390). A Kaplan-Meier plot of the OS results is shown in Figure 3 (page 12). The final OS results are scheduled to occur when 198 death events have occurred.

To assess the value of additional follow for overall survival, a Bayesian survival model was applied to the data, and the predictive probability of success was computed. The Bayesian survival model first fits a piecewise-continuous baseline hazard model to the currently observed data (March 16, 2015 cutoff), and then predicts the survival times for those without an event. Using this model to predict an additional 12 months of follow-up, the predictive probability for success (upper bound of confidence interval for HR < 0) of OS is approximately 58%.

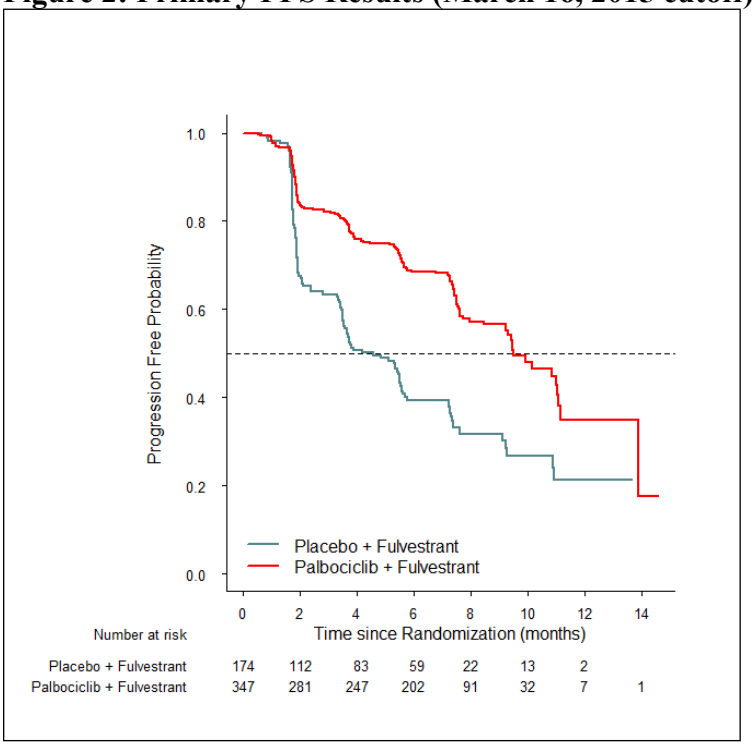
Reviewers Comment: The OS results at this time are too immature to make a definite statement regarding survival. Nonetheless, there does not appear to be any detriment to survival at this time.

Figure 1: Primary PFS Results (Dec 5, 2014 cutoff)



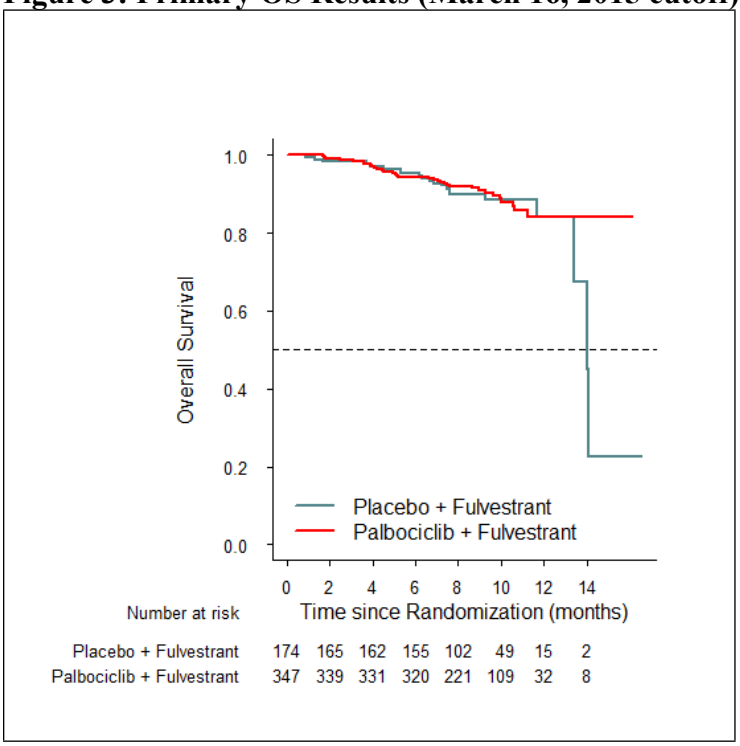
Source: Reviewers Analysis

Figure 2: Primary PFS Results (March 16, 2015 cutoff)



Source: Reviewers Analysis

Figure 3: Primary OS Results (March 16, 2015 cutoff)



Source:Reviewers Analysis

3.2.6 Blinded Independent Central Review Results

To help assess whether any potential bias occurred with the primary investigator-assessed PFS results, a BICR PFS audit study was conducted. In this study, a random sample (selection done by a third party not affiliated with the sponsor) of 40% of the total sample (n=211) was selected for additional review by a BICR. Table 4 (page 14) provides some demographic and disease characteristics of the 40% random sample.

To help assess randomness of the audit sample, Fisher's exact test was used on demographic variables to test whether the 40% audit sample appeared to be a random sample. For all demographic variables tested (10), the nominal p-value was above 0.05, suggesting that the audit sample was random and a fair representation of the total ITT population. Note that the number of subjects with progressive disease on the control arm differed between the audit sample and the ITT population. Nonetheless, the result did not reach an extremely high level of significance, suggesting that random chance is at play.

Reviewers Comment: The audit sample appears to be a fair representation of the ITT sample. The use of a third party to select the sample and the use of statistical tests provide support for this statement.

Using the audit sample, three methods were utilized to assess how well the BICR audit results support the primary PFS results. The PhRMA method (see section 3.2.2 for reference and details) estimated the early discrepencay rate (EDR) and late disprecencay rate (LDR) difference (control – treatment). For EDR, the rate difference was 21.4% with an EDR of 42.9% in the palbociclib arm and 21.4% in the placebo arm. For LDR, the rate difference was -39.7% with an LDR of 25.0% in the palbociclib arm and 64.7% in the placebo arm. In a situation with bias, we would expect the EDR rate difference to be negative and the LDR rate difference to be positive. Since the exact opposite occurred (EDR rate difference is positive and LDR rate difference is negative), the PhRMA method suggests little bias in the primary investigator PFS results.

Two additional methods were utilized to assess bias. Both methods attempt to estimate the BICR hazard ratio as if a full BICR review was completed. The first method, the NCI method (see section 3.2.2 for reference and details), estimated a hazard ratio equal to 0.24 with a 1-sided upper confidence limit equal to 0.34. The second method, the MI method (see Appendix), developed by the reviewer, estimated a hazard ratio equal to 0.24 with a 95% CI = (0.16, 0.37). As such, both methods provide strong evidence that the BICR audit supports the conclusions of the primary PFS results.

Reviewers Comment: The BICR audit results support the conclusions of the primary PFS analysis.

Table 4: BICR Audit Sample Characteristics

	Audit Sample N=211	ITT Sample N=521	Nominal p-value from Fisher's Exact Test
Treatment Arm			
Palbociclib + Ful	147 (69.7%)	347 (66.6%)	0.22
Placebo + Ful	64 (30.3%)	174 (33.3%)	
Menopausal Status			
Pre/Peri-Meno	162 (76.8%)	414 (79.5%)	0.21
Post-Menopausal	49 (23.2%)	107 (20.5%)	
Visceral Metastases			
Yes	125 (59.2%)	311 (59.7%)	0.86
No	86 (40.7%)	210 (40.3%)	
Prior Chemotherapy			
Yes	159 (75.3%)	389 (74.5%)	0.71
No	52 (24.6%)	133 (25.5%)	
Hormonal Sensitivity			
Yes	163 (77.3%)	410 (78.7%)	0.51
No	48 (22.8%)	111 (21.3%)	
Progressive Disease During Study (Palbociclib arm)			
Yes	42 (28.6%)	102 (29.4%)	0.77
No	105 (71.4%)	245 (70.6%)	
Progressive Disease During Study (Placebo Arm)			
Yes	28 (43.8%)	93 (53.5%)	0.05
No	36 (56.3%)	81 (46.6%)	

Source: Reviewers Analysis

3.3 Patient Reported Outcome Results

During the study, the sponsor collected patient reported outcome data using three specific instruments: the EORTC QLQ-C30, the EORTC QLQ-BR23, and the EQ-5D. Patient reported outcomes (PRO) data, based upon questionnaires, was taken on day 1 of cycle 1,2,3,4, and then every other cycle, e.g. 6, 8, 10.

There is one issue with the timing of the questionnaire and treatment. Treatment with palbociclib was provided on Days 1-21 of every cycle followed by one week off treatment till Day 28. The PRO data was then collected on Day 1 of the next cycle. Since subjects had one week to recover from possible adverse events while on treatment, this may affect how subjects report physical functioning symptoms, e.g. pain or fatigue.

Completion rates for all three instruments appeared to be very good. For the EORTC-C30, only 56 (10.8%) subjects did not complete all scheduled questionnaires. And of these 56 subjects, 27 did not complete the End-Of-Treatment questionnaire. Also, when a patient completed the EORTC-C30, 95% of the time she answered all questions, and 98% she missed only one question. For the EORTC-B23 and the EQ-5D, non-completion rates were similar (10.6%, 13.8%) to the EORTC-C30.

Reviewers Comment: Missing data does not appear to be an issue with this patient reported outcomes data

The EORTC-C30 has 15 specific scales that are a combination of scores from the 30 questions. These 15 scales include a global QoL scale, 5 functioning scales, and 9 symptom scales. Higher scores numbers imply better outcomes for global QoL and the 5 functioning scales. The opposite is true for the 9 symptom scales; specifically lower scores imply less severe symptoms.

Using a repeated-measures mixed model, the global QoL scale had -0.9 change from baseline (95% CI = (-2.5, 0.7)) in the palbociclib arm and -4.0 change from baseline (95% CI = (-6.3, 1.7)) in the placebo arm. These results favor the palbociclib arm. For the 5 functional scales, only emotional functioning scale appeared differs slightly, favoring the palbociclib arm. Finally, for the symptoms scale, only the pain scale and the nausea and vomiting scale appeared to differ, favoring the palboclib arm once again.

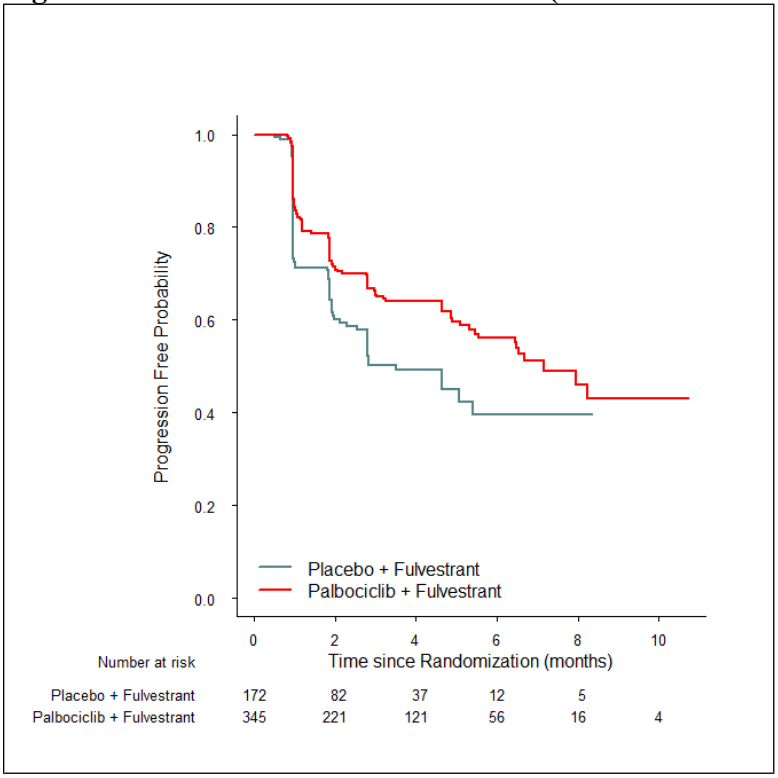
Reviewers Comment: There does appear a difference in QoL for the palbociclib arm and the placebo arm. Since this analysis was exploratory, i.e. no alpha control, and the change does not reach a 10 point difference, (b) (4) *A 10-point difference is typically a level the clinical outcome assessment staff sets for relevance.*

In the pre-specified analysis plan, the sponsor specifically described one analysis for a time-to-deterioration of pain as an exploratory endpoint. The analysis describes a time-to-event analysis for the first deterioration of >=10 points over baseline on the pain scale. The pain scale combines scores from two specific questions on the EORTC-C30 questionnaire. The first question (Question 9) asked, “In the past week, did you feel pain?” The second question (Question 19) asked, “In the past week, did pain interfere with your daily activities?” For both questions, a subject could answer four choices: not at all (1), a little (2), quite a bit (3), very much (4).

To convert the two questions into the pain scale, an average of two scores is taken and the scale is then converted into 0-100 scale. Based upon the data transformation, a >=10 increase in the pain scale is equivalent to answering either question 9 or question 19 one point higher than the baseline measure.

A Kaplan-Meier plot of the pre-specified analysis is presented in
Figure **4** (page 16). The hazard ratio for this analysis is 0.66 with a 95% CI = (0.51, 0.88). The median time to deterioration for the placebo arm is 3.5 months (95% CI = (2.5, 5.4)) and the median time to deterioration for the palbociclib arm is 7.2 months (95% CI = (5.6, NE)).

Figure 4: Time to Deterioration of Pain (>=10 increase in pain over baseline)



Source: Reviewers Analysis

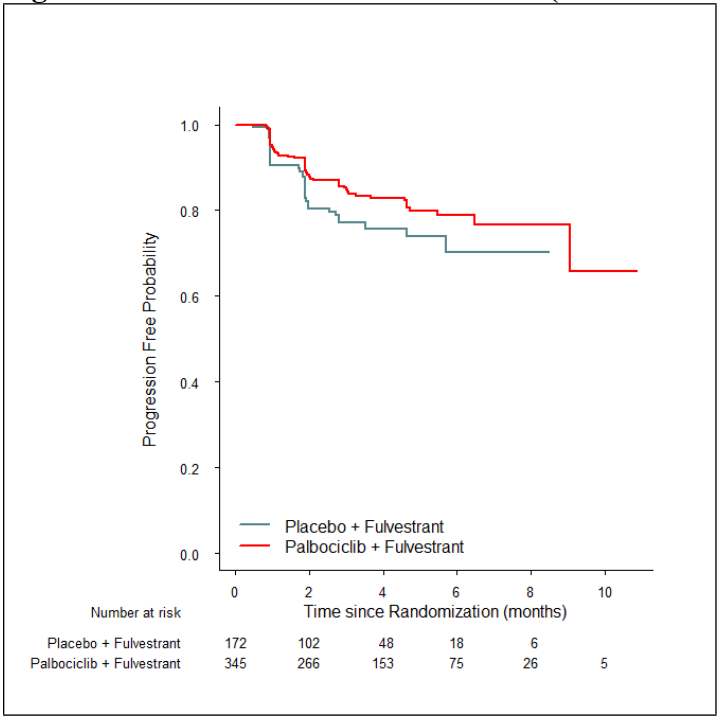
Since a 10 point drop over baseline is equivalent to a single question being answered higher than baseline, additional analyses were conducted to see if the results hold up under more stringent conditions. The first two of these analyses considered a 20 point drop over baseline and a 35 point drop over baseline. These analyses correspond to a 2 and 3 point increase in the average raw scale. The 20 point drop results are shown in
Figure **5** (page 17). As shown, there still does appear to be separation between the curves favoring the palbociclib arm (HR = 0.673 95% CI = (0.447, 1.011)). Medians are not able to estimable for the 20 point drop analysis. Similar results were seen for the 35 point drop.

The final analysis considered a confirmed pain deterioration of 10 points and 20 points. For this analysis, a subject must have two consecutive visits with pain deterioration (e.g. two consecutive visits where the pain score drops 10 or 20 points below the baseline score). When this event occurs, the date of the event is backdated to the first visit with the pain deterioration. The results of the confirmed pain to deterioration (>=10 points) are considered in Figure 6 (page 17). Once again the results show separation between the palbociclib arm and the placebo arm (HR = 0.616, 95% CI: 0.40, 0.92). The 20 point confirmed results give similar estimates HR = 0.396 (95% CI: 0.202, 0.778).

Reviewers Comment: There does appear to be a difference between the palbociclib arm and the placebo arm regarding time to deterioration of pain. Compared the pre-specified analysis

(>=10 points increase), other analyses had few number of events. The magnitude of difference and the clinical interpretation of this endpoint are subject to debate.

Figure 5: Time to Deterioration of Pain (>=20 increase in pain over baseline)



Source: Reviewers Analysis

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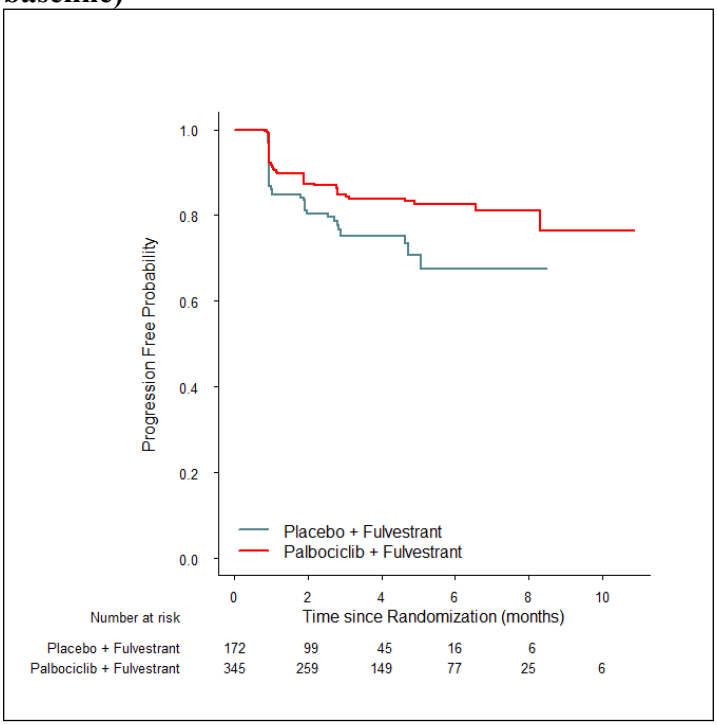
ON ORIGINAL

Figure 6: Time to Confirmed Deterioration of Pain (consecutive >=10 increase in pain over baseline)



Source: Reviewers Analysis

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

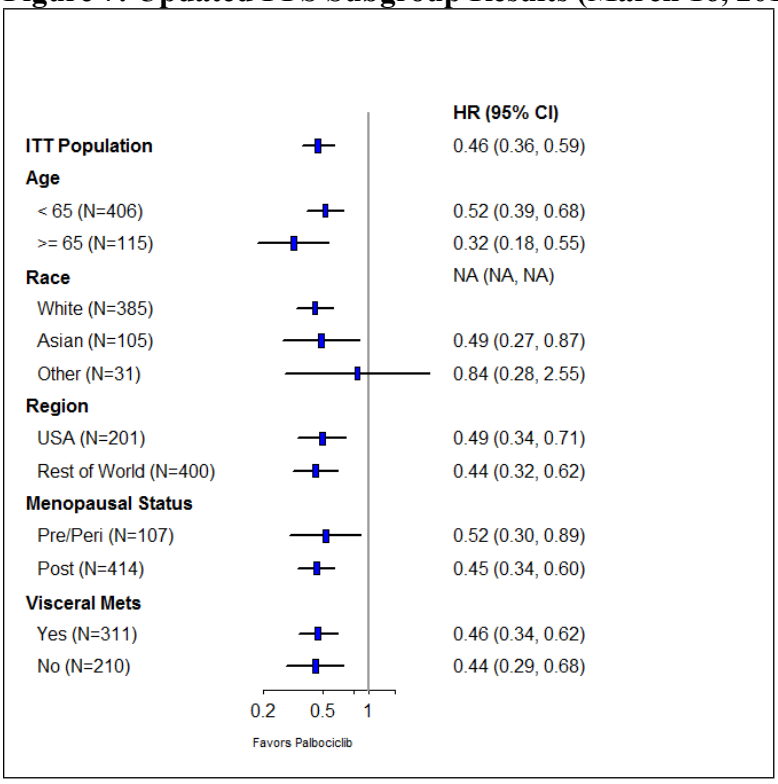
Subgroup results of the primary investigator PFS results at the time of the updated analysis are presented in

APPEARS THIS WAY ON ORIGINAL

Figure 7 (page 18). The results showed no outlier subgroups based on the exploratory analyses.

Reviewers Comment: No outlier subgroups were identified.

Figure 7: Updated PFS Subgroup Results (March 16, 2015 cutoff)



*No adjustments made for multiplicity.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There did not appear to be any major statistical issues with this application. This application utilized a BICR audit to reinforce the results of the primary PFS results. The clinical review team and the clinical outcome assessment staff should determine whether (b) (4)

5.2 Conclusions and Recommendations

Paloma-3 was a well-designed large, phase 3, trial that overcomes many of the limitations of Paloma-1, the basis for the original accelerated approval. Based on the data from Paloma-3, the combination of palbociclib + fulvestrant shows a statistically significant improvement in PFS when compared to fulvestrant alone in previously treated patients. Whether the data and analyses provided in this submission showed an overall favorable benefit/risk profile in supporting a traditional approval is deferred to the clinical review team.

5.3 Labelling Recommendations

It is recommended to include PFS results at the time of the updated analysis (March 16, 2015). The updated results provide more complete follow-up, and the timing and number of events mimic the results of the originally planned final PFS analysis.

(b) (4)

APPENDIX: Description of Multiple Imputation BICR Analysis

This appendix provides a brief description of the multiple imputation (MI) BICR analysis described in Section 3.2.2 and used in Section 3.2.6. The MI method is based upon the idea of "filling-in" the PFS times not seen by the BICR. To do this, the method uses the relationship between the BICR PFS time and the primary investigator (INV) time on the audited samples, and then imputes the missing BICR PFS times not seen. The MI method also does this for the unknown censoring indicators. Note that since the audit sample selected is a random sample, the missing BICR PFS are missing at random (MAR), and in fact missing completely at random (MCAR).

To impute the missing BICR PFS times, the method assumes that the BICR PFS time (T) is a mixture distribution. In particular

$$T = p*t + (1-p)*Y$$

where p is assumed to be an independent binominal random variable with probability π, t is the known INV PFS time, and

$$Y \sim Normal(\beta_0 + \beta_1 t + \beta_2 c + \beta_3 ct, \sigma^2).$$

In the distribution for Y, c is the treatment arm and σ^2 is the variance. In a sense, the model assumes that the BICR PFS times are equal to the INV PFS time with probability π, otherwise the BICR PFS times are a normally distributed about the INV PFS time.

Using this distribution, the MI method models all values of the BICR times. Then using Markov-Chain Monte Carlo (MCMC) techniques, the parameters $\beta_0, \beta_1 t, \beta_2, \beta_3, \sigma^2$, are updated as well as the missing t for all the BICR times that were not audited. A special jumping is rule is used to update the missing t, since this random variable shares time between a discrete space and a continuous space. To impute the missing censoring indicators, it is assumed that the unknown censoring indicators following a logistic regression distribution, with a similar mean structure as Y. The MCMC chain is run for 100,000 iterations, with a burn-in of 10,000 iterations. Mixing does not appear to be an issue for the chain.

Using the MCMC procedure, the MI method imputes 50 complete datasets by taking every 2,000th iteration as a random draw. Then using standard MI techniques, hazard ratios and standard errors are estimated on each of the 50 complete datasets and combined using the usual MI techniques (see for example Little and Rubin. Statistical Analysis of Missing Data. 2nd edition. Wiley, 2003.)

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/s/

ERIK W BLOOMQUIST
02/05/2016

SHENGHUI TANG
02/05/2016

RAJESHWARI SRIDHARA
02/05/2016

NDA/BLA Number: **Applicant: Pfizer** **Stamp Date: 10/15/2015**

NDA 207103
Ibrance (Palbociclib)

NDA/BLA Type: Priority

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	√			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

NA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	√			
Appropriate references for novel statistical methodology (if present) are included.			√	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as	√			

described by applicant appears adequate.				

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/s/

ERIK W BLOOMQUIST
11/09/2015

SHENGHUI TANG
11/10/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207103Orig1s002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY FILING FORM

Application Information

BLA Number (sBLA)	207103	**SDN**	193
Applicant	Pfizer	**Submission Date**	10/15/15
Generic Name	Palbociclib	**Brand Name**	Ibrance™
Drug Class	Kinase inhibitor		
Approved Indication	IBRANCE, in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor (HER2)-negative advanced breast cancer as initial endocrine-based therapy.		
Newly Proposed Indication in sBLA	(b) (4)		
Dosage Regimen	Recommended starting dose: 125 mg once daily taken with food for 21 days followed by 7 days off treatment.		
Dosage Form	Capsules: 125 mg, 100 mg, and 75 mg	**Route of Administration**	oral
OCP Division	Division V	**OND Division**	**OHOP/ DOP1**

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Jeanne Fourie Zirkelbach, PhD and Wentao Fu, PhD	Qi Liu, PhD
Pharmacometrics	Jerry Yu, PhD	Yaning Wang, PhD
Genomics		

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	11/10/2015	**74-Day Letter Date**	
Review Due Date	1/15/2016	**PDUFA Goal Date**	2/1/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies ☑ Yes ☐ No Clinical Pharmacology Summary ☑ Yes ☐ No

Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies		
Study Type	**Count**	**Comment(s)**
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☑ Drug-Drug Interaction	4	A5481039: A phase 1, open-label, fixed-sequence, 2-cohort, 2-period study to investigate the effect of modafinil and pioglitazone given as multiple doses on single dose pharmacokinetics of palbociclib in healthy volunteers. Note this trial will be reviewed by Dr. Wentao Fu. To evaluate trough concentrations of palbociclib when given in combination with fulvestrant or fulvestrant plus goserelin compared to historical palbociclib data (data from registration trial **1023**). To compare fulvestrant and goserelin trough concentrations when given in combination with palbociclib to those when given without palbociclib (data from registration trial **1023**) .
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☐ Relative Bioavailability		
☐ Bioequivalence		
☐ Food Effect		
☐ Other		
Human Pharmacokinetics		
Healthy Subjects – ☑ Single Dose	1	A5481032 A Phase 1, Open-Label Study to Investigate the Effect of Dose and Ethnicity on Palbociclib (PD-0332991) Pharmacokinetics in Japanese Healthy Volunteers
Healthy Subjects – ☐ Multiple Dose		
Patients – ☐ Single Dose		
Patients – ☑ Multiple Dose		A5481023- Registration Trial: Multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial of fulvestrant (Faslodex®) with or without PD-0332991 (palbociclib) ± goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy. Collected sparse PK sampling.
☐ Mass Balance Study		
☑ Other (e.g. dose proportionality)		
Intrinsic Factors		
☑ Race	2	A5481010 (Phase 1 portion) in Japanese Patients A5481032 A Phase 1, Open-Label Study to Investigate the Effect of Dose and Ethnicity on Palbociclib (PD-0332991) Pharmacokinetics in

		Japanese Healthy Volunteers
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☑ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☑ Population Pharmacokinetics	1	PopPK modeling (registration trial **1023**)
☐ Exposure-Efficacy	2	exposure/response analysis for PFS (registration trial **1023**)
☐ Exposure-Safety	2	PK/PD modeling for neutropenia (registration trial **1023**)

Total Number of Studies	**In Vitro**		**In Vivo**	6
Total Number of Studies to be Reviewed				6

Criteria for Refusal to File (RTF)

RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose	☑Yes ☐No ☐N/A	

adjustment?		
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	See 10. Below.
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☑N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☐Yes ☑No ☑N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	During the Pre-sNDA Mtg on June 16, 2015, FDA agreed that Pfizer could submit their Clin Pharm information (Population pharmacokinetic analysis and exposure/response analysis for efficacy endpoint PFS from Study 1023) as a standalone document, submitted within 45 days of the sNDA submission. The sponsor has stated they expect to submit this information on or about Nov 27th, 2015.
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☑N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☑Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to	☑Yes ☐No ☐N/A	

assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

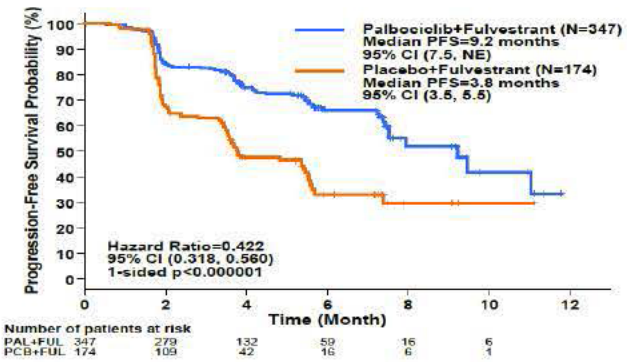
Trial 1023 (Applicant Protocol Summary):
Protocol Title:
Multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial of fulvestrant (Faslodex®) with or without PD-0332991 (palbociclib) ± goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy. Collected sparse PK sampling.

Rationale and Design:
The Study 1023 design was based on encouraging early data in postmenopausal women with newly diagnosed estrogen receptor (ER)-positive, HER2-negative metastatic breast cancer, which indicated that addition of palbociclib to letrozole significantly extended progression free survival (PFS) with a tolerable safety profile (Study 1003, PALOMA-1). There are limited clinical data on the activity of palbociclib in patients whose disease recurred on or soon after antihormonal therapy, a population that may be less sensitive to retreatment with antihormonal therapy. Overcoming resistance to endocrine therapy in breast cancer is still a major challenge and represents an unmet need in women resistant to endocrine therapy.

This study was an international, multicenter, 2:1 randomized, double-blind, placebo-controlled, parallel-group, Phase 3 clinical study with the primary objective of demonstrating the superiority in prolonging PFS (as assessed by the Investigator) of palbociclib in combination with fulvestrant (Faslodex®) over fulvestrant plus placebo in women with HR positive, HER2-negative metastatic breast cancer, regardless of their menopausal status, whose disease had progressed after prior endocrine therapy. Secondary endpoints (PFS, OR, DR, CBR, OS), pharmacokinetic (PK), PRO and safety of the 2 treatment arms were also compared. Pre- and perimenopausal women were to receive therapy with the luteinizing hormone-releasing hormone (LHRH) agonist goserelin (Zoladex® or generic). Approximately 417 eligible women were planned to be randomized assigned on a 2:1 basis to receive either palbociclib plus fulvestrant (approximately 278 women; investigational arm), or placebo plus fulvestrant (approximately 139 women; comparator arm).

Efficacy Results:
At the data cutoff date, 05 Dec 2014, 102 (29.4%) out of 347 patients in the palbociclib plus fulvestrant arm and 93 (53.4%) out of 174 patients in the placebo plus fulvestrant arm had experienced disease progression or death. At the time of data cutoff, the study met its primary objective of prolonging investigator-assessed PFS at the interim analysis; the results crossed the pre-specified Haybittle-Peto efficacy boundary (α=0.00135), demonstrating a statistically significant prolongation in PFS and a clinical meaningful treatment effect. The combination of palbociclib plus fulvestrant was superior to placebo plus fulvestrant, with median investigator assessed PFS of 9.2 months (95% CI: 7.5, not estimable) vs 3.8 months (95% CI: 3.5, 5.5) and a HR of 0.422 (95% CI: 0.318, 0.560, 1-sided $p<0.000001$).

Figure S1. Kaplan-Meier Plot of Progression-Free Survival, Investigator Assessment - Intent-to-Treat Population



Pharmacokinetic Results:
The ratio of the adjusted geometric means (90% CI) for palbociclib steady-state C_{trough} in the presence and absence of goserelin was 90.35% (80.20%, 101.79%) in the ANOVA model and 88.28% (78.64%, 99.12%) for the final ANCOVA model accounting for baseline body weight. The ratio of the adjusted geometric means (90% CI) for goserelin steady-state C_{trough} in the presence and absence of palbociclib was 110.41% (54.16%, 225.05%) in an ANOVA model. ***These results confirmed a lack of a clinically significant drug-drug interaction (DDI) between palbociclib and goserelin when the two drugs are coadministered.***

The ratio of the adjusted geometric means (90% CI) for palbociclib steady-state C_{trough} in the presence and absence of fulvestrant was 128.96% (117.57%, 141.46%) in the ANOVA model and 127.61% (116.67%, 139.57%) for the final ANCOVA model accounting for baseline body weight. The ratio of the adjusted geometric means (90% CI) for fulvestrant steady-state C_{trough} in the presence and absence of palbociclib was 122.06% (101.06%, 147.42%) in the ANOVA model. ***These results confirmed a lack of a clinically significant DDI between palbociclib and fulvestrant when the two drugs are coadministered.***

The ratio of the adjusted geometric means (90% CI) for fulvestrant steady-state C_{trough} in the presence or absence of goserelin was 103.11% (79.61%, 133.55%) in an ANOVA model for the palbociclib treatment arm and 123.88% (87.14%, 176.09%) in an ANOVA model for the placebo treatment arm. ***These results suggest that coadministration of goserelin does not have a clinically significant impact on fulvestrant plasma PK.***

Safety:
The most common treatment-emergent adverse events (TEAEs) (≥25%) observed following treatment with palbociclib and fulvestrant were Neutropenia, Fatigue, Nausea, White blood cell (WBC) count decreased, and Anaemia, and the most common TEAEs (≥25%) observed following treatment with placebo plus fulvestrant were Fatigue and Nausea. Most of these events were treatment-related.

Protocol A5481039 (Applicant Protocol Summary)

Protocol Title:
A Phase 1, Open-Label, Fixed-Sequence, 2-Cohort, 2-Period Study to Investigate the Effect of Modafinil and Pioglitazone Given as Multiple Doses on Single-Dose Pharmacokinetics of Palbociclib (PD-0332991) in Healthy Volunteers.

Objectives:
The primary objectives of this study were: 1) to investigate the effect of multiple doses of the moderate cytochrome P450, family 3, subfamily A (CYP3A) inducer modafinil on the pharmacokinetics (PK) of a single oral 125 mg dose of palbociclib administered in the fed state, 2) to investigate the effect of multiple doses of the weak CYP3A inducer pioglitazone on the PK of a single oral 125 mg dose of palbociclib administered in the fed state.

Study Design:
This was a Phase 1, open-label, fixed-sequence, 2-cohort, 2-period study to investigate the effect of multiple doses of the moderate and weak CYP3A enzyme inducers, modafinil and pioglitazone, respectively, on palbociclib PK in healthy volunteers. This study was conducted in a staged approach, first with Cohort 1 (modafinil). Then, preliminary analysis of PK data from Cohort 1 was to be used to determine the need to conduct Cohort 2 (pioglitazone). Fourteen (14) subjects were planned to be enrolled for each Cohort for a total of 28 subjects planned for the entire study.
Results:
This study was designed to be a fixed-sequence, 2-cohort, 2-period study and was to be conducted in a staged approach, first with

Cohort 1 (the moderate CYP3A inducer modafinil). Preliminary analysis of PK data from Cohort 1 was used to determine whether Cohort 2 (the weak CYP3A inducer pioglitazone) would be conducted. Based on the preliminary result of Cohort 1, which showed a <40% reduction of palbociclib exposure in the presence of steady-state modafinil, the decision was made not to proceed with Cohort 2 as the potential effect of pioglitazone on palbociclib PK was expected to be limited. The assessment in Cohort 2 was not considered necessary for providing dosing recommendations and hence the second primary objective of the study was not assessed. This study was considered complete after the completion of Cohort 1.

Table S4. Statistical Summary of Treatment Comparisons for Palbociclib Pharmacokinetic Parameters

Plasma Palbociclib Parameter [units]	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Palbociclib + Modafinil (Test)	Palbociclib Alone (Reference)		
AUC_{inf} [ng•hr/mL]	1227	1799	68.21	(61.62, 75.51)
AUC_{last} [ng•hr/mL]	1177	1732	67.96	(61.15, 75.52)
C_{max} [ng/mL]	52.52	59.34	88.51	(80.55, 97.25)

One (1) subject was not compliant with the Period 2 outpatient modafinil dosing regimen and was excluded from all summaries for the palbociclib + modafinil treatment.
Abbreviation: AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time; AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of last quantifiable concentration; CI = confidence interval; C_{max} = maximum observed plasma concentration
a The ratios (and 90% CIs) are expressed as percentages.

Protocol 1032 (Applicant Protocol Summary):

Protocol Title:
A Phase 1, Open-Label Study to Investigate the Effect of Dose and Ethnicity on Palbociclib (PD-0332991) Pharmacokinetics in Japanese Healthy Volunteers
Primary Objectives:
 To investigate the dose proportionality of 4 single oral dose levels of palbociclib, when given to healthy Japanese volunteers in a fed state.
 To investigate the effect of ethnicity on the pharmacokinetics (PK) of a single oral dose of palbociclib 125 mg given under fed conditions to healthy Japanese subjects and demographic-matched healthy non-Asian subjects.
Study Design:
This was a Phase 1, open-label, parallel cohort study to investigate 1) the dose-proportionality of 4 single oral dose levels of palbociclib administered under fed conditions in healthy Japanese volunteers (all 4 grandparents must be Japanese and born in Japan), and 2) to investigate, via 2 parallel cohorts, the PK of a single oral dose of palbociclib 125 mg administered under fed conditions in Japanese and demographic-matched non-Asian healthy volunteers. Approximately 14 healthy volunteers were to be enrolled to each population cohort to ensure that 12 evaluable subjects from each cohort completed the study.
Pharmacokinetic Results:
Plasma Palbociclib PK and Dose-Proportionality in Japanese Subjects *All Subjects in Cohort 1:* Following administration of single oral doses of palbociclib under fed conditions, peak concentration (Cmax) was observed at a median time for Cmax (Tmax) of approximately 6 hours following administration of single oral doses of palbociclib 75 mg to 150 mg under fed conditions. Mean elimination terminal half-life (t½) value ranged from 22.5 to 23.6 hours for all treatments. Inter-subject variability (geometric percent coefficient of variation [%CV]) for palbociclib exposures ranged between 22%-25% for AUCinf and 24%-33% for Cmax.

Cohort 1 Completed Subjects: In the Cohort 1 Completed Subjects Analysis Set, palbociclib exposure (AUCinf and Cmax) increased with increasing dose from 75 mg to 150 mg and the increases appeared to be dose-proportional. Dose-normalized median concentration-time profiles by dose showed superposition and box-plots of the individual Cmax(dn) and AUCinf(dn) demonstrate relative consistency in the central tendency and range of the observed parameters across doses, both supporting dose-proportionality of palbociclib in the Japanese population across the dose range of 75 to 150 mg.

Effect of Ethnicity on Palbociclib PK (Japanese Relative to Non-Asian Subjects) Following administration of single oral doses of palbociclib 125 mg given under fed conditions to healthy Japanese subjects and demographic-matched healthy non-Asian subjects, plasma exposure in Japanese subjects was generally higher than that in non-Asian subjects. Time to peak concentration (Tmax) was similar between cohorts, with observed median Tmax values of 6.05 hours for Japanese subjects and 6.02 hours for non-Asian subjects. Apparent mean elimination t½ was also similar between cohorts, with observed mean values of 22.82 hours for Japanese subjects and 23.91 hours for non-Asian subjects.

Results for the supplemental *ad hoc* statistical comparison of palbociclib exposure between the demographic-matched cohorts of Japanese and non-Asian subjects excluding outliers, are presented in Table S4. When single oral doses of palbociclib 125 mg were

administered with food, palbociclib geometric mean AUCinf and Cmax values were 30% and 35% higher, respectively, in Japanese subjects when compared to the demographic-matched non-Asian subjects. The ratios of adjusted geometric means (90% CI) of palbociclib AUCinf and Cmax were 129.83% (111.66%, 150.96%) and 135.24% (110.53%, 165.49%), respectively, for palbociclib given to Japanese subjects relative to the non-Asian subjects under fed conditions.

Variability in palbociclib PK parameters was similar between cohorts. Inter-subject variability (geometric %CV) for palbociclib exposures, as measured by AUCinf and Cmax, were 24% and 33%, respectively, for Japanese subjects. The inter-subject variability (geometric %CV) for palbociclib AUCinf and Cmax were 26% and 39%, respectively, for the non-Asian population.

Table S4. Statistical Summary of Treatment Comparison for Palbociclib Single Oral Dose of 125 mg in Demographic-Matched Japanese and Non-Asian Subjects, Outliers Excluded

	Adjusted Geometric Means			
Parameter [units]	Cohort 1: Japanese Subjects (Test)	Cohort 2: Non-Asian Subjects (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio[a]
AUC_{inf} [ng•hr/mL]	2136	1645	129.83	(111.66, 150.96)
AUC_{last} [ng•hr/mL]	2076	1591	130.53	(112.15, 151.91)
C_{max} [ng/mL]	72.05	53.28	135.24	(110.53, 165.49)

One (1) subject in Cohort 2 was excluded as an outlier.
Abbreviations: AUC = area under the concentration-time profile, AUC_{inf} = AUC from time zero extrapolated to infinite time, AUC_{last} = AUC from time zero to the time of the last quantifiable concentration, CI = confidence interval, C_{max} = maximum observed concentration
a. The ratios (and 90% CIs) are expressed as percentages.

Conclusion:

Following single oral doses of palbociclib 125 mg administered with food, palbociclib geometric mean AUCinf and Cmax values were 30% and 35% higher, respectively, in Japanese subjects when compared to demographic-matched non-Asian subjects. The ratios of adjusted geometric means (90% CI) for palbociclib AUCinf and Cmax were 129.83% (111.66%, 150.96%) and 135.24% (110.53%, 165.49%), respectively, for Japanese subjects relative to non-Asian subjects.

Relevant Applicant Submitted labeling Changes:

(b) (4)

[redacted]

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/s/

JEANNE FOURIE ZIRKELBACH
02/10/2016

QI LIU
02/10/2016

CLINICAL PHARMACOLOGY REVIEW

FDA	20-7103 (IND 69,324)
Submission Date:	10/15/15 and 11/21/15
Brand Name:	Ibrance™
Generic Name:	Palbociclib (PD-0332991 or PF-00080665)
Formulation:	75, 100, 125 mg capsules
DCP Reviewer:	Wentao Fu, PhD and Jeanne Fourie Zirkelbach, PhD
DCP Team Leader:	Qi Liu, PhD
Pharmacometrics Reviewer:	Jingyu (Jerry) Yu, PhD
Pharmacometrics Team Leader:	Yaning Wang, PhD
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Pfizer Inc.
Submission Type; Code:	Suppl-2 Efficacy, SDN 193, 194, 221
Dosing regimen:	Ibrance capsules taken orally with food (b) (4) The recommended palbociclib dose is 125 mg once daily taken with food for 21 days followed by 7 days off treatment.
Indication:	(b) (4)

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1 Executive Summary

On 2/3/15, Accelerated Approval was granted to palbociclib (IBRANCE™), based on the efficacy and safety data from trial 1003 (PALOMA-1). The indication for Accelerated Approval was palbociclib (Ibrance) in combination with letrozole, for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease.

The objectives of the current Efficacy Supplement-2 (SDN 193, 194, 221) are as follows:

1. (b) (4) The palbociclib dosing regimen is the same as that for the initial approval, (b) (4) The proposed dosing regimen is 125 mg palbociclib taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib capsules should be taken with food (b) (4)

2. To provide the final study report to fulfill Post Marketing Requirement 2860-3 identified in the 2/3/2015 Original Approval Letter as follows:

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

(b) (4) results from the randomized double-blind placebo-controlled phase 3 trial (A5481023, Study 1023, PALOMA 3), comparing palbociclib + fulvestrant (with or without goserelin) [N=347] with placebo + fulvestrant (with or without goserelin) [N=174] in women with HR-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy were submitted. Palbociclib or placebo was administered orally once daily on Days 1 to 21 of each 28-day cycle. In Cycle 1, fulvestrant was administered intramuscularly on Day 1 and 15, and thereafter every 28 ±7 days, starting from Day 1, Cycle 1. The addition of palbociclib to fulvestrant resulted in a statistically significant improvement in the primary endpoint, investigator-assessed progression free survival (PFS). The median PFS was 9.2 months (95% CI: 7.5, not estimable) in the palbociclib + fulvestrant arm and 3.8 months (95% CI: 3.5, 5.5) in the placebo + fulvestrant arm.

At the fixed dose of 125 mg palbocicib, there was a flat exposure-response relationship for PFS in women enrolled in trial 1023.

In vivo, coadministration of multiple doses of a modafinil (moderate CYP3A inducer) had no clinically significant effect on palbociclib exposure. There was no drug interaction between palbociclib and fulvestant, or between palbociclib and goserelin when these drugs were co-administered in trial 1023.

In vivo, palbociclib exposure was increased by 30% in Japanese subjects (N=13) versus non-Asian subjects (N=12). No initial dose adjustment is needed for patients with Japanese ethnicity, and dose adjustments based on adverse events (as in the current Ibrance Package Insert) for all patients taking palbociclib should be followed.

Recommendations

The current submission is acceptable from a clinical pharmacology perspective (Divisions of Clinical Pharmacology V and Pharmacometrics). The current submission fulfills the postmarketing requirement identified in the February 3, 2015 approval letter as 2860-3 "Submit the final report for your ongoing drug interaction trial (A5481039) entitled, "A phase 1, open-label, fixed-sequence, 2-cohort, 2-period study to investigate the effect of modafinil and pioglitazone given as multiple doses on single dose pharmacokinetics of palbociclib (PD-0332991) in healthy volunteers", to assess the effect of modafinil (a moderate CYP3A inducer) on the pharmacokinetics of palbociclib in healthy volunteers". The adequacy of specific drug information is provided below:

Decision	Sufficiently Supported?	Recommendations and Comments
Evidence of Effectiveness	☒ Yes ☐ No ☐ NA	Pivotal trial
Proposed dose for general population	☒ Yes ☐ No ☐ NA	The proposed dose appears sufficiently efficacious and safe in the proposed patient population. Please refer to the clinical reviews for safety and efficacy.
Dose adjustment in specific patients or patients with co-medications	☒ Yes ☐ No ☐ NA	The final study report and datasets for trial (A5481039) evaluating the effect of modafinil (a moderate CYP3A inducer) on palbociclib exposure in healthy volunteers was submitted and adequate to fulfill PMR 2860-3.
Pivotal bioequivalence studies	☐ Yes ☐ No ☒ NA	
Labeling	☒ Yes ☐ No ☐ NA	

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations.

1.2 Post Marketing Requirements

None

Comments to the Applicant:

None.

1.3 Summary of Clinical Pharmacology Findings

Palbociclib (IBRANCE™) is a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). Interaction with the D-type cyclins activates CDK4/CDK6, which in turn, phosphorylate the retinoblastoma protein (Rb), a critical checkpoint for G1/S cell cycle progression and commitment to cellular proliferation. The proposed indication for (b) (4) The proposed dosing regimen 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. Palbociclib should be taken with food (b) (4)

At the fixed dose of 125 mg palbocicib, there was a flat exposure-response relationship for PFS in women with *HR-positive*, HER2-negative advanced or metastatic breast cancer enrolled in trial 1023.

Based on the Original Approval, in vitro, palbociclib is metabolized by CYP3A4 and SULT2A1.
In vivo, coadministration of multiple doses of a modafinil (moderate CYP3A inducer) had no clinically significant effect on palbociclib exposure. There was no drug interaction between palbociclib and fulvestant, or between palbociclib and goserelin when these drugs were co-administered in trial 1023.

In vivo, palbociclib exposure was increased by 30% in Japanese subjects (N=13) versus non-Asian subjects (N=13). No initial dose adjustment is needed for patients with Japanese ethnicity, and dose adjustments based on adverse events (as in the current Ibrance Package Insert) for all patients taking palbociclib should be followed.

Signatures:

Jeanne Fourie Zirkelbach PhD and Wentao Fu PhD
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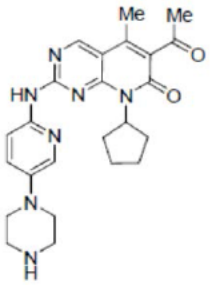
2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The immediate release capsules for oral administration each contains 75 mg, 100 mg, or 125 mg of palbociclib (PD-0332991; (b) (4) freebase).

Figure 1. Structural Formula of palbociclib



- **Established names:** Palbociclib (PD-0332991; (b) (4) freebase)
- **Molecular Weight:** 447.54 Daltons
- **Molecular Formula:** $C_{24}H_{29}N_7O_2$
- **Chirality:** Palbociclib is an achiral molecule.
- **Dissociation Constant (pKa):** There are two dissociation constants of palbociclib, pKa1 = 7.4 (the secondary piperazine nitrogen) and pKa2 = 3.9 (the pyridine nitrogen).
- **Chemical Name:** 6-Acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
- **Solubility:** At or below pH 4, palbociclib behaves as a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Interaction with the D-type cyclins activates CDK4/CDK6, which in turn, phosphorylate the retinoblastoma protein (Rb), a critical checkpoint for G1/S cell cycle progression and commitment to cellular proliferation. Palbociclib (PD 0332991) is a selective, reversible inhibitor of CDK4 and CDK6 that prevents cellular proliferation by prohibiting progression of the cell cycle from G1 into the S phase. The proposed indication is (b) (4)

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosing regimen is the same as that of the Original Approval (b) (4) The palbociclib dosing regimen 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. Palbociclib should be taken with food [redacted] (b) (4)

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?

Table 1 below summarizes the design features of the clinical trials that were used to support the Clinical Pharmacology and Biopharmaceutics Section of the NDA. Consistent with the original marketing application, all of these studies measured plasma concentrations of palbociclib to assess PK parameters and exposure response relationships.

Table 1. Clinical trials that were used to support the Clinical Pharmacology and Biopharmaceutics.

Study No.	Study Type	Study Treatment	Palbociclib Formulation (Fasted/Fed Condition)	N	Full PK Sampling	Sparse Sampling	NCA	PopPK/ PK-PD[a]
A5481023	Phase 3 efficacy and safety (combination of palbociclib with fulvestrant ± goserelin	Palbociclib 125 mg QD on Schedule 3/1; Fulvestrant 500 mg on Days 1 and 15 of Cycle 1, then every 28 days starting from Day 1 of Cycle 1 Goserelin administered as per local standard of care (Subcutaneous administration at least 4 weeks before study treatment start, then every 28 days thereafter) for pre and perimenopausal patients.	Free base capsule[1] with food	347		X		X
A5481032	Phase 1 dose proportionality and Japanese ethnicity effect	Cohort 1; Japanese subjects) A: Palbociclib 75 mg B: Palbociclib 125 mg C: Palbociclib 100 mg D: Palbociclib 150 mg Cohort 2; non-Asian subjects) Palbociclib 125 mg	Free base capsule[1] after moderate-fat meal	27 14 13	X		X	
A5481039	Phase 1 DDI (modafinil and pioglitazone[b])	Cohort 1: Period 1: Palbociclib 125 mg on Day 1 Period 2: Modafinil 200 mg QD on Days 1 through 7; 400 mg QD on Days 8 through 32 Palbociclib 125 mg on Day 28 Cohort 2[b] Period 1: Palbociclib 125 mg on Day 1 Period 2: Pioglitazone 45 mg QD on Days 1 through 19 Palbociclib 125 mg on Day 15	Free base capsule[1] (after moderate-fat meal)	14 NA[b]	X NA	X[c]	X	

Applicant's Population PK and Population Pharmacokinetic-Pharmacodynamic (PK-PD) Reports:

Population PK Analysis and Exposure-response Analysis (PMAR-EQDD-A548b-DP4-508):

An exposure-response analysis was performed by the Applicant to explore the relationship between PFS and palbociclib exposure in women with hormone receptor-positive, HER2-negative metastatic breast cancer that has progressed after prior endocrine therapy. This analysis was based on the available PK data (plasma palbociclib Ctrough) from trial 1023 with a cut-off date of 16 March 2015. A total of 484 patients were included in the exposure-response analysis, including 310 patients from the palbociclib + fulvestrant arm with available palbociclib CL/F estimates and 174 patients from the placebo + fulvestrant arm. The primary analysis included data from only the test arm (palbociclib + fulvestrant) in Study 1023 to explore and quantify the exposure-response relationship using a Cox proportional hazards model with two stratification factors, sensitivity to prior hormonal therapy and presence of visceral metastases. Additional analyses were also conducted using data from both test arm and control arm (placebo +

fulvestrant) in Study 1023 to identify other significant prognostic factors for PFS in the study population (See Pharmacometrics Review, Appendix 4.1 for details).

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The major efficacy outcome measure of trial 1023 was to assess the effect of palbociclib plus fulvestrant compared with that of fulvestrant alone on investigator-assessed PFS. A statistically-significant and clinically-meaningful improvement in PFS or time to progression has been the basis for approval of several drugs for treatment of breast cancer.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

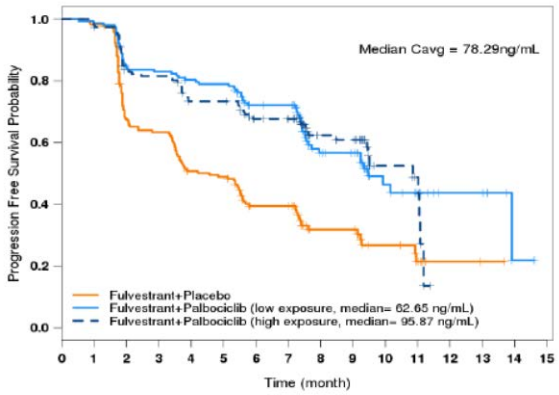
Yes. See the Clinical Pharmacology review for the original submission.

2.2.4 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

The exposure-response (E-R) relationship for PFS appeared to be flat for the target population based on a series of analyses with the available PK data from 310 patients in the treatment arm (Palbociclib Plus Fulvestrant Arm, n=347) in Study 1023. PK/PD analysis for safety endpoints (e.g., neutropenia) suggested that higher exposure of palbociclib was associated with lower neutrophil counts, which is consistent with findings in original NDA submission (see Pharmacometrics Review section in clinical pharmacology review on Jan 15, 2015). These findings support the proposed dosing regimen in the overall patient population.

In addition, longer PFS was found to be correlated with lower baseline AST level, fewer number of disease sites at enrollment (1 disease site relative to more disease sites), higher sensitivity to prior hormonal therapy, a smaller number of prior regimens (1 prior regimen relative to more regimens) and trial sites in Asia/Pacific or Europe (relative to North America). (See Pharmacometrics Review, Appendix 4.1 for details).

Figure 2. Kaplan-Meier Plot of Control Arm, the Low and the High Palbociclib Exposure Group (Trial 1023).



Source Data: ePharm artifact ID=10461618.
C_{avg}=Average palbociclib concentration (time-independent).
Low exposure group=patients with $C_{avg} \leq$ the median C_{avg} (78.29 ng/mL) in patients from palbociclib plus fulvestrant arm.
High exposure group=patients with $C_{avg} >$ the median C_{avg} (78.29 ng/mL) in patients from palbociclib plus fulvestrant arm.

2.2.5 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

There are no unresolved dosing or administration issues, the current proposed dosing regimen for palbociclib is the same as that for the Original Application, (b) (4)

Pharmacokinetic characteristics of the drug and its major metabolites

2.2.6 What are the single dose and multiple dose pharmacokinetic (PK) parameters?

Trial describing the PK of palbociclib in patients with advanced breast cancer (trial 1023):
The study included limited PK sampling, conducted to assess the potential for a clinically significant drug-drug interaction (DDI) between palbociclib and fulvestrant or between palbociclib and goserelin and to evaluate the exposure/response relationship for efficacy endpoints, such as PFS.

For approximately 40 patients included in an early safety review, plasma PK samples were drawn predose on Day 1 and Day 15 of Cycle 1 and Cycle 2, and Day 1 of Cycle 3 for DDI assessments. For patients who receive palbociclib and fulvestrant, PK samples were analyzed for palbociclib and fulvestrant concentrations. For patients who received fulvestrant and placebo, PK samples were analyzed for fulvestrant. For pre and perimenopausal women also receiving goserelin, PK samples were analyzed for palbociclib, fulvestrant and goserelin concentrations. For patients who received fulvestrant, goserelin and placebo, PK samples were analyzed for fulvestrant and goserelin. Concentrations of fulvestrant and goserelin were compared between the palbociclib and placebo subgroups. The concentrations of palbociclib were compared with historical data. In all other patients (ie, those patients not participating the early safety review), PK samples were drawn predose on Day 15 of Cycle 1 and Cycle 2 for palbociclib determination.

Single dose
The single dose PK of palbociclib were fully characterized in the original NDA submission Clinical Pharmacology Review.

Multiple doses
The multiple-dose (125 mg once daily) PK of palbociclib (isethionate capsule formulation) were previously characterized in patients with advanced solid malignant tumors (trial 1001 and 1003) (See Clinical Pharmacology Review, Original NDA Review).

The steady state geometric mean palbociclib C_{trough} values following daily 125 mg oral doses of palbociclib by drug combination from trial 1023 are presented in Table 2, and are comparable to the steady state palbociclib geometric mean C_{trough} values reported for trial 1003 in the Original NDA Clinical Pharmacology review.

Table 2. Summary of plasma palbociclib steady-state plasma trough concentrations (C_{trough}) (ng/mL) following daily 125 mg oral doses of palbociclib by unique drug combination (trial 1023) and as a single agent (trial 1003).

Study	Unique Drug Combination	N	Geometric Mean (Geometric % CV)
1023	Palbocicib + Fulvestrant + Goserelin	43	72.0 (48)
1023	Palbocicib + Fulvestrant - Goserelin	175	77.8 (40)
1023	Palbocicib + Fulvestrant Total[a]	218	76.6 (41)
1003	Palbociclib	71	60.8 (42)

%CV=percent coefficient of variation; N=total number of patients providing trough concentration values in each study. Palbociclib +
[a]Fulvestrant Total was determined as the sum of [Palbocicib + Fulvestrant + Goserelin] Arm and the [Palbocyclib + Fulvestrant – Goserelin] Arm.

2.2.7 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Based on the Original Clinical Pharmacology review, the PK of palbociclib is comparable for patients and healthy volunteers.

2.2.8 What are the characteristics of drug metabolism?

Based on the Original Clinical Pharmacology review, in vitro screens with human hepatocytes, liver cytosolic and S9 fractions and recombinant sulfotransferase (SULT) enzymes indicated that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

2.2.9 What are the characteristics of drug excretion?

Clearance
The geometric mean (%CV) CL/F of palbociclib was 63.1 L/h (29%) (trial 1003) (See Original Submission Clinical Pharmacology Review).

Half-life
The palbociclib mean (±SD) terminal elimination half-fife ($T_{1/2}$) is 28.8 hours (±5) in patients with advanced breast cancer (trial 1003) (See Original Submission Clinical Pharmacology Review).

2.2.10 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Palbociclib has approximately dose-proportional steady state pharmacokinetics over the daily dose range of 25 to 225 mg (See Original Submission Clinical Pharmacology Review).

2.2.11 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The inter-subject variability of palbociclib PK parameters appear comparable between patients with cancer and healthy subjects. The geometric mean (%CV) for the palbociclib (isethionate salt) CL/F value at steady state (125 mg, once daily) in patients with cancer in trial 1003 was 63.1 L/h (29%). The geometric mean (%CV) for palbociclib (commercial free base) CL/F following a single-dose (125 mg) of palbociclib in healthy volunteers was 76.9 L/h (26%) (See Original Submission Clinical Pharmacology Review).

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, weight, height, genetic polymorphisms and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

In the original submission, the applicant population pharmacokinetic analysis assessed the influence of covariates age, sex, body weight, renal impairment (CrCL values ≥ 30 mL/min) and hepatic impairment (mild) on the between-patient differences in palbociclib PK parameters. The FDA pharmacometrics reviewer concluded that there is no need for dose adjustment based on any of these covariates.

Relationship between Japanese Ethnicity and Exposure
In the current submission, trial 1032 was an open-label parallel study that investigated the effect of Japanese ethnicity on palbociclib PK, and was conducted in the United States. When single oral doses of palbociclib 125 mg were administered with food, palbociclib geometric mean AUCinf and Cmax values were 30% and 35% higher, respectively, in Japanese subjects when compared with the demographic-matched non-Asian subjects. No initial dose adjustment is needed for patients with Japanese ethnicity, and dose adjustments based on adverse events (as in the current Ibrance Package Insert) for all patients taking palbociclib should be followed.

The study assessed the PK of a single oral 125 mg dose of palbociclib (commercial free base capsule formulation) administered under fed conditions in Japanese (1st-, 2nd-, or 3rd-generation Japanese; all 4 grandparents must be Japanese and born in Japan) and demographic-matched non-Asian (not from Asian or Polynesian origins) healthy subjects. The non-Asian cohort racial breakdown was White (N=5) and Black (N=7). Following administration of palbociclib in each treatment period, PK samples were obtained for up to 120 hours postdose. Summary plasma palbociclib PK parameters for Japanese and non-Asian healthy subjects are summarized in Table 3 below. Plasma PK parameters were available

from 13 subjects in Cohort 1 and from 13 subjects in Cohort 2. However, the PK data from one subject (ID: 10011020) in cohort 2 were excluded from the final summary of plasma palbociclib PK parameter values and from the final statistical comparison for Japanese subjects and non-Asian subjects (Table 3 and Table 4). The data from subject 10011020 were excluded based on the applicant's outlier analysis using studentized marginal residuals.

Table 3. Summary of Plasma Palbociclib Pharmacokinetic Parameter Values for Japanese and Non-Asian Subjects Following a Single Oral 125 mg Dose with Food (1032)

Parameter	**Palbociclib 125 mg Capsule in Cohort 1 (Japanese subjects)**	**Palbociclib 125 mg Capsule in Cohort 2 (non-Asian subjects)**
N,n	13,13	12,12
AUCinf [ng.hr/mL]	2136 (24)	1645 (20)
AUClast [ng.hr/mL]	2076 (24)	1591 (20)
Cmax [ng/mL]	72.1 (33)	53.3 (26)
Tmax [hr]	6.1 (4.0-12.0)	7.0 (4.0-12.0)
T1/2 [hr]	22.8 (±3.2)	23.8 (±2.3)
CL/F [L/hr]	58.5 (24)	76.1 (20)
Vz/F [L]	1907 (28)	2597 (24)

%CV=percent coefficient of variation; N= number of subjects in the treatment group; n=number of subjects where $t_{½}$, AUC_{inf}, AUC_{inf}(dn), CL/F, and V_z/F were determined; Std Dev=standard deviation; $t_{½}$=terminal plasma half-life; T_{max}=time to first occurrence of C_{max}; V_z/F=apparent volume of distribution.
Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean (±Std Dev) for $t_{½}$.

The statistical summary of treatment comparisons following a single oral 125 mg dose of palbociclib with food are summarized below in Table 4.

Table 4. Statistical Summary of Treatment Comparison for Palbociclib Single Oral 125 mg Dose in Demographic-Matched Japanese (N=13) and Non-Asian (N=12) Subjects. (1032).

	Adjusted Geometric Means			
Parameter [units]	**Cohort 1: Japanese Subjects (Test)**	**Cohort 2: Non-Asian Subjects (Reference)**	**Ratio (Test/Reference) of Adjusted Means[a]**	**90% CI for Ratio**
AUC_{inf} [ng•hr/mL]	2136	1645	130	(112-151)
C_{max} [ng/mL]	72.1	53.3	135	(111-165)

Abbreviations: AUC_{inf}=area under the plasma concentration-time curve from time 0 to infinity; CI=confidence interval; C_{max}=maximum observed plasma concentration. [a] The ratios (and 90% CIs) are expressed as percentages.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Patients with Japanese Ethnicity:

No initial dose adjustment is needed for patients with Japanese ethnicity, and dose adjustments based on adverse events (as in the current Ibrance Package Insert) for all patients taking palbociclib should be followed.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effects of extrinsic factors such as herbal products, smoking and alcohol use on the dose-exposure and/or dose-response for palbociclib were not assessed in a formal study.

Drug-drug interactions

2.4.2 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

As a substrate (*in vitro*)

In vitro screens with human hepatocytes, liver cytosolic and S9 fractions and recombinant sulfotransferase (SULT) enzymes indicate that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib (See Original NDA Clinical Pharmacology Review).

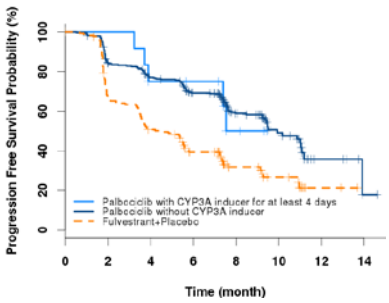
In vivo, coadministration of a strong CYP3A inducer (rifampin) decreased the plasma exposure of palbociclib in healthy subjects by 85% (See Original NDA Clinical Pharmacology Review).

In vivo evaluation of the effect of a moderate CYP3A inducer, modafinil, on the single dose palbociclib pharmacokinetics in healthy volunteers (A5481039):

In the current submission, results from trial 1039 showed that multiple oral doses of modafinil (moderate CYP3A inducer) did not have a clinically significant effect on plabocicib exposure. Specifically coadministration of modafinil decreased the geometric mean palbociclib AUCinf and Cmax by 32% and 11%, respectively, relative to a single 125 mg palbociclib dose given alone.

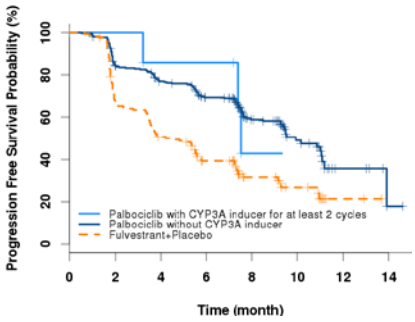
To justify no dose adjustment with moderate CYP3A inducers, the applicant submitted exploratory univariate analyses to compare the PFS in patient subgroups in the palbociclib plus fulvestrant arm stratified by moderate inducer use, and in patients in the placebo plus fulvestrant arm from trial 1023. Figure 3 and Figure 4 show the Kaplan-Meier (KM) curves of three subgroups: Patients who took an inducer in palbociclib plus fulvestrant arm for at least 4 days (Figure 3, 13 patients) or for at least 2 cycles (Figure 4, 7 patients); patients who did not take an inducer in palbociclib plus fulvestrant arm; and patients in placebo plus fulvestrant arm. Results suggest that the coadministration of a moderate CYP3A inducer did not negatively impact the efficacy of palbociclib plus fulvestrant treatment in trial 1023.

Figure 3. Kaplan-Meier Plot of Progression-Free Survival for Patients With Use of CYP3A Inducers for At Least 4 Days, Patients Without Use of CYP3A Inducers in Palbociclib Plus Fulvestrant Arm and Patients in Placebo Plus Fulvestrant Arm (Data Cut-off Date: 16 March 2015, Sponsor Figure from Information Request dated: 1.15.16, SDN 261).



There are 13 patients included in the subgroup with use of CYP3A inducers for at least 4 days, 321 patients in the subgroup without CYP3A inducers and 174 patients from the placebo plus fulvestrant arm, respectively.

Figure 4. Kaplan-Meier Plot of Progression-Free Survival for Patients With Use of CYP3A Inducers for At Least 2 Cycles, Patients Without Use of CYP3A Inducers in Palbociclib Plus Fulvestrant Arm and Patients in Placebo Plus Fulvestrant Arm (Data Cut-off Date: 16 March 2015; Sponsor Figure from Information Request dated: 1.15.16, SDN 261).



There are 7 patients included in the subgroup with use of CYP3A inducers for at least 2 cycles, 321 patients in the subgroup without CYP3A inducers and 174 patients from the placebo plus fulvestrant arm, respectively.

Trial 1039 was a phase 1, open-label, fixed-sequence, 2-period study in 14 health volunteers. Subjects received Reference treatment (palbociclib alone) in Period 1 and then Test treatment (palbociclib + modafinil) in Period 2. In Period 1, palbociclib (a single125 mg orally dose) was administrated on Day 1. In Period 2, modafinil was administrated for 32 days (200 mg PO QD for 7 days starting from day 1 followed by 400 mg PO QD for 25 days) and palbociclib (a single125 mg orally dose) was administrated on Day 28. Palbociclib was administered with a moderate-fat, standard-calorie breakfast in both Periods. Modafinil was administrated without regard to food except on Day 28 of Period 2 when it was coadministered with palbociclib with breakfast. PK sampling to measure plasma palbociclib concentrations was performed pre-dose and for 120 hours post-dose. Two subjects (subject 10011001 discontinued during Period 2 without received palbociclib + modafinil treatment and subject 10011014 was not compliant with the Period 2 outpatient modafinil dosing regimen) was not included in Period 2 summary.

Table 5 summarizes the plasma palbociclib PK parameters following a single oral dose of palbociclib alone and co-administration of palbociclib with modafinil. Results of the statistical comparisons of palbociclib exposure parameters are summarized in Table 6.

Table 5. Summary of Plasma Palbociclib Pharmacokinetic Parameters Following Administration of a

Single Oral Dose of Palbociclib (125 mg) Alone and in the Presence of Steady-State Modafinil Concentrations (400 mg QD) (1039)

Plasma Palbociclib Parameter [Units]	Summary Statistics[a] by Treatment	
	Palbociclib Alone	Palbociclib + Modafinil
N	14	12
AUC_{inf} [ng•hr/mL]	1799 (24)	1220 (25)
AUC_{last} [ng•hr/mL]	1732 (25)	1169 (25)
C_{max} [ng/mL]	59.34 (30)	51.63 (26)
T_{max} [hr]	6.00 (6.00-12.0)	8.00 (6.00-12.0)
T_{last} [hr]	120 (96.0-120)	95.8 (71.8-120)
$t_{½}$ [hr]	22.81 ± 4.58	19.35 ± 3.83
CL/F [L/hr]	69.48 (24)	102.5 (25)
Vz/F [L]	2245 (30)	2814 (25)

Abbreviations: %CV = percent coefficients of variation; QD = once daily; SD = standard deviation N = Number of subjects in the treatment and contributing to the summary statistics.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max} and T_{last}; arithmetic mean (±SD) for $t_{½}$.

Table 6. Statistical Summary of Treatment Comparisons for Palbociclib Pharmacokinetic Parameters (1039).

Plasma Palbociclib Parameter [units]	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Palbociclib + Modafinil (Test)	Palbociclib Alone (Reference)		
AUC_{inf} [ng•hr/mL]	1227	1799	68.21	(61.62, 75.51)
AUC_{last} [ng•hr/mL]	1177	1732	67.96	(61.15, 75.52)
C_{max} [ng/mL]	52.52	59.34	88.51	(80.55, 97.25)

a. The ratios (and 90% CIs) are expressed as percentages.

(b) (4)

An in vivo trial previously evaluated the drug interaction potential between letrozole and palbociclib when the two drugs are coadministered (See Original Submission Clinical Pharmacology Review).

2.4.6 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Letrozole: **D**ata from a drug interaction trial in patients with breast cancer showed that there was no drug interaction between palbociclib and letrozole when the two drugs were coadministered. (See

Original Submission Clinical Pharmacology review).

Tamoxifen: See Original Submission Clinical Pharmacology review.

Fulvestrant and Goserelin: Based on results from trial 1023, fulvestrant does not cause a significant change in the steady state palbociclib exposure (Table 7 and Table 8), and palbociclib does not cause a change in fulvestrant exposure (Table 11). Based on results from trial 1023, goserelin does not cause a significant change in the steady state palbociclib exposure (Table 7 and Table 9), and palbociclib does not cause a change in goserelin exposure (Table 12). Based on results from trial 1023, and goserelin does not cause a significant change in the steady state fulvestrant exposure (Table 10).

Based on the current FASLODEX package insert, there are no known drug-drug interactions with fulvestrant. The package insert states that although, fulvestrant (FASLODEX) is metabolized by CYP 3A4 *in vitro*, drug interactions studies with ketoconazole or rifampin did not alter fulvestrant pharmacokinetics. Dose adjustment is not needed in patients co-prescribed CYP3A4 inhibitors or inducers. Following fulvestrant monthly dosing with an additional dose on Day 15 of the first cycle, steady-state concentrations of fulvestrant are achieved within the first month of study treatment.

Based on the current (ZOLADEX) package insert, no formal drug-drug interaction studies have been performed with goserelin. No confirmed interactions have been reported between goserelin and other drugs.

Study 1023 was designed with the intention of confirming the lack of clinically significant DDI using sparse PK sample collection (trough concentration only) for each analyte.

Assessment of fulvestrant and goserelin DDI potential on palbociclib PK:
The steady state geometric mean palbociclib C_{trough} values following daily 125 mg oral doses of palbociclib by drug combination from trial 1023 are presented in Table 7, and are comparable to the steady state palbociclib geometric mean C_{trough} values reported in the Original NDA Clinical Pharmacology review.

Results, assessing the DDI potential for fulvestrant and goserelin to impact the plasma PK of palbociclib are presented in Table 8 and Table 9. For DDI study design features see Section 2.2.8.

Statistical comparisons of the palbociclib within-subject mean steady-state Ctrough in the presence and absence of fulvestrant, both ignoring (ANOVA) and accounting for (ANCOVA) demographic differences between the treatment groups are shown in Table 8. Since it was established that the presence or absence of goserelin did not have a significant impact on palbociclib PK in Study 1023 (see data below), the "palbociclib plus fulvestrant Total" unique drug combination was the most appropriate selection for the Test treatment group to assess the potential for fulvestrant to perpetrate a DDI on palbociclib plasma PK in statistical models sing historical data as the Reference treatment. The final ANCOVA model to describe the potential for fulvestrant to perpetrate a DDI on palbociclib plasma PK confirmed the lack of a clinically significant DDI.

Statistical comparisons of the palbociclib within-subject mean steady-state Ctrough in the presence and absence of goserelin, both ignoring (ANOVA) and accounting for (ANCOVA) demographic differences between the treatment groups are shown in Table 9. All of the applicant tested ANOVA and ANCOVA models to describe the potential for goserelin to perpetrate a DDI on palbociclib plasma confirmed the lack of a clinically significant DDI. The final ANCOVA model which accounted for only differences in

baseline body weight resulted in a ratio of the adjusted geometric means (90% CI) for palbociclib steady-state Ctrough of 88.28% (78.64%, 99.12%).

Table 7. Summary of plasma palbociclib steady-state PK parameters following daily 125 mg oral doses of palbociclib by unique drug combination (1023).

Unique Drug Combination	Parameter [Units]	Parameter Summary Statistics[1] by Treatment		
		Cycle 1/Day 15	Cycle 2/Day 15	Combined[2]
Palbociclib + Fulvestrant + Goserelin	N	35	33	43
	C_{trough} [ng/mL]	62.04 (51)	69.39 (50)	72.04 (48)
Palbociclib + Fulvestrant - Goserelin	N	130	127	175
	C_{trough} [ng/mL]	73.23 (42)	76.91 (42)	77.79 (40)
Palbociclib + Fulvestrant Total	N	165	160	218
	C_{trough} [ng/mL]	70.70 (44)	75.29 (44)	76.62 (41)
Palbociclib Historical Data[3]	N	--	--	98
	C_{trough} [ng/mL]	--	--	58.77 (45)

Abbreviation: CV: coefficient of variation, N: Number of patients contributing to the geometric mean estimation
1. Geometric mean (% CV)
2. Within-patient mean of steady-state Ctroughs.
3. From Studies 1001, 1002, and 1003.
Fulvestrant Total was determined as the sum of [Palbocicib + Fulvestrant + Goserelin] Arm and the [Palbocyclib + Fulvestrant – Goserelin] Arm.

Table 8. Statistical summary of treatment comparison for pharmacokinetic parameters, assessment of fulvestrant DDI potential on palbociclib pharmacokinetics (1023).

Statistical Model	Parameter [units]	Adjusted Geometric Means: Palbociclib + Fulvestrant Total (Test)	Adjusted Geometric Means: Palbociclib Historical Data[1] (Reference)	Ratio (Test/Reference) of Adjusted Means[2]	90% CI for Ratio[2]
ANOVA	N	217	98		
	C_{trough} [ng/mL]	75.79	58.77	128.96	(117.57, 141.46)
ANCOVA, Full[3]	N	217	98		
	C_{trough} [ng/mL]	76.58	58.59	130.72	(119.13, 143.43)
ANCOVA, Final[4]	N	217	98		
	C_{trough} [ng/mL]	75.18	58.92	127.61	(116.67, 139.57)

Abbreviation: CI: confidence interval, DDI: drug-drug interaction, N: Number of patients contributing to the geometric mean estimation
1. From studies 1001, 1002, and 1003.
2. The ratios (and 90% CIs) are expressed as percentages.
3. Based on log-transformed ANCOVA with final values back-transformed from the log scale. Unique drug combination is the fixed factor with age and baseline weight as the covariates in the full model.
4. Based on log-transformed ANCOVA with final values back-transformed from the log scale. Unique drug combination is the fixed factor with baseline weight as the only covariate in the final model.
One outlier, Patient 10531003, was excluded from these final analyses since the absolute value of the studentized residual was >5 in all statistical models.

Table 9. Statistical summary of treatment comparison for palbociclib pharmacokinetic parameters, assessment of goserelin DDI potential on palbociclib pharmacokinetics (1023).

Statistical Model	Parameter [units]	Adjusted Geometric Means: Palbociclib + Fulvestrant + Goserelin (Test)	Adjusted Geometric Means: Palbociclib + Fulvestrant - Goserelin (Reference)	Ratio (Test/Reference) of Adjusted Means[1]	90% CI for Ratio[1]
ANOVA	N	43	174		
	C_{trough} [ng/mL]	72.04	79.74	90.35	(80.20, 101.79)
ANCOVA, Full[2]	N	43	174		
	C_{trough} [ng/mL]	73.88	79.38	93.07	(81.91, 105.75)
ANCOVA, Final[3]	N	43	174		
	C_{trough} [ng/mL]	70.64	80.01	88.28	(78.64, 99.12)

Abbreviation: CI: confidence interval, DDI: drug-drug interaction, N: Number of patients contributing to the geometric mean estimation
1. From studies 1001, 1002, and 1003.
2. The ratios (and 90% CIs) are expressed as percentages.
3. Based on log-transformed ANCOVA with final values back-transformed from the log scale. Unique drug combination is the fixed factor with age and baseline weight as the covariates in the full model.
4. Based on log-transformed ANCOVA with final values back-transformed from the log scale. Unique drug combination is the fixed factor with baseline weight as the only covariate in the final model.
One outlier, Patient 10531003, was excluded from these final analyses since the absolute value of the studentized residual was >5 in all statistical models.

Assessment of goserelin DDI potential on fulvestrant PK:

Statistical comparisons of the fulvestrant within-subject mean steady-state Ctrough in the presence and absence of goserelin from both the palbociclib and placebo treatment groups are shown in Table 10. In the palbociclib treatment arm, the ratio of the adjusted geometric means (90% CI) for fulvestrant steady-state Ctrough was 103.11% (79.61%, 133.55%) in an ANOVA model. In the placebo treatment arm, the ratio of the adjusted geometric means (90% CI) for fulvestrant steady-state Ctrough was 123.88% (87.14%, 176.09%) in an ANOVA model. Thus, ANOVA models to describe the potential for goserelin to perpetrate a DDI on fulvestrant plasma PK, in both the palbociclib and placebo treatment arms, confirmed the lack of a clinically significant DDI.

Table 10. Statistical Summary of Treatment Comparison For Fulvestrant Pharmacokinetic Parameters, Assessment of Goserelin DDI Potential on Fulvestrant Pharmacokinetics

Statistical Model	Parameter [units]	Adjusted Geometric Means: Palbociclib + Fulvestrant + Goserelin (Test)	Adjusted Geometric Means: Palbociclib + Fulvestrant - Goserelin (Reference)	Ratio (Test/Reference) of Adjusted Means[1]	90% CI for Ratio[1]
ANOVA[2]	N	9	28		
	C_{trough} [ng/mL]	11.05	10.72	103.11	(79.61, 133.55)
Statistical Model	**Parameter [units]**	**Placebo + Fulvestrant + Goserelin (Test)**	**Placebo + Fulvestrant - Goserelin (Reference)**	**Ratio (Test/Reference) of Adjusted Means[1]**	**90% CI for Ratio[1]**
ANOVA[2]	N	5	14		
	C_{trough} [ng/mL]	10.36	8.36	123.88	(87.14, 176.09)

Abbreviation: N: number of subjects contributing to the geometric mean estimation . The ratios (and 90% CIs) are expressed as percentages.
2. Based on log-transformed ANOVA with final values back-transformed from the log scale. Unique drug combination was the fixed factor.

Assessment of palbociclib DDI potential on fulvestrant PK and on goserelin PK:

Fulvestrant steady-state exposures were comparable in the presence and absence of concurrent palbociclib dosing. Fulvestrant geometric mean steady-state Ctrough in the presence of concurrent

palbociclib administration (without regard for goserelin dosing) in Study 1023 was 10.80 ng/mL, which was comparable to the geometric mean steady-state trough value of 8.85 ng/mL from the placebo arm.

Statistical comparisons of the fulvestrant within-subject mean steady-state Ctrough in the presence and absence of palbociclib are shown in Table 11. Since it was established that the presence or absence of goserelin did not have an impact on fulvestrant PK in Study 1023, the "palbociclib plus fulvestrant Total" drug combination was the most appropriate selection for the Test treatment group and the "placebo plus fulvestrant Total" drug combination was the most appropriate selection for the Reference group to assess the potential for palbociclib to perpetrate a DDI on fulvestrant plasma PK in statistical models. The ratio of the adjusted geometric means (90% CI) for fulvestrant steady-state Ctrough was 122.06% (101.06%, 147.42%) in the ANOVA model (Table 11). Thus, the ANOVA model to describe the potential for palbociclib to perpetrate a DDI on fulvestrant plasma PK confirmed the lack of a clinically significant DDI.

Table 11. Statistical Summary of Treatment Comparison For Fulvestrant Pharmacokinetic Parameters, Assessment of Palbociclib DDI Potential on Fulvestrant Pharmacokinetics

		Adjusted Geometric Means			
Statistical Model	Parameter [units]	Palbociclib + Fulvestrant Total (Test)	Placebo + Fulvestrant Total (Reference)	Ratio (Test/Reference) of Adjusted Means[1]	90% CI for Ratio[1]
ANOVA[2]	N	37	19		
	C_{trough} [ng/mL]	10.80	8.85	122.06	(101.06, 147.42)

Abbreviation: CI: confidence interval, DDI: drug-drug-interaction, N: number of subjects contributing to the geometric mean estimation
1. The ratios (and 90% CIs) are expressed as percentages.
2. Based on log-transformed ANOVA with final values back-transformed from the log scale. Unique drug combination is the fixed factor in the base model.

Goserelin steady-state exposures were comparable in the presence and absence of concurrent palbociclib dosing, based on similar median and geometric mean of goserelin Ctrough observed on Day 1 of Cycles 2 and 3 and within-subject mean goserelin steady-state exposures, respectively. Goserelin steady-state exposures, as measured by the geometric mean of the within-subject mean steady-state Ctrough from Day 1 of Cycles 2 and 3, were 302.9 pg/mL and 274.4 pg/mL in the presence and absence of concurrent palbociclib administration, respectively.

Statistical comparisons of the goserelin within-subject mean steady-state Ctrough in the presence and absence of palbociclib are shown in Table 12. The ratio of the adjusted geometric means (90% CI) for goserelin steady-state Ctrough was 110.41% (54.16%, 225.05%) in an ANOVA model. Thus, the ANOVA model to describe the potential for palbociclib to perpetrate a DDI on goserelin plasma PK confirmed the lack of a clinically significant DDI.

Table 12. Summary of Plasma Goserelin Steady-State Pharmacokinetic Parameters by Unique Drug Combination (1023).

Unique Drug Combination	Parameter [Units]	Parameter Summary Statistics[1] by Treatment		
		Cycle 2/Day 1	Cycle 3/Day 1	Combined[2]
Palbociclib + Fulvestrant + Goserelin	N	9	7	9
	C_{trough} [pg/mL]	295.1 (153)	344.8 (64)	302.9 (115)
Placebo + Fulvestrant + Goserelin	N	5	3	5
	C_{trough} [pg/mL]	302.5 (74)	288.5 (40)	274.4 (49)

Abbreviation: CV: coefficient of variation, N=Number of subjects contributing to the geometric mean estimation, NC=not calculated
1. Geometric mean (% CV); 2. Within-subject mean of steady-state Croughs

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes, plasma concentrations of the active parent, palbociclib, were measured in the clinical pharmacology and biopharmaceutics studies.

2.6.2 Which metabolites have been selected for analysis and why?

Not applicable.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total plasma concentration of palbociclib was measured in the clinical trials, and this was appropriate based on the original submission clinical pharmacology review.

2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf)

Methods for the analysis of palbociclib in human plasma samples collected during clinical studies were described in the original NDA submission Clinical Pharmacology review.

Modafinil Plasma Concentrations:
Plasma samples obtained in protocol 1039 were analyzed for modafinil, modafinil acid and modafinil sulfone by [redacted] (b) (4) using HPLC with MS/MS detection (A5489020). For modafinil and modafinil sulfone, the lower limit of quantitation (LLOQ) was 0.100 µg/mL and the linear calibration range was appropriate at 0.100 µg/mL to 50.0 µg/mL for both analytes. For modafinil acid, the LLOQ was 0.0200 µg/mL and the linear calibration range was appropriate at 0.0200 to 10.0 µg/mL. The linearity of the methods were evaluated by analyzing calibration standards over the nominal concentration ranges provided above using a linear weighted, 1/concentration squared, least-squares regression algorithm to plot the peak area ratio of the analyte to its internal standard versus concentration.

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

See the Original Submission Clinical Pharmacology review.

2.6.6 What is the QC sample plan?

See the Original Submission Clinical Pharmacology review.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The red text is the proposed changes added by the Applicant. Yellow highlighted text shows changes added by the clinical pharmacology reviewer.

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

4 APPENDICES

4.1 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

1.1.1 Does the exposure-response (E-R) relationship for efficacy and safety support the proposed dose?

Yes. E-R relationship for PFS appeared to be flat for the target population based on a series of analysis with the available PK data from 310 patients in the treatment arm (Palbociclib Plus Fulvestrant Arm, n=347) in Study 1023. PK/PD analysis for safety endpoints (e.g., neutropenia) suggested that higher exposure of palbociclib was associated with lower neutrophil counts, which is consistent with findings in original NDA submission (see pharmacometric review section in clinical pharmacology review on Jan 15, 2015). These finding support the proposed dose regimen in overall patient population.

In addition, longer PFS was found to be correlated with lower baseline AST level, fewer number of disease sites at enrollment (1 disease site relative to more disease sites), higher sensitivity to prior hormonal therapy, a less number of prior regimens (1 prior regimen relative to more regimens) and trial sites at Asia/Pacific or Europe (relative to North America).

1.2 Recommendations

The Division of Pharmacometrics in Office of Clinical Pharmacology has reviewed the information contained in this NDA submission. This NDA is considered acceptable from a pharmacometrics perspective.

2 RESULTS OF SPONSOR'S ANALYSIS

Data

The E-R analysis was conducted using the available data from Study 1023 which was a Phase 3 trial with the primary objective of demonstrating the superiority of palbociclib in combination with fulvestrant over fulvestrant plus placebo in women with HR-positive, HER2-negative metastatic breast cancer, regardless of their menopausal status, whose disease had progressed after prior endocrine therapy.

Of the 521 patients, 347 patients were randomized to receive palbociclib 125 mg orally once daily (QD) on Days 1 to 21 of each cycle with duration of 28 days (3/1 schedule) plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, every 28 days thereafter starting from Day 1 of Cycle 1. The other 174 patients were randomized to receive placebo QD on Days 1 to 21 of each cycle with duration of 28 days plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, every 28 days thereafter starting from Day 1 of Cycle 1. Trough PK samples were drawn on Day 15 of Cycle 1 and Cycle 2 for determination of palbociclib concentrations.

Method

Due to the sparseness of the PK data collected in Study 1023 (only trough data), Bayesian analysis was applied based on a previous Pop PK model for palbociclib and observed PK data from Study 1023 to obtain the individual PK parameters.

C_{avg} is not sensitive to the timing of dose modifications and could not reflect the time-varying change in the palbociclib exposure, hence, using C_{avg} to explore the exposure-response analysis might be biased given the different timings of dose interruptions and reductions in relation to each patient's event time. Thus, a time-varying average concentration, C_{avgt}, was derived for each patient. In the efficacy dataset, the event times of all patients in this trial were provided for each patient in a time sequential order until the time of each patient's own event or censor time (event times were not given after the event or censor occurred to the patient), and average daily dose intensities from the first dosing day up to all applicable event times (represented as ADIT hereafter) were calculated for each patient at risk until that patient had an event or was censored. For example, if there were "n" patients with events in this trial and the events occurred at times t_1, t_2, …, t_{n-1}, t_n, multiple ADIT values (e.g., $ADIT_{0\sim t1}$, $ADIT_{0\sim t2}$,… $ADIT_{0\sim ti-1}$, and $ADIT_{0\sim ti}$) for each patient were calculated (t_i is the event time or censor time of the ith patient; ADIT were not to be calculated after t_i for the ith patient). Subsequently, each individual patient's relevant ADIT values in conjunction with their post-hoc estimate for CL/F were used to calculate multiple C_{avgt} values for each patient (e.g., $C_{avg,0-t1}$, $C_{avg,\ 0-t2}$,…, $C_{avg,0\sim ti-1}$, and $C_{avg,0-ti}$) using the equation below. Using C_{avgt} would allow the evaluation of exposure-response relationship for each patient at risk at all applicable event times.

$$\text{Time-varying average concentration } (C_{avgt,0-t},\ \text{ng/mL}) = \frac{\text{Average daily dose intensity } (ADIT_{0-t}) / (CL/F)}{24\ \text{h}}$$

Kaplan-Meier analysis and Cox proportional hazards analysis (univariate and multivariate) were used to evaluate E-R relationship for PFS based on the data from combination arm.

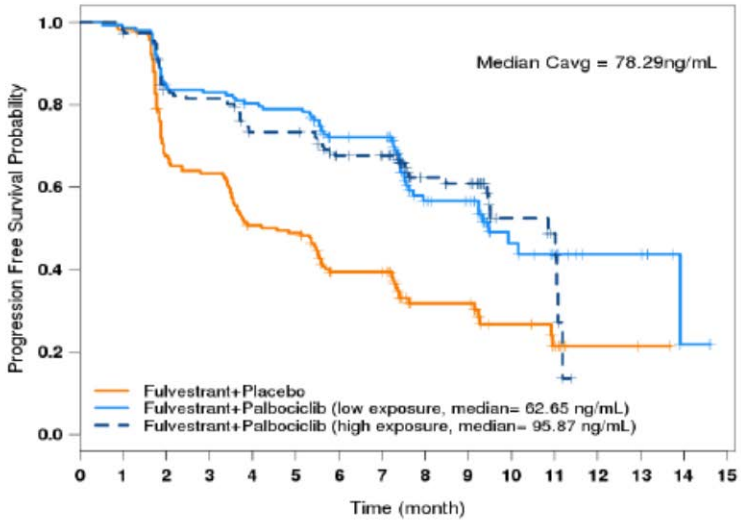
In addition, pooled data from both combination and control arm were used to identify prognostic factors and quantify the effect of these factors on PFS in the target population.

Results and Conclusions

Kaplan-Meier analysis

The 310 patients from test arm were divided into the low and the high palbociclib exposure groups according to C_{avg}. The Kaplan-Meier plot of 2 exposure groups versus control arm is presented in Figure 1. The plot shows that both 2 exposure groups had substantially higher PFS probability compared to control treatment, but the PFS probability over time for 2 exposure groups are similar.

Figure 1: Kaplan-Meier Plot of Control Arm, the Low and the High Palbociclib Exposure Group



Source Data: ePharm artifact ID=10461618.
C_{avg}=Average palbociclib concentration (time-independent).
Low exposure group=patients with $C_{avg} \leq$ the median C_{avg} (78.29 ng/mL) in patients from palbociclib plus fulvestrant arm.
High exposure group=patients with $C_{avg} >$ the median C_{avg} (78.29 ng/mL) in patients from palbociclib plus fulvestrant arm.

Sources: Sponsor's report, PMAR-EQDD-A548b-DP4-508, "Population Pharmacokinetic and Exposure-Response Analyses to Evaluate the Relationship Between Palbociclib Exposure and Progression-Free Survival (PFS) in Women With Metastatic Breast Cancer That Has Progressed After Prior Endocrine Therapy" , Page 10

Multivariate Cox proportional hazards analysis

With the other covariates included, the effect of C_{avgt} was not statistically significant with 95% CI of hazard ratio including 1 (Table 1). This model was considered as a full model. Multiple covariates were added into the full model separately as the post-treatment neutrophil response of patients. The results showed none of these covariates was significantly correlated with PFS, and the inclusion of any of them did not significantly change the exposure effect on PFS quantified in the multivariate analysis. Therefore, the covariate related to neutrophil response was not included in the full Cox model. A backward elimination process was performed from it by the Wald test with a statistical criterion of $p<0.01$. C_{avgt} was removed from the model and removal of any of the remaining covariates led to a more than 6.6 increase in OFV. The result of a final model from the backward elimination process is shown in Table 2.

Table 1: Effect of Covariates via Multivariate Analysis in a Full Cox Proportional Model Using Data From Palbociclib Plus Fulvestrant Arm

Variable	Coefficient [c]	Hazard ratio (95% CI)	p-value for significance
C_{avgt} (ng/mL)	-0.00557	0.994 (0.988, 1.001)	0.113
BAST	0.0107	1.01 (1.003, 1.018)	0.00507
BPLT	-0.00340	0.997 (0.994, 0.999)	0.0129
NUM_DSITEC (≥3) [a]	0.541	1.717 (1.156, 2.551)	0.00743
REGION (Asia/Pacific) [b]	-0.473	0.623 (0.383, 1.014)	0.0567
REGION (Europe) [b]	-0.778	0.459 (0.285, 0.741)	0.00143

Source Data: ePharm artifact ID=10469351.
A total of 21,925 observations of all 310 patients from test arm were included in the above analysis.
C_{avgt}=Time-varying average palbociclib concentration; NUM_DSITEC=Number of disease sites; BAST=Baseline aspartate aminotransferase; BPLT=Baseline platelet count; CI=Confidence interval.
a. Hazard ratios were calculated relative to 1 or 2 disease sites.
b. Hazard ratios were calculated relative to North America. The p-value for variable REGION was 0.0037 (ePharm artifact ID=10514077).
c. Negative coefficient means a higher value of a variable is associated with lower hazard rate and higher progression-free survival probability; vice versa for positive coefficient.

Sources: Sponsor's report, PMAR-EQDD-A548b-DP4-508, "Population Pharmacokinetic and Exposure-Response Analyses to Evaluate the Relationship Between Palbociclib Exposure and Progression-Free Survival (PFS) in Women With Metastatic Breast Cancer That Has Progressed After Prior Endocrine Therapy" ,Page 12

Table 2: Effect of Significant Covariates in the Candidate Final Cox Proportional Model Using Data From Palbociclib Plus Fulvestrant Arm

Variable	Coefficient [c]	Hazard ratio (95% CI)	p-value for significance
BAST	0.0106	1.011 (1.003, 1.018)	0.0062
BPLT	-0.00367	0.996 (0.994, 0.999)	0.0067
NUM_DSITEC (≥3) [a]	0.549	1.732 (1.165, 2.573)	0.0066
REGION (Asia/Pacific) [b]	-0.511	0.600 (0.370, 0.973)	0.0383
REGION (Europe) [b]	-0.823	0.439 (0.273, 0.705)	0.0007

Source Data: ePharm artifact ID=10469413.
All 310 patients from test arm were included in the above analysis.
NUM_DSITEC=Number of disease sites; BAST=Baseline aspartate aminotransferase; BPLT=Baseline platelet count; CI=Confidence interval.
a. Hazard ratios were calculated relative to 1 or 2 disease sites.
b. Hazard ratios were calculated relative to North America. The p-value for variable REGION was 0.0016.
c. Negative coefficient means a higher value of a variable is associated with lower hazard rate and higher progression-free survival probability; vice versa for positive coefficient.

Sources: Sponsor's report, PMAR-EQDD-A548b-DP4-508, "Population Pharmacokinetic and Exposure-Response Analyses to Evaluate the Relationship Between Palbociclib Exposure and Progression-Free Survival (PFS) in Women With Metastatic Breast Cancer That Has Progressed After Prior Endocrine Therapy" , Page 12

Additional analyses with data from both combination arm and control arm identified the following prognostic factors: baseline AST level, number of disease sites, sensitivity to prior hormonal therapy, number of prior regimens and region (Table 3). None of interaction terms between treatment and each of other covariates was significant with the criterion of p-value <0.01. Longer PFS was also correlated with lower baseline AST level, fewer number of disease sites at enrollment (1 disease site relative to more disease sites), higher sensitivity to prior hormonal therapy, a less number of prior regimens (1 prior regimen relative to more regimens) and trial sites at Asia/Pacific or Europe (relative to North America).

Table 3: Effect of Significant Covariates in a Cox Proportional Model Using Data From Both Combination Arm and Control Arm

Variable	Coefficient [f]	Hazard ratio (95% CI)	p-value for significance
TRT [a]	-0.931	0.394 (0.304, 0.512)	<0.0001
BAST	0.0105	1.011 (1.006, 1.015)	<0.0001
NUM_DSITEC (2) [b]	0.650	1.916 (1.340, 2.740)	0.0004
NUM_DSITEC (≥3) [b]	0.973	2.647 (1.901, 3.686)	<0.0001
PR_HOR (Yes) [c]	-0.490	0.613 (0.453, 0.829)	0.0015
REGION (Asia/Pacific) [d]	-0.455	0.635 (0.452, 0.891)	0.0087
REGION (Europe) [d]	-0.461	0.631 (0.459, 0.866)	0.0044
PR_REGMC (2) [e]	0.224	1.251 (0.889, 1.759)	0.1985
PR_REGMC (≥3) [e]	0.513	1.671 (1.188, 2.349)	0.0032

Source Data: ePharm artifact ID=10586154.
A total of 483 patients from both test arm and control arm were included in the above analysis. One patient, NSID=10801008 from control arm, was excluded due to missing value for NUM_DSITEC.
TRT=Treatment; BAST=Baseline aspartate aminotransferase; NUM_DSITEC=Number of disease sites; PR_HOR=Prior hormonal therapy; PR_REGMC=Number of prior regimens; CI=Confidence interval.
a. Hazard ratio was calculated relative to control arm.
b. Hazard ratios were calculated relative to 1 disease site. The p-value for variable NUM_DSITEC was <0.0001.
c. Hazard ratio was calculated relative to patients who were not sensitive to prior hormonal therapy.
d. Hazard ratio was calculated relative to patients from sites in North America.
e. Hazard ratio was calculated relative to patients with only 1 prior regimen.
f. Negative coefficient means a higher value of a variable is associated with lower hazard rate and higher progression-free survival probability; vice versa for positive coefficient.

Sources: Sponsor's report, PMAR-EQDD-A548b-DP4-508, "Population Pharmacokinetic and Exposure-Response Analyses to Evaluate the Relationship Between Palbociclib Exposure and Progression-Free Survival (PFS) in Women With Metastatic Breast Cancer That Has Progressed After Prior Endocrine Therapy" , Page 13

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/s/

JEANNE FOURIE ZIRKELBACH
02/04/2016

WENTAO FU
02/04/2016

JINGYU YU
02/05/2016

YANING WANG
02/05/2016

QI LIU
02/05/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207103Orig1s002

OTHER REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****PRE-DECISIONAL AGENCY MEMO****

Date: Februrary 16, 2016

To: Amy Tilley
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products

From: Nick Senior, PharmD, JD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Comments on NDAs 207103; 021344
IBRANCE (palbociclib) capsules, for oral use
FASLODEX (fulvestrant) injection

OPDP has reviewed the proposed product labeling (PIs) for IBRANCE (palbociclib) capsules, for oral use and FASLODEX (fulvestrant) injection as requested in the consults dated November 13, 2015, and January 29, 2016, respectively. The following comments, using the proposed substantially complete, marked-up version of the PIs emailed to OPDP by Amy Tilley on February 2, 2016, are provided below. Specifically, OPDP has reviewed the HIGHLIGHTS OF PRESCRIBING INFORMATION, along with Sections 1, (INDICATIONS AND USAGE), 2 (DOSAGE AND ADMINISTRATION), 5 (WARNINGS AND PRECAUTIONS), 6 (ADVERSE REACTIONS), 8 (USE IN SPECIFIC POPULATIONS), 13 (NONCLINICAL TOXICOLOGY), and 14 (CLINICAL STUDIES) of both labels.

Please note that comments on the proposed Opdivo patient labeling will be provided under a separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs.

Ibrance:

- Clinical Studies: Please consider adding the 95% confidence intervals for the overall response rate and duration of response, as this gives a fuller pictures of the actual patient response to Ibrance therapy.

Faslodex:

- Overall: Please consider updating the Fulvestrant label to be consistent with all accepted changes to the Ibrance label.
- Clinical Studies:
  - We recommend the deletion of this section as the updated information renders this information irrelevant and unnecessary.
  - (b) (4)

If you have any questions, please feel free to contact me (contact information: 240-402-4256; Nicholas.Senior@fda.hhs.gov)

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

NICHOLAS J SENIOR
02/16/2016

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

PATIENT LABELING REVIEW

Date:	February 16, 2016
To:	Geoffrey Kim, MD Director **Division of Oncology Products 1 (DOP1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Nicholas Senior, PharmD, JD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	IBRANCE (palbociclib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number/ Supplement Number:	NDA 207103/S-002
Applicant:	Pfizer, Inc.

1 INTRODUCTION

On October 15, 2015, Pfizer, Inc. submitted for the Agency's review a Prior Apprvoal Supplement (PAS)- to their approved New Drug Application (NDA) 207103/S-002 for IBRANCE (palbociclib) capsules. With this efficacy supplement the Applicant proposes to expand the indication for IBRANCE (palbociclib) capsules. The proposed new indication is for the treatment of HR positive, HER-2 negative advanced or metastatic breast cancer in combination with fulvestrant in women [redacted] (b) (4)

IBRANCE (palociclib) capsules received Accelerated Approval on February 3, 2015 and is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP1) on November 13, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for IBRANCE (palbociclib) capsules.

2 MATERIAL REVIEWED

- Draft IBRANCE (palbociclib) PPI received on October 14, 2015, and received by DMPP and OPDP on February 1, 2016.
- Draft IBRANCE (palbociclib) Prescribing Information (PI) received on October 14, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 1, 2016.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible

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

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
02/16/2016

NICHOLAS J SENIOR
02/16/2016

SHARON R MILLS
02/16/2016

LASHAWN M GRIFFITHS
02/16/2016

From: Kovacs, Sarrit
To: Tilley, Amy; Wedam, Suparna (FDA); Amiri Kordestani, Laleh (FDA)
Cc: Bloomquist, Erik; Johnson, Laura Lee (CDER); Chen, Wen-Hung; Papadopoulos, Elektra; COA Staff; Kovacs, Sarrit
Subject: COA Staff email response to DOP1 consult for NDA 207103 S-002
Date: Wednesday, February 10, 2016 1:35:22 PM

Dear Amy, Suparna, and Laleh,

This email is in response to your November 10, 2015 COA consult request (see email below). This email will be filed into DARRTS as the COA Staff response to your consult request.

Your consult request stated the following:
"[redacted (b) (4)] *Please evaluate and comment on the instruments that were used, the time points of the data collection, completion rates, and the clinical significance of the results* [redacted (b) (4)] *Please note that PROs were secondary endpoints with no alpha allocations and considered exploratory in nature."*

The COA Staff have the following comments:

1. Given that the PRO endpoints [redacted (b) (4)] were not pre-specified and are considered exploratory, [redacted (b) (4)] even if the PRO measures were pre-specified and there were no multiplicity concerns, we would need to examine the analyses to make sure that the applicant assessed the clinical meaningfulness of the statistically significant findings (e.g., anchor-based analyses to define clinically meaningful responders, as well as cumulative distribution function curves using an anchor measure such as a patient global impression of severity).
2. With regard to pain (time to deterioration of pain; deterioration defined as an increase in pain score of ≥10 points from baseline), which was pre-specified on the endpoint hierarchy [redacted (b) (4)] it is unclear whether an increase in 10 points on a 0-100 scale is clinically meaningful (perhaps 20 or 30 points would be more clinically meaningful).
   a. The pain scale combined scores from two specific questions on the EORTC QLQ-C30 questionnaire. The first question (Question 9) asked, "In the past week, did you feel pain?" The second question (Question 19) asked, "In the past week, did pain interfere with your daily activities?" For both questions, a subject could answer one of four choices: not at all (1), a little (2), quite a bit (3), very much (4).
   b. To convert the two questions into the pain scale score, an average of two scores was taken and the scale was then converted into 0-100 scale. Based upon the data transformation, a ≥10 increase in the pain score is equivalent to answering either question 9 or question 19 one point higher than the baseline score, even if the other item stayed the same.
3. The COA Staff recommended that the Review Division submit the following information request to the sponsor to get more detailed time-to-event analyses on the two pain items in EORTC QLQ-C30 in the context of analgesic use, [redacted (b) (4)]
   a. Perform additional analyses for the pre-specified time to event analysis for pain (TTD) separately for each of the two pain items (#9 and #19). Please do not convert observed score to 0-100 scale, instead, use the observed 1, 2, 3, and 4 scores. Provide results for TTD analyses using a responder definition of delay in increase of pain ≥ 1 point and ≥ 2 points. Please conduct the TTD analysis accounting for analgesic use at each time point.

   The review team examined the completion rates of EORTC QLQ-C30 and concluded that the completion rate was high and the missing data was not a concern. However, the review team analyzed the data looking at a ≥20 increase in the pain score as a responder definition and decided against sending an IR to the sponsor given the lack of statistical significance and modest magnitude of effect, which was not deemed sufficiently clinically meaningful [redacted (b) (4)]

Please let me know if you have any questions.

Thank you,

Sarrit

Sarrit M. Kovacs, Ph.D.
Clinical Outcome Assessments Reviewer
COA Staff (formerly SEALD Study Endpoints)
FDA/CDER/OND/IO
(240) 402-2431 (x22431)
sarrit.kovacs@fda.hhs.gov

From: oasfda@fda.gov [mailto:oasfda@fda.gov]
Sent: Tuesday, November 10, 2015 11:14 AM
To: Agosto, Teicher; Bloomquist, Erik; Wedam, Suparna (FDA); Leishear, Kira; Chen, Xiao H; COA Staff; Tilley, Amy; Fahnbulleh, Frances; Redd, Naomi; Fourie Zirkelbach, Jeanne; Patel, Mona; Hughes, Minerva; Crich, Joyce; Amiri Kordestani, Laleh (FDA); Chen, Wei; Walker, Amanda; Mathew, Davis; Zhao, Liang; Charlab Orbach, Rosane; Cole, Jessica; Rand, Margaret
Subject: Finalized - NDA 207103 Clinical Outcome Assessments Consult Request (FRM-CONSULT-13)

Proceed to DARRTS Welcome Screen

Finalized - Clinical Outcome Assessments Consult Request (FRM-CONSULT-13)

The following communication has been signed and finalized.

Functions

Communication	Communication Group	Communication Name
FRM-CONSULT-13	CONSULT	Clinical Outcome Assessments Consult Request

Linked Submissions

Application Type and Number	Sponsor	Preferred Product Name	Submission Type and Number	Submission Classification	Group ID
NDA-207103	PFIZER INC	Ibrance (palbociclib)	SUPPL-2	Efficacy	981118

Signers

Signer	Proxy Signer	Signed Status	Signed Date
TILLEY, AMY R.		signed	11/10/2015

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/s/

SARRIT M KOVACS
02/10/2016

WEN-HUNG CHEN
02/10/2016

ELEKTRA J PAPADOPOULOS
02/11/2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigator Dr. Dennis Slamon, M.D. (Site 1137; Study A5481023) , data submitted to the Agency in support of sNDA 207103 S-002 appear reliable and can be used in support of the application.

Dr. Dennis Slamon (Site 1137) was selected for inspection based upon the large number of study subjects enrolled at this site and the fact that this site generated primary efficacy results pertinent to decision making. The primary efficacy endpoint, investigator assessed tumor response per RECIST1.1. , was verified for all 14 enrolled subjects at this site. There was evidence of reporting errors for a few AEs, there were protocol deviations for a few out of window tumor assessments, and some Patient Reported Outcomes questionnaires that were not completed during the study. These inspectional observations represent a small proportion of the total number of AEs reported, tumor assessments conducted and PRO questionnaires completed for this site and should not importantly impact subject safety or overall study outcomes.

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

II. BACKGROUND

Pfizer, Inc. seeks (b) (4) Study A5481023, the key study supporting this supplement application, is an international, multicenter, 2:1 randomized, double-blind, placebo-controlled, parallel-group, Phase 3 clinical study with the primary objective of demonstrating the superiority in prolonging Progression Free Survival (PFS) of palbociclib in combination with fulvestrant (Faslodex®) over fulvestrant plus placebo in women with HR-positive, HER2-negative metastatic breast cancer, regardless of their menopausal status, whose disease had progressed after prior endocrine therapy. The inspection was performed as a data audit for sNDA 207103 S-002, specifically Study A5481023.

Study A5481023: "Multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial of fulvestrant (Faslodex®) with or without PD-0332991 (palbociclib) ± goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy."

Number of subjects: 527 randomized
Number of sites: 144
Number of countries where subjects were enrolled: 17

Study Period:

Date of first subject enrolled: September 26, 2013
Data cut-off date: December 05 2014

Primary efficacy endpoint: Progression-Free Survival (PFS), per RECIST 1.1, (as assessed by the Investigator). PFS is defined as 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 occurred first.
Secondary efficacy endpoints: Overall Survival (OS), Objective Response, Duration of Response, and Clinical Benefit Response.
Sponsor's interpretation of primary efficacy outcome: Time to PFS event in months.

Objectives of Inspection:

a. Verify primary efficacy endpoint for all enrolled subjects.
b. Verify secondary efficacy endpoint, OS, for all enrolled subjects.
c. Identification, documentation and reporting of AEs for all enrolled subjects.
d. General compliance with the investigational plan.

III. RESULTS (by site):

Dr. Dennis Slamon (Site 1137) was selected for inspection based upon the large number of study subjects enrolled at this site, and this site generated primary efficacy results pertinent to decision making.

Name of CI, Site #, Address.	**Protocol # and # of Subjects**	**Inspection Date**	**Final Classification**
CI#1: Dennis Slamon, M.D., Ph.D. (Site # 1137) UCLA Dept. of Medicine Hematology-Oncology Los Angeles CA 90095-178	Protocol: A5481023 Number of Subjects enrolled: 14	January 14-28, 2016	Pending Interim classification VAI
CI #2: Nicholas Turner, M.D. (Site 1201) Royal Marsden hospital Royal Marsden NHS Foundation Trust Fulham Road London SW3 6JJ	Protocol: A5481023 Number of Subjects enrolled: 9	DOP1 Cancelled: Site was not available for inspection prior to planned Action Date.	N/A

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dennis Slamon, M.D., Ph.D. (Site # 1137)

a. What was inspected: This inspection was performed as a data audit for sNDA #207103 S-002. This inspection reviewed the conduct of one clinical study site (A5481023). The inspection audited Dr. Dennis Slamon, M.D. (Site #1137). The site screened 19 subjects and 14 were enrolled and treated. At the time of this inspection 7 subjects had completed the study. The study records of all 14 enrolled subjects were audited. The subjects' source records were compared with data listings provided in the NDA and with the subjects' eCRFs for primary and secondary efficacy endpoints, adverse events/SAEs, discontinuations, and concomitant medications. There were no limitations to the inspection.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be good. The inspection revealed no significant deficiencies. The primary efficacy endpoint, tumor response per RECISTS1.1, determined by the clinical investigator, was verified. There was evidence of underreporting adverse events. In addition, there was a number of protocol deviations observed. A Form FDA 483 was issued citing 2 inspectional observations. Observations related to subject safety and data reliability are summarized below.

1. There was evidence of underreported AEs. Five out of fourteen subject records reviewed revealed discrepancies between source documents and the eCRF pertaining to AEs. Most were Grade1/2 and had start dates and end dates in source/AE logs, but were listed as ongoing in subject eCRFs. For example, Subject 1137-1001 had an AE of neutropenia, grade 2, recorded in the eCRF with a start date of 3/26/14 with no stop date, while the corresponding laboratory report documents grade 1 on 3/26/14.

2. Three subjects had a total of six tumor assessments that were performed out of the protocol-specified window of every 8 weeks (±7 days). Deviations ranged from 1 to 12 days with one exception. Subject 1137-1006 had their Cycle 11 scan completed 28 days out of window.

3. Four out of fourteen subjects did not complete one or more Patient Reported Outcomes (PRO) questionnaires. One of eight secondary objectives for this study was to compare PRO measures between treatment arms. For example, Subject 1137-1003 did not complete the required questionnaire at the Cycle10/Day1 visit on 11/3/14.

OSI Reviewer Note: The PDs related to out of window Tumor Assessments and missed PRO questionnaires were reported to the sponsor and are included in the datalistings submitted to the application. With respect to misreporting of AEs, it does not appear that these had been reported to the sponsor prior to the site inspection. These deviations represent a small proportion of the total number of AEs reported, tumor assessments conducted, and PRO questionnaires completed for this site. The Form FDA 483 inspectional

observations were shared with the DOP1 Medical Officer, Suparna Wedam, on January 29, 2016.

c. Assessment of data integrity: Notwithstanding the observations noted above, the data for Dr. Slamon's site, associated with Study A5481023 submitted to the Agency in support of sNDA 207103 S-002, appear reliable based on available information.

Lauren C. Iacono-connors -S

Digitally signed by Lauren C. Iacono-connors -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300091981, cn=Lauren C. Iacono-connors -S
Date: 2016.02.10 10:53:31 -05'00'

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
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CONCURRENCE:

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Team Leader,
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/s/

SUSAN D THOMPSON
02/10/2016

KASSA AYALEW
02/10/2016

Selected Requirements of Prescribing Information
REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

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

Application: NDA 207103/S-002

Application Type: Efficacy Supplement

Drug Name(s)/Dosage Form(s): Ibrance® (palbociclib) Capsules 75 mg, 100 mg, and 125 mg

Applicant: Pfizer, Inc.

Receipt Date: 10-15-15

Goal Date: 4-15-16 **Target Date:** 2-29-16

1. Regulatory History and Applicant's Main Proposals

Reference is made to the Ibrance® NDA 207103 approved on February 3, 2015. On April 9, 2013, palbociclib (PD-0332991) was designated as a Breakthrough Therapy development program for ER-positive, HER2-negative breast cancer. Reference is also made to the submission of the clinical protocol under IND 069324 on August 8, 2014, and notification on March 13, 2015, of the trial completion for Study A5481039.

The applicability of the Breakthrough Therapy designation for this sNDA was confirmed during the April 30, 2015, teleconference. During the pre-sNDA meeting on June 16, 2015, it was agreed that the sponsor would submit the clinical pharmacology information (Summary of Clinical Pharmacology Update and Pop-PK exposure analysis) within 45 days of the sNDA submission without impact to the PDUFA review clock.

The sponsor requested Priority Review of the sNDA submitted on October 15, 2015, seeking (b) (4) dditionally, the final study report for Study A5481039 titled, "A PHASE 1, OPEN-LABEL, FIXED-SEQUENCE, 2-COHORT, 2-PERIOD STUDY TO INVESTIGATE THE EFFECT OF MODAFINIL AND PIOGLITAZONE GIVEN AS MULTIPLE DOSES ON SINGLE DOSE PHARMACOKINETICS OF PALBOCICLIB (PD-0332991) IN HEALTHY VOLUNTEERS" was provided in this sNDA in Module 5, Section 5.3.3.4.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

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

Comment:

NO 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment: *There is no horizontal line between the TOC and the FPI.*

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

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

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format

is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

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

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

NO 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

NO 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *The Initial U.S. Approval statement is not bolded.*

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

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

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

YES 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES

20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

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

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

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

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

YES 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

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

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

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

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Subsection Title
2.2 Subsection Title
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Subsection Title
5.2 Subsection Title
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
6.2 or 6.3 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Subsection Title
7.2 Subsection Title
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Subpopulation X
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Subsection Title
14.2 Subsection Title
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

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/s/

AMY R TILLEY
12/09/2015

ALICE KACUBA
12/09/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 207103 BLA#	NDA Supplement #: S-002 BLA Supplement #: S-	Efficacy Supplement Category: (b) (4)
Proprietary Name: Ibrance® Established/Proper Name: palbociclib Dosage Form: Capsules Strengths: 75 mg, 100 mg, and 125 mg		
Applicant: Pfizer Inc. Agent for Applicant (if applicable):		
Date of Application: 10-15-15 Date of Receipt: 10-15-15 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 4-22-16	Action Goal Date (if different): 2-29-16	
Filing Date: 12-14-15	Date of Filing Meeting: 11-10-15	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)	

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response (b) (4) [redacted]
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 069324	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	Priority
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☒		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 3 years exclusivity ***Note:*** *An applicant can receive exclusivity without requesting it;*	☒	☐	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☒	☐		PeRC Date=1-13-16

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Full Waiver requested.
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☐	☒	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

[4]

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☒	☐	☐	
Has a review of the available pregnancy and lactation data been included?	☐	☒	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☐	☒	☐	No carton / container labels or CMC information submitted.
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☒	

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

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

If no, request in 74-day letter.				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☒	
All labeling/packaging sent to OSE/DMEPA?	☐	☒	☐	No Carton and Container Labels submitted.
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	Clinical Outcome Assessment (COA)
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☐	X	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 6-16-15 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 10, 2015

BACKGROUND: Palbociclib capsule is to be taken orally and is a first in class highly selective, reversible, small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. CDK4/6 are downstream of multiple signaling pathways which lead to cellular proliferation.

Palbociclib has been designated as a Breakthrough Therapy for metastatic breast cancer on April 30, 2015, regarding this indication and original April 9, 2013, breast cancer breakthrough therapy designation.

Pfizer is requesting Priority Review of the supplemental NDA and is seeking (b) (4) [redacted]

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Amy Tilley	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	Laleh Amiri Kordestani		Y
Division Director/Deputy	Geoffrey Kim Amna Ibrahim		Y Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Efficacy: Suparna Wedam Safety: Amanda Walker	Y Y
	TL:	Laleh Amiri Kordestani	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Jeanne Fourie Zirkelbach	Y
	TL:	Qi Liu	Y
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	N/A	
Biostatistics	Reviewer:	Eric Bloomquist	N
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wei Chen	Y
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	N/A	
	RBPM:	N/A	
• Drug Substance	Reviewer:	N/A	
• Drug Product	Reviewer:	N/A	
• Process	Reviewer:	N/A	
• Microbiology	Reviewer:	N/A	
• Facility	Reviewer:	N/A	
• Biopharmaceutics	Reviewer:	N/A	
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)	N/A		
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	N/A	
	TL:	N/A	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Nicholas Senior	N
	TL:	Jessica Cleck-Derenick	N
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer: OSE/PMS:	Francis Fahnbulleh	Y
	TL:	N/A	
OSE/DRISK (REMS)	Reviewer:	Morgan Walker	N
	TL:	Barbara Fuller	N

OC/OSI/DSC/PMSB (REMS)	Reviewer:	Lauren Iacono-Connor	Y
	TL:	Susan Thompson	N
Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees	Kathryn Fedenko		N
	Jenney Susan		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments	☐ Not Applicable

List comments:	☒ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**: Sponsor to send the Updated Summary Clinical Pharmacology by day 45.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☐ YES ☒ NO ☐ YES ☒ NO

Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	Team agreed to clin pharm information (Summary of clinical Pharmacology Update and Pop-PK exposure analysis) within 45 days of submission without impact to PDUFA review clock.
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Geoffrey Kim, M.D. **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

AMY R TILLEY
11/24/2015

ALICE KACUBA
11/25/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207103Orig1s002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Revised Exclusivity Summary supersedes February 19, 2016
Exclusivity Summary

EXCLUSIVITY SUMMARY

NDA # 207103 SUPPL # 002 HFD # 150

Trade Name Ibrance®

Generic Name palbociclib

Applicant Name Pfizer Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

SE1

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

YES ☒ NO ☐

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

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

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 207103

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

Study: A5481023

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

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

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

b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

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

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

Study: A5481023

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

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

Investigation #1		!
		!
IND # 069324	YES ☒	! NO ☐
		! Explain:

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

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

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

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

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Amy Tilley
Title: Regulatory Project Manager
Date: May 15, 2017

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

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

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

/s/

AMY R TILLEY

05/15/2017

This Revised Exclusivity Summary supersedes the February 19, 2016 Exclusivity Summary for Supplement 2.

JULIA A BEAVER

05/15/2017

May 15, 2017

Please refer to the revised exclusivity review checked in on 5/15/2017.

EXCLUSIVITY SUMMARY

NDA # 207103 SUPPL # 002 HFD # 150

Trade Name Ibrance®

Generic Name palbociclib

Applicant Name Pfizer Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

SE1

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

YES ☒ NO ☐

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

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

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 207103

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the

answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

Efficacy Studies: A5481023
Safety Studies: A5481008 and A5481034

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

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

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

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

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

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

Efficacy Studies: A5481023
Safety Studies: A5481008 and A5481034

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

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

Investigation #1 !
!
IND # 069324 YES ☒ ! NO ☐
! Explain:

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

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

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

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

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Amy Tilley
Title: Regulatory Project Manager
Date: February 18, 2016

Name of Office/Division Director signing form: Geoffrey Kim, M.D.
Title: Director, DOP1

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

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

/s/

AMY R TILLEY
02/19/2016

GEOFFREY S KIM
02/19/2016

Note: The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

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

Complete the section(s) of this template that are relevant to your *current submission.*

Definitions:

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

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

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

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

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

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

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

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

BACKGROUND

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

BLA/NDA#: sNDA 207103/002

PRODUCT PROPRIETARY NAME: Ibrance **ESTABLISHED/GENERIC NAME: palbociclib**

APPLICANT/SPONSOR: Pfizer Inc.

PREVIOUSLY APPROVED INDICATION/S:
(1) IBRANCE is a kinase inhibitor indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.
(2) _____
(3) _____
(4) _____

PROPOSED INDICATION/S:

(b) (4)

(2) _____
(3) _____
(4) _____

BLA/NDA STAMP DATE: October 15, 2015

PDUFA GOAL DATE: April 15, 2016 **TARGET DATE: February 29, 2016**

SUPPLEMENT TYPE: Efficacy Supplement

SUPPLEMENT NUMBER: 002

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

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

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

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes ☒ ***No*** ☐

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ ***No*** ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ ***No*** ☒

If Yes, PMR #_____ NDA _____

Does the division agree that this is a complete response to the PMR? Yes ☐ ***No*** ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

☐ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***

☐ ***Pediatric Record***

1 Pediatric age group(s) to be waived. All as the disease/condition does not exist in children.

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

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

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

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

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

3 Provide justification for Waiver: Disease/condition does not exist in children.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language: N/A

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

- actinic keratosis
- adjunctive treatment of major depressive disorder
- age-related macular degeneration
- Alzheimer's disease
- amyloidosis
- amyotrophic lateral sclerosis
- androgenic alopecia
- atherosclerotic cardiovascular disease
- autosomal dominant polycystic kidney disease (ADPKD)
- benign monoclonal gammopathy
- benign prostatic hyperplasia
- cancer:
  - basal cell and squamous cell skin cancer
  - bladder
  - **breast**
  - cervical
  - colorectal
  - endometrial
  - esophageal
- cancer (continued):
  - follicular lymphoma
  - gastric
  - hairy cell leukemia
  - hepatocellular
  - indolent non-Hodgkin lymphoma
  - lung (small & non-small cell)
  - multiple myeloma
  - oropharynx (squamous cell)
  - ovarian (non-germ cell)
  - pancreatic
  - prostate
  - refractory advanced melanoma
  - renal cell
  - uterine
- chronic lymphocytic leukemia
- chronic obstructive pulmonary disease
- cryoglobulinemia
- diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)

dry eye syndrome (keratoconjunctivitis sicca)

erectile dysfunction

essential thrombocytosis

Huntington's chorea

infertility & reproductive technology

ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke

memory loss

menopause and perimenopausal disorders

mesothelioma

myelodysplasia

myelofibrosis & myeloproliferative disorders

osteoarthritis

overactive bladder

Parkinson's disease

paroxysmal nocturnal hemoglobinuria

plasma cells and antibody production disorders

polycythemia vera

postmenopausal osteoporosis

prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis

reduction of thrombotic cardiovascular events in patients with coronary artery disease

replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

retinal vein occlusions

stress urinary incontinence

temporary improvement in the appearance of caudal lines

treatment of incompetent great saphenous veins and varicosities

type 2 diabetic nephropathy

vascular dementia/vascular cognitive disorder/impairment

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

/s/

AMY R TILLEY
12/08/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Dennis J. Slamon, M.D., Ph.D.
2825 Santa Monica Blvd., Suite 200
Santa Monica, CA 90404

Dear Dr. Slamon:

Between January 14, 2016 and January 28, 2016, Ms. Alexandra Pitkin, representing the U.S. Food and Drug Administration (FDA), conducted an investigation and met with you and your staff to review your conduct of a clinical investigation (Protocol A5481023, "Multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial of fulvestrant (Faslodex®) with or without PD-0332991 (palbociclib) ± goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy") of the investigational drug Ibrance® (palbociclib) performed for Pfizer, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Ms. Pitkin presented and discussed with you Form FDA 483, Inspectional Observations. We have reviewed the Form FDA 483, the establishment inspection report, and the documents submitted with the report. We acknowledge your February 19, 2016 written response to the inspection findings and note that you have implemented corrective actions to prevent the recurrence of the inspection findings.

We appreciate the cooperation shown to Investigator Pitkin during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Bldg. 51, Rm. 5350
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

SUSAN D THOMPSON
08/11/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 207103 BLA #	NDA Supplement # 002 BLA Supplement #	If NDA, Efficacy Supplement Type: SE1 *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Ibrance® Established/Proper Name: palbociclib Dosage Form: Capsules		Applicant: Pfizer Inc. Agent for Applicant (if applicable):
RPM: Amy Tilley		Division: DOP1

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

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

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

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

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

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

❖ Actions	
• Proposed action • User Fee Goal Date is April 16, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

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

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

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

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

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

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

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

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

Comments:

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

CONTENTS OF ACTION PACKAGE

Officer/Employee List

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

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date: Approval 2-19-16
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☐ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 12-9-15 DMEPA: ☒ None DMPP/PLT (DRISK): ☒ 2-16-16 OPDP: ☒ 2-16-16 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	11-25-15 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 1-13-16 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	4-9-13
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ 6-16-15
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ 2-18-16
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ 2-11-16
PMR/PMC Development Templates *(indicate total number)*	☒ 1 PMC
Clinical	
❖ Clinical Reviews	

• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ None
• Clinical review(s) *(indicate date for each review)*	11-10-15; 2-11-16
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical Review 2-11-16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ COA 2-11-16
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ 2-10-16
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ See Biostatistics Review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ See Biostatistics Review
Statistical Review(s) *(indicate date for each review)*	☒ 11-10-15; 2-5-16
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ See Clin Pharm Review
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ 2-5-16; 2-8-16
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ See Nonclinical Review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ 11-10-15; 2-8-16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☒ None
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	2-2-16
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☐ Acceptable Re-evaluation date: ☐ Withhold recommendation ☒ Not applicable

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

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

/s/

AMY R TILLEY
02/19/2016

ALICE KACUBA
02/22/2016

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Amiri Kordestani, Laleh (FDA)
Subject:	TIME SENSITIVE sNDA 207103-002 Ibrance - FDA revised PI/PPI
Date:	Thursday, February 18, 2016 2:08:55 PM
Attachments:	sNDA 207103-2 Ibrance - FDA revd 2-18-16.doc
Importance:	High

Michelle,

Attached is the FDA revised PI/PPI for your review. We request your response **by 9 am Friday, Feb 19, 2016.**

Confirm receipt of this email.

Regards.
Amy Tilley

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

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/s/

AMY R TILLEY
02/18/2016

PMR/PMC Development Template

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

NDA #	207103/s002
Product Name: Ibrance® (palbociclib)	
PMC 3040-1 Description:	*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."*

PMC Schedule Milestones:		
	Final Protocol Submission:	07/2013 (submitted)
	Trial Completion:	12/2017
	Final Report Submission:	06/2018

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

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

   The final OS results of Trial A5481023 (PALOMA-3) will be important to further understand the clinical meaningfulness of palbociclib treatment in combination with fulvestrant.

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

The final OS results of Trial A5481023 (PALOMA-3) will be important to further understand the clinical meaningfulness of palbociclib treatment in combination with fulvestrant.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

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

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

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

Clinical *Trial 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."*

Required

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

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

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

_____

☐ Other

_____

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

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

PMR/PMC Development Coordinator:

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

_____

(signature line for BLAs)

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/s/

SUSAN JENNEY
02/18/2016

KATHERINE M FEDENKO
02/18/2016

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Amiri Kordestani, Laleh (FDA)
Subject:	TIME SENSITIVE sNDA 207103-2 Ibrance - FDA Revised PI and PPI
Date:	Tuesday, February 16, 2016 12:20:46 PM
Attachments:	sNDA 207103-2 Ibrance - FDA revd PI 2-16-16.doc IBRANCE PPI DMPP-OPDP marked copy (3) 2-16-16.doc
Importance:	High

Michelle,

Attached are the FDA revised PI and PPI for your review. Please combine the PI and PPI into one document prior to either 1) emailing us any further Pfizer revisions or 2) officially submitting the PI/PPI if you have no further revisions. We request your response **no later than 9:00 am Thursday, Feb 18, 2016.**

Please, note that we have added additional labeling changes to be consistent with other PLLR formatting.

Kindly confirm receipt of this email.

Regards.
Amy Tilley

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

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

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/s/

AMY R TILLEY
02/16/2016

From: Kacuba, Alice
To: michelle.y.kite@pfizer.com
Cc: Tilley, Amy
Subject: FW: Quest how to resp to spon Draft ASCO IBRANCE (palbociclib) burst sNDA 207103/s002
Date: Friday, February 12, 2016 11:58:08 AM
Importance: High

Hi,

Amy forwarded your email inquiry to me. The review team is working hard to wrap this up. I understand from Amy that there has been some labeling discussion already. Please note that federal gov't is closed Monday. While we can't estimate exactly when we will both come to "agreed upon labeling", Oncology has a strong history of working with Sponsors and Amy is experienced in getting things out as soon as they are cleared. I do expect a busy week or so ahead, providing that there are no delays or obstacles in labeling discussions.

OHOP office sends out the ASCO Burst to you so that you can check facts and provide any edits.

Please contact me with any other issues.

Thank you.
Alice
Alice Kacuba, RN, MSN, GWCPM, RAC
Chief, Project Management Staff
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Friday, February 12, 2016 10:51 AM
To: Tilley, Amy
Cc: Kacuba, Alice
Subject: Fwd: Draft ASCO IBRANCE (palbociclib) burst sNDA 207103/s002

Hi Amy,

I received the below call and email from OHOP this morning about the BURST publication and wanted to ask if it's possible to get an update on the review and when we may expect the draft USPI? This is with an aim to provide guidance to the large, multi-disciplinary team from Pfizer that is lined up to support the approval and get IBRANCE+fulvestrant to MBC patients. We want to ensure we are ready to go as soon as FDA is and just want to provide some guidance to our groups on the

timing. Given the 4 days since we submitted the last USPI iteration, we are just seeking an update so we can plan our resources – and we know FDA is working hard on their side and appreciate their efforts.

Thanks,
Michelle

Begin forwarded message:

> **From:** "Gallauresi, Beverly" <Beverly.Gallauresi@fda.hhs.gov>
> **Date:** February 12, 2016 at 7:38:21 AM PST
> **To:** "Michelle.Y.Kite@pfizer.com" <Michelle.Y.Kite@pfizer.com>
> **Subject: Draft ASCO IBRANCE (palbociclib) burst sNDA 207103/s002**
>
> Good morning Michelle,
>
> It was a pleasure speaking with you. As discussed, please note the attached draft ASCO IBRANCE (palbociclib) burst for your review/edit/comments. Please use track changes for any edits or comments and please return to me by Tuesday, February 16th at 10:00 AM EST.
>
> If you have any questions please call or e-mail me.
>
> Best regards,
> Beverly
>
> Beverly Gallauresi MPH, RN
> Senior Regulatory Health Project Manager| Oncology Program
> Office of Hematology and Oncology Products (OHOP) | CDER | FDA
> 10903 New Hampshire Avenue | Bldg 22, Room 2202 | Silver Spring, MD 20993
> (301.796.9438 (phone) • 301.796.9909 (fax) | ✉ beverly.gallauresi@fda.hhs.gov
>
> <Draft ASCO palbociclib (IBRANCE) burst to Pfizer 2_12_16 .doc>

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/s/

AMY R TILLEY
02/12/2016

From: Tilley, Amy
To: "Yu-Kite, Michelle"
Subject: RE: TIME SENSITIVE sNDA 207103-002 Ibrance - PMC language and Milestones
Date: Wednesday, February 10, 2016 4:58:12 PM

You may officially submit the PMC milestones and kindly inform me when you do so I can be on the lookout for the submission.

Regards.

Amy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Wednesday, February 10, 2016 4:47 PM
To: Tilley, Amy
Subject: RE: TIME SENSITIVE sNDA 207103-002 Ibrance - PMC language and Milestones

Hi Amy,

For the PMC milestones, see below with the dates filled in.

Thanks,
Michelle

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Wednesday, February 10, 2016 11:28 AM
To: Yu-Kite, Michelle
Subject: TIME SENSITIVE sNDA 207103-002 Ibrance - PMC language and Milestones
Importance: High

Michelle, below is the PMC regarding the Efficacy Supplement for Ibrance. Please review the language and fill in your PMC Schedule Milestones.

We request this information **no later than 2 pm, February 11, 2016.**

PMC Description:	*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."*

PMC Schedule Milestones:

Trial Completion:	12/31/2017
Final Report Submission:	06/30/2018

Kindly confirm receipt of this email.
Regards.
Amy Tilley

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

APPEARS THIS WAY ON ORIGINAL

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/s/

AMY R TILLEY
02/10/2016

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Fedenko, Katherine; Jenney, Susan; Amiri Kordestani, Laleh (FDA)
Subject:	TIME SENSITIVE sNDA 207103-002 Ibrance - PMC language and Milestones
Date:	Wednesday, February 10, 2016 2:28:17 PM
Importance:	High

Michelle, below is the PMC regarding the Efficacy Supplement for Ibrance. Please review the language and fill in your PMC Schedule Milestones.

We request this information **no later than 2 pm, February 11, 2016.**

PMC Description:

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."

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

Kindly confirm receipt of this email.

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
02/10/2016

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Cc:	Kacuba, Alice
Subject:	RE: TIME SENSITIVE sNDA 207103/002 Ibrance - FDA Revised PI
Date:	Thursday, February 04, 2016 4:43:19 PM

Michelle, I am not at liberty to predict the exact action date, I can tell you that the review process continues and is not stalled. Please submit your information asap after your proposed ready date.

Any further Qs on this topic, contact my Chief Alice Kacuba and cc me.

Regards.
Amy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Wednesday, February 03, 2016 12:20 PM
To: Tilley, Amy
Subject: RE: TIME SENSITIVE sNDA 207103/002 Ibrance - FDA Revised PI

Hi Amy,

Can I ask what FDA's estimated or target approval timeframe is so that we can coordinate with OPDP appropriately? We know it is subject to change, but would appreciate a heads-up e.g. Next Friday or the following week or week of 22 Feb?

Thanks,
Michelle

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Wednesday, February 3, 2016 7:31 AM
To: Yu-Kite, Michelle
Subject: TIME SENSITIVE sNDA 207103/002 Ibrance - FDA Revised PI
Importance: High

Michelle,

Attached is the FDA Revised PI regarding sNDA 207103/002 Ibrance. Please note at the top of Table 2 there is blue shading please delete this shading.

We request your emailed response **no later than 9 am on Monday, February 8, 2016.** As always, please follow up with an official submission to the sNDA.

Please confirm receipt of this email.

Regards.
Amy Tilley

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

20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
02/04/2016

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Amiri Kordestani, Laleh (FDA); Wedam, Suparna (FDA); Tang, Shenghui; Bloomquist, Erik; Palmby, Todd; Chen, Wei
Subject:	TIME SENSITIVE sNDA 207103/002 Ibrance - FDA Revised PI
Date:	Wednesday, February 03, 2016 10:30:53 AM
Attachments:	FDA revd Ibrance PI - 2-3-16.doc
Importance:	High

Michelle,

Attached is the FDA Revised PI regarding sNDA 207103/002 Ibrance. Please note at the top of Table 2 there is blue shading please delete this shading.

We request your emailed response **no later than 9 am on Monday, February 8, 2016.** As always, please follow up with an official submission to the sNDA.

Please confirm receipt of this email.

Regards.
Amy Tilley

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

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/s/

AMY R TILLEY
02/03/2016

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Amiri Kordestani, Laleh (FDA)
Subject:	TIME SENSITIVE sNDA 207103-2 - FDA Revised PI
Date:	Tuesday, January 26, 2016 2:56:08 PM
Attachments:	sNDA 207103-002 - FDA revised PI 1-26-16.docx
Importance:	High

Michelle,

Attached is the FDA revised Ibrance PI for your review.

Please **respond by 10 am on Monday, February 1, 2016**, via email and follow up with an official submission to the sNDA.

Kindly confirm receipt of this email.

Regards.
Amy Tilley

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

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/s/

AMY R TILLEY
01/26/2016

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Amiri Kordestani, Laleh (FDA); Walker, Amanda
Subject:	TIME SENSITIVE re sNDA 207103/2 Ibrance - Clinical Safety IR
Date:	Wednesday, January 20, 2016 7:35:22 PM
Importance:	High

Michelle,

Please clarify the following discrepancies between the Table 45 in the original CSR and Table 14.3.1.5.12 in the 90-day safety update regarding the following TEAEs associated with permanent discontinuation of palbo/placebo:

- Anemia (n=2 in original CSR; only n=1 in safety update)

- Neutropenia (n=2 in original CSR; only n=1 in safety update)

Please provide an **email response by Monday 5pm EST, Jan 25, 2016**. As always, please follow up with an official submission to the sNDA.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
01/20/2016

From: Tilley, Amy
To: "Yu-Kite, Michelle"
Bcc: Ibrahim, Amna; Wedam, Suparna (FDA); Walker, Amanda
Subject: RE: IBRANCE (palbociclib) sNDA 207103
Date: Tuesday, January 19, 2016 3:52:37 PM

Michelle, at this time there is no need for a mid-cycle review meeting.

Have a nice day.

Amy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Tuesday, January 19, 2016 3:44 PM
To: Tilley, Amy
Subject: Re: IBRANCE (palbociclib) sNDA 207103

Hi Amy,

Thank you for responding so quickly. No our team is not requesting a mid-cycle meeting - from our side there are no outstanding issues to discuss.

Thanks,

Michelle

On Jan 19, 2016, at 12:38 PM, Tilley, Amy <Amy.Tilley@fda.hhs.gov> wrote:

> I just found out that the Turner site in UK does not need to be inspected.
>
> Let me check on our end if we want to have a mid-cycle review meeting with you. Do folks on your end want to have the meeting and if so what is their rationale?
>
> *Amy*
>
> **From:** Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
> **Sent:** Tuesday, January 19, 2016 1:06 PM
> **To:** Tilley, Amy
> **Subject:** IBRANCE (palbociclib) sNDA 207103
>
> Hi Amy,
>
> Hope this finds you well. I recently was informed that there is an inspection scheduled at one our PALOMA-3 (1023) sites, at Dr. Nicholas Turner on March 7-11. I wondered if this would, therefore impact the previously targeted date of 8 Feb 2016 of FDA communicating the proposed labeling and any PMR/C (as noted in the No Filing Review Issues letter dated 9 Dec 2015)?
>
> Also, do you know if there is a current project for a mid-cycle review meeting?

Sorry to bombard you with so many questions on your first day back. Please feel free to give me a call at (858) 736-5128 if it's more convenient than email.

Thanks,
Michelle Yu-Kite

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/s/

AMY R TILLEY
01/19/2016

From: O"Donnell, Jeannette
To: "Yu-Kite, Michelle"
Cc: Tilley, Amy
Subject: RE: FDA Communication: sNDA 207103-002/Ibrance/IR/Safety Update - Time Sensitive
Date: Friday, January 15, 2016 2:16:00 PM

Dear Michelle,

Please disregard the IR in which we request you submit the corresponding written report for the safety update. It was overlooked in the electronic submission. Thank you for working with me to clarify this matter.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

From: O'Donnell, Jeannette
Sent: Friday, January 15, 2016 1:27 PM
To: 'Yu-Kite, Michelle'
Cc: Tilley, Amy
Subject: FDA Communication: sNDA 207103-002/Ibrance/IR/Safety Update - Time Sensitive
Importance: High

Dear Michelle,

In reference to sNDA 207103, thank you for the safety update. Please also submit the corresponding written report.

Please submit by **9:00 am, Tuesday January 19, 2016**. Please submit by 1) email to facilitate review 2) formal submission to the NDA.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845

Email: *Jeannette.Odonnell@fda.hhs.gov*

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/s/

JEANNETTE L O'DONNELL
01/15/2016

From:	O"Donnell, Jeannette
To:	"Yu-Kite, Michelle"
Cc:	Tilley, Amy
Subject:	FDA Communication: sNDA 207103-002/Ibrance/IR/Safety Update - Time Sensitive
Date:	Friday, January 15, 2016 1:26:00 PM
Importance:	High

Dear Michelle,

In reference to sNDA 207103, thank you for the safety update. Please also submit the corresponding written report.

Please submit by **9:00 am, Tuesday January 19, 2016**. Please submit by 1) email to facilitate review 2) formal submission to the NDA.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
01/15/2016

From: O"Donnell, Jeannette
To: "Yu-Kite, Michelle"
Subject: FDA Communication: sNDA 207103-002/Ibrance/label IR data set?/ Time sensitive
Date: Monday, January 11, 2016 1:54:00 PM
Importance: High

Dear Michelle,

On behalf of Amy Tilley and in reference to sNDA 207103-002 we have the following question:

(b) (4)

Please respond by no later than **COB tomorrow, January 12, 2015**. As Amy is currently out of office please reply to all by 1) email to facilitate review 2) formal submission to the NDA. If you have any further questions please do not hesitate to ask.

Thanks,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
01/11/2016

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Cc:	O"Donnell, Jeannette
Bcc:	Amiri Kordestani, Laleh (FDA); Wedam, Suparna (FDA)
Subject:	TIME SENSITIVE sNDA 207103/002 Ibrance - Clinical IR sent 1-6-16
Date:	Wednesday, January 06, 2016 4:37:10 PM
Importance:	High

Michelle,

Please respond to the Clinical IR below **no later than Friday Jan 8, 2016**, and follow up with an official submission to the sNDA.

1. Please provide any efficacy data available (b) (4) (from sponsored or research studies).

2. Please provide any safety and efficacy data available with male breast cancer patients (from sponsored or research studies).

3. Please provide the number of events that have occurred on Study 1008 as of January 1, 2016 and whether any further data is available.

When you respond via email please **"Reply to All"** as I may be out of the office.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
01/06/2016

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Amiri Kordestani, Laleh (FDA); Wedam, Suparna (FDA)
Subject:	URGENT TIME SENSITIVE sNDA 207103/002 Ibrance - Clinical IR
Date:	Tuesday, January 05, 2016 4:00:19 PM
Importance:	High

Michelle,

Please respond to the Clinical Information Request below **by 4:00 pm Wednesday, January 6, 2016**, and follow up with an official response to the sNDA.

In the CSR analysis dataset eedrsp, there are two endpoints, Progression-Free Survival (Method1) (eecode = 11) and Progression-Free Survival (Method1-variation) (eecode = 13). Can you explain the difference between these two endpoints and how they are both calculated? It appears you Progression-Free Survival (Method1-variation) (eecode = 13) for the primary analysis.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
01/05/2016

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Thursday, December 31, 2015 11:51 AM
To: 'michelle.y.kite@pfizer.com'
Cc: Tilley, Amy; Kacuba, Alice
Subject: FDA Information Request for NDA 207103/S-002, Ibrance® (palbociclib) Capsules; 75 mg, 100 mg, and 125 mg
Attachments: Table 6_IR_151231.doc

Importance: High

Dear Ms. Kite,

Please submit by return e-mail and official submission your response to the attached Information Request. We request that you provide your response by Tuesday, January 5, 2016. Also, please acknowledge receipt of this email by return email.

Thank you,

Frank Cross, RPM

(for Amy Tilley, RPM)

Sincerely,

Frank Cross, Jr.

Frank Cross, Jr., MA, MT (ASCP)

Senior Regulatory Health Project Manager

Division of Oncology Products 1

Office of Hematology and Oncology Products

Office of New Drugs

Center for Drug Evaluation and Research

US Food and Drug Administration

White Oak Bldg 22, 2nd floor, Room 2110

10903 New Hampshire Avenue

Silver Spring, MD 20993
(301) 796-0876 (office)

(301) 796-9845 (fax)

(301) 796-2330 (Division Main #)

frank.crossjr@fda.hhs.gov <mailto:frank.crossjr@fda.hhs.gov>

Please clarify the discrepancy that we have observed in **Table 6. Adverse Reactions in Study 2** of the proposed Ibrance Prescribing Information (See Table below). Based on our analysis, the percentage of patients who reported diarrhea in the placebo arm was 18% (all grades) and 1.2% (grade 3). In addition, we believe the following PTs should be included in the definition of rash: erythema, skin lesion, skin ulcer, and toxic skin eruption.

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/s/

FRANK H CROSS
12/31/2015

From: Tilley, Amy
To: "Yu-Kite, Michelle"
Bcc: Chen, Xiao H
Subject: TIME SENSITIVE sNDA 207103-002 - CMC IR
Date: Thursday, December 17, 2015 3:36:41 PM

Michelle,

Regarding your claim for Categorical Exclusion from the filing of environmental assessment requirements for Ibrance capsules under 21 CFR Part 25.31(b), provide your justification using the calculated Expected Introduction Concentration (EIC) for Ibrance based on the projected annual manufacturing of palbociclib API.

Please provide your emailed response **by 1pm, Friday, December 18, 2015**, and follow up with an official response to the NDA supplement.

Regards.

Amy Tilley

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

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AMY R TILLEY
12/17/2015

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Amiri Kordestani, Laleh (FDA); Bloomquist, Erik; Wedam, Suparna (FDA)
Subject:	TIME SENSITIVE sNDA 207103-2 - Clin-Stat IR
Date:	Tuesday, December 15, 2015 11:21:36 AM

Michelle,

We request your response **by 4 pm, Friday, December 18, 2015.**

Provide the following information regarding results for Patient Reported Outcomes in Study 1023:

1. Perform two additional analyses for the prespecified time to event analysis for pain (TTD). Provide results for analyses using a responder definitions of delay in increase of pain ≥20 points and ≥30 points.

2. Please explain how information regarding analgesic use was captured and incorporated into the analyses for TTD.

3. Please provide detailed censoring rules that were used in TTD analyses.

4. Please provide the number of patients who completed all scheduled questionnaires including the baseline and the end of treatment questionnaire. Please also provide the number of patients who only missed one scheduled questionnaire.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
12/15/2015

From: Tilley, Amy
To: "Yu-Kite, Michelle"
Subject: RE: sNDA 207103-S-002 Ibrance - Filing Letter
Date: Wednesday, December 09, 2015 3:43:22 PM

Michelle, because this label will be the one we will use going forward and since it takes the place of the original proposed that you submitted initially with the sNDA, yes you will need to also submit the label in SPL.

Thanks.

Amy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Wednesday, December 09, 2015 3:39 PM
To: Tilley, Amy
Subject: RE: sNDA 207103-S-002 Ibrance - Filing Letter

Thank you Amy. Referring to the USPI, we acknowledge the updated guidance for the SRPI. We are working on corrections to the USPI mentioned in the Filing Letter. Can you confirm that for the submission due on Friday, that the SPL does not need to be included?

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Wednesday, December 9, 2015 12:23 PM
To: Yu-Kite, Michelle
Subject: sNDA 207103-S-002 Ibrance - Filing Letter

Michelle,

Attached is the Ibrance Filing letter for supplement 002.

In the letter it states the following but if you need more time to submit the label with the changes noted below just let me know.

"During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:
1. Place a horizontal line between the TOC and the FPI.
2. Bold the product title in Highlights.
3. Bold the "Initial U.S. Approval" statement in Highlights.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **December 11, 2015.** The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances."

Amy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Wednesday, December 02, 2015 12:43 PM
To: Tilley, Amy

Subject: RE: sNDA 207103-S-002 Ibrance - PAS Ack Letter

Hi Amy,

I was wondering if you have an estimate when we may hear back about our request for priority review for sNDA 207103 S-002?

Also, I will be sending our remaining response to the clinical IR later this afternoon.

Thanks,
Michelle

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Friday, October 30, 2015 6:55 AM
To: Yu-Kite, Michelle
Subject: sNDA 207103-S-002 Ibrance - PAS Ack Letter

Michelle,

Attached is the PAS Acknowledgement Letter regarding sNDA 207103-S-002 for Ibrance.

Regards.
Amy Tilley

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

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/s/

AMY R TILLEY
12/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207103/S-002

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Pfizer Inc.
Attention: Michelle Y. Kite
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Ms. Kite:

Please refer to your supplemental New Drug Application (sNDA) dated October 15, 2015, received October 15, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Ibrance® (palbociclib) Capsules; 75 mg, 100 mg, and 125 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is April 15, 2016.

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 8, 2016. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

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

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

1. Place a horizontal line between the TOC and the FPI.
2. Bold the product title in Highlights.
3. Bold the "*Initial U.S. Approval"* statement in Highlights.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by December 11, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

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

PROMOTIONAL MATERIAL

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

Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

GEOFFREY S KIM
12/09/2015

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Chen, Xiao H; Amiri Kordestani, Laleh (FDA)
Subject:	RE: TIME SENSITIVE sNDA 2007103-2 Ibrance - CMC IR
Date:	Tuesday, December 08, 2015 12:54:23 PM

Michelle, see 21 CFR 25.31 below.

[Code of Federal Regulations]
[Title 21, Volume 1]
[Revised as of April 1, 2015]
[CITE: 21CFR25.31]

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER A--GENERAL

PART 25 -- ENVIRONMENTAL IMPACT CONSIDERATIONS

Subpart C--Categorical Exclusions Sec. 25.31 Human drugs and biologics.
The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS:

(a) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety.

(b) Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

(c) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

(d) Withdrawal of approval of an NDA or an abbreviated application.

(e) Action on an IND.

(f) Testing and release by the Food and Drug Administration of lots or batches of a licensed biologic product.

(g) Establishment of bioequivalence requirements for a human drug or a comparability determination for a biologic product subject to licensing.

(h) Issuance, revocation, or amendment of a standard for a biologic product.

(i) Revocation of a license for a biologic product.

(j) Action on an application for marketing approval for marketing of a biologic product for transfusable human blood or blood components and plasma.

[62 FR 40592, July 29, 1997, as amended at 63 FR 26697, May 13, 1998; 64 FR 399, Jan. 5, 1999; 70 FR 14980, Mar. 24, 2005]

Amy

From: Tilley, Amy
Sent: Tuesday, December 08, 2015 12:37 PM
To: 'Yu-Kite, Michelle'
Subject: RE: TIME SENSITIVE sNDA 2007103-2 Ibrance - CMC IR

Since the proposed indication population is not the same and is larger we will need either the EA or the CE.

Amy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Tuesday, December 08, 2015 12:34 PM
To: Tilley, Amy
Subject: Re: TIME SENSITIVE sNDA 2007103-2 Ibrance - CMC IR

Hi Amy,

An EA was not included in S002 as we did not include any CMC information.

Please let me know if this is still needed even though no CMC information was included as there were no new updates to submit.

Thanks,

Michelle

Sent from my iPhone

On Dec 8, 2015, at 11:28 AM, Tilley, Amy <Amy.Tilley@fda.hhs.gov> wrote:

> Michelle,
>
> Submit an environmental analysis (EA) or request a categorical exclusion (CE) for NDA 207103 S002 in accordance to 21 CFR 25.31. **Please respond by 12 noon, Friday, Dec 11, 2015.**

If an EA or CE has already been submitted please let us know the location within the global submit.

Regards.
Amy Tilley

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

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/s/

AMY R TILLEY
12/08/2015

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Amiri Kordestani, Laleh (FDA); Walker, Amanda
Subject:	TIME SENSITIVE sNDA 207103-2 Ibrance - Clinical IR Safety
Date:	Monday, December 07, 2015 6:39:11 PM
Importance:	High

Michelle,

Please respond to the following Clinical IR by Dec 14, 2015.

1. Please clarify why the "ADVERS" dataset does not contain a Grade 5 AE for subject 10791002 who died from DIC likely secondary to disease progression.

2. Please clarify why the following SAEs were not considered by the Sponsor to be *possibly* related to study drug given the known side effect profile of Palbociclib.

Subject 10071003 - cellulitis

Subject 10101005 - PE

Subject 10771007 - UTI

Subject 10841003 - pneumonia

Subject 11661005 - PE

Subject 119881001 - URI and Pyrexia

Kindly confirm receipt of this email.

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
12/07/2015

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Amiri Kordestani, Laleh (FDA); Walker, Amanda; Wedam, Suparna (FDA)
Subject:	TIME SENSITIVE sNDA 207103-2 Ibrance - Clinical IR
Date:	Wednesday, November 25, 2015 3:12:04 PM
Importance:	High

Michelle,

We are requesting your emailed reply **no later than 12 noon on Wednesday Dec 2, 2015,** then follow up with an official submission to the sNDA.

Please provide more information regarding subject 11661006. She was documented as having a Grade 5 "deterioration of general condition" in the ADVERS dataset and is described as having death secondary to "disease progression" in Section 12.3.1.1 of the Study Report (page 200). After reviewing the AE narrative (page 1390), it appears that the patient was neutropenic (ANC 350) with fever, tachycardia, and hypotension with a blood culture positive for E.coli shortly before her death on (b) (6). Furthermore, no AEs are reported in the dataset during the time period of her hospitalization and subsequent death other than "deterioration of general condition". It appears that patient died from neutropenic sepsis. Please clarify.

Kindly confirm receipt of this emailed request.

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
11/25/2015

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Amiri Kordestani, Laleh (FDA); Wedam, Suparna (FDA); Walker, Amanda
Subject:	TIME SENSITIVE sNDA 207103-2 Ibrance - Clin IR
Date:	Friday, November 20, 2015 9:59:31 AM

Michelle,

Please provide the following information **no later than 3 pm on Wednesday, Dec 2, 2015**, via email and as an official submission to the sNDA:

1. Plan or manual detailing the procedures for BICR (ie, exactly what information could be provided to (b) (4), how was the 40% random sample chosen, etc).

2. Any information available regarding the use of palbociclib in males.

3. Any information available regarding the use of palbociclib in combination with tamoxifen.

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
11/20/2015

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Amiri Kordestani, Laleh (FDA); Wedam, Suparna (FDA); Walker, Amanda
Subject:	sNDA 207103-2 Ibrance - Clinical IR
Date:	Thursday, November 19, 2015 4:02:45 PM

Michelle,

In regards to your Efficacy Supplement, Table 6 in your proposed label reports the adverse events from Study 1023. Please clarify the method used to determine which AEs are presented in the table (e.g. cut-off for incidence, difference between the two groups, etc.)

Please respond at your earliest convenience via email and then follow up with an official submission to the sNDA.

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
11/19/2015

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

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO: **CDER-DMPP-PatientLabelingTeam**	FROM: (Name/Title, Office/Division/Phone number of requestor) Amy Tilley/RPM/OHOP/DOP1/301-796-3994

REQUEST DATE:	NDA/BLA NO.:	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)
November 13, 2015	sNDA 207103-002	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling)
Ibrance (palbociclib)	Priority		

SPONSOR:	
Pfizer Inc.	PDUFA Date: 4-15-16 **Target Date: 2-29-16**

TYPE OF LABEL TO REVIEW

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

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

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION – Changing Indication (b) (4)

EDR link to submission: EDR Location: \\CDSESUB1\evsprod\NDA207103\207103.enx

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

COMMENTS/SPECIAL INSTRUCTIONS: DOP1 requests PLT to review the PPI regarding Ibrance (palbociclib) sNDA 207103-002 Efficacy Supplement.

Filing/Planning Meeting: 11-10-15

Mid-Cycle Meeting: 1-12-16

Labeling Meetings: 1-11-16; 1-14-16; 1-19-16; and 1-26-16

Wrap-Up Meeting: 2-2-16

SIGNATURE OF REQUESTER
Amy Tilley *{See appended electronic signature page}*

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☒ eMAIL (BLAs Only) ☒ DARRTS

Version: 12/9/2011

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/s/

AMY R TILLEY
11/13/2015

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

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-OPDP-RPM	Amy Tilley/RPM/OHOP/DOP1/301-796-3994

REQUEST DATE:	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
November 13, 2015		sNDA 207103/002	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Ibrance (palbociclib)	Priority		

NAME OF FIRM:	
Pfizer Inc.	PDUFA Date: 4-15-16 **Target Date: 2-29-16**

TYPE OF LABEL TO REVIEW

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

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION Changing Indication (b) (4)

For OSE USE ONLY
☐ REMS

EDR link to submission: EDR Location: \\CDSESUB1\evsprod\NDA207103\207103.enx

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: DOP1 requests OPDP to review both the PI and the PPI of Ibrance (palbociclib) sNDA 207103-002.

Mid-Cycle Meeting: 1-12-16
Labeling Meetings: 1-11-16; 1-14-16; 1-19-16; and 1-26-16
Wrap-Up Meeting: 2-2-16

SIGNATURE OF REQUESTER
Amy Tilley *{See appended electronic signature page}*

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☒ eMAIL ☐ HAND

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/s/

AMY R TILLEY
11/13/2015

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: 11/10/2015

To: Ni Aye, Khin, M.D., DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Kassa Ayalew, M.D.,M.P.H., Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Thompson, M.D. Team Leader, GCPAB
CDER OSI PM Track
Lauren Iacono-Connors, Ph.D., OSI Reviewer
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Suparna Wedam, M.D., Clinical Reviewer, DOP1
Laleh Amiri-Kordestani, M.D., Acting Clinical Team Leader, DOP1
Geoffrey Kim M.D., Division Director, DOP1

From: Amy Tilley, Regulatory Health Project Manager, DOP1

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: sNDA 207103/2
IND#: 069324
Applicant/ Applicant contact information (to include phone/email): Pfizer Inc.
Drug Proprietary Name: Ibrance®
Generic Drug Name: palbociclib
NME or Original BLA (Yes/No/Not Applicable*): No
Application Submission Date: 10/15/2015
Review Priority (Standard or Priority or Not Applicable*): Priority

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No/Not Applicable*): No

Proposed New Indication(s): (b) (4)

(b) (4)

PDUFA: 04/15/2016
Action Goal Date: Feb 29, 2016
Inspection Summary Goal Date: Feb 4, 2016

OSI/DGCPC Consult
version: 09/12/2013

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Site 1137 PI: Dennis Slamon UCLA Dept. of Medicine Hematology-Oncology Los Angeles CA 90095-178 Phone: 310-825-5268 Fax: 310-794-5517 dslamon@mednet.ucla.edu	A5481023	14	inv-PFS
Site 1201 PI: Nicholas Turner Royal Marsden hospital Royal Marsden NHS Foundation Trust Fulham Road London SW3 6JJ Phone: +442071535574 Fax: +4420751535340 Nicolas.turner@icr.ac.uk	A5481023	9	inv-PFS

III. Site Selection/Rationale

- *The above two sites were selected as they were among some of the highest accruing sites. We have some concern based on review of* [redacted] (b) (6) *for the investigators of both of these sites. In addition, a high number of major protocol deviations were reported at the UCLA site.*

Rationale for OSI Audits

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
_X___ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable. N/A

Should you require any additional information, please contact Amy Tilley at *301-796-3994.*

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/s/

AMY R TILLEY
11/10/2015

GEOFFREY S KIM
11/10/2015

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Amiri Kordestani, Laleh (FDA); Wedam, Suparna (FDA); Walker, Amanda
Subject:	URGENT re sNDA 207103/2 Ibrance - Clin-OSI IR
Date:	Tuesday, November 10, 2015 12:05:58 PM
Importance:	High

Michelle,

Please provide the name and address for the independent third party that conducted the BICR for Study 1023.

We request your response **no later than 3 pm today, Nov 10, 2015.** As always, please follow up with an official response to the sNDA.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
11/10/2015

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

REQUEST FOR Clinical Outcome Assessment CONSULTATION

TO: Clinical Outcome Assessments (COA) Staff **CDER/OND-IO White Oak Bldg 22, Mail Drop 6411** **COAStaff@fda.hhs.gov**	**FROM: Review Division: DOP1** **Medical Reviewer: Efficacy= Suparna Wedam; Safety= Amanda Walker; MOTL = Laleh Amiri-Kordestani** **Project Manager: Amy Tilley**

DATE OF CONSULT REQUEST	Application# IND/NDA/BLA#	LETTER# OR SUBMISSION#	TYPE OF DOCUMENT (Meeting; Protocol/SPA; PDUFA Product Review)	REQUESTED COMPLETION DATE*
November 9, 2015	sNDA 207103/2	SDN=193 eCTD=99	Efficacy Supplement	January 1, 2016

DRUG ESTABLISHED NAME	DRUG TRADE NAME	NAME OF SPONSOR	SPONSOR SUBMIT DATE
Palbociclib	Ibrance	Pfizer Inc.	October 15, 2015

***For voluminous clinical outcome assessment submissions (e.g. COA "dossier" or content validity documentation greater than 50 pages), it may take longer than 30 days after briefing package is received to complete a review. Please discuss the review timeframe with the COA Staff PM.**

DEVELOPMENT PHASE (e.g., pre-IND/NDA/BLA; IND/BB-IND Phase 1, 2, 3; NDA/BLA): Efficacy Supplement of AA NDA

GOAL DATE (if NDA/BLA/SPA): PDUFA=4-15-16 DOP1 wishes to take early Action on or about **Feb 15, 2016**

ELECTRONIC LINK (if applicable): \\CDSESUB1\evsprod\NDA207103\207103.enx

BACKGROUND PACKAGE (deliver PAPER to Clinical Outcome Assessments Staff mailbox in Bldg 22, Rm 6411): N/A

DELIVERABLE: (e.g., sponsor meeting, WRO, advice letter (not WRO), NDA/BLA Labeling, general advice for internal use)

LABEL MTGS: TBS to start in January 2016

MEETINGS (if applicable) (please send invite to **COAStaff@fda hhs.gov**) Filing Mtg: 11-10-15 Midcycle and Wrap Up Mtgs TBS

Meeting type (A, B, C): N/A

Internal Meeting date: N/A
Sponsor/Industry Meeting date: N/A

PLEASE make certain the meeting request and/or background briefing package is included with this consult. It should contain the following applicable information needed to start the Clinical Outcome Assessment Review: study protocol(s); endpoint concept(s); instrument(s); indication(s); study population(s); prior related reviews. Division PM, please provide the following specific information on this consult form:

Instrument(s): Global QOL, EORTC QLQ-BR23, EQ-5D

Indication(s) [redacted] (b) (4)

Specific Questions/Comments for Clinical Outcome Assessments Staff:

[redacted] (b) (4) Please evaluate and comment on the instruments that were used, the time points of the data collection, completion rates, and the clinical significance of the results [redacted] (b) (4) Please note that PROs were secondary endpoints with no alpha allocations and considered exploratory in nature.

Requester: Amy Tilley, DOP1/RPM

Name/Phone number/email address/office location	Amy Tilley/301-796-3994/amy.tilley@fda.hhs.gov/WO22 Rm 2108

Glossary:
Concept of interest: The specific goal of a measurement (i.e. the *thing* that is to be measured by an assessment).
Instrument: A means to capture data (e.g. questionnaire, diary) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results.

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/s/

AMY R TILLEY
11/10/2015

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Iacono-Connor, Lauren; Amiri Kordestani, Laleh (FDA)
Subject:	Ibrance sNDA 207103/2 - OSI IR
Date:	Monday, November 09, 2015 6:10:11 PM
Importance:	High

Michelle, while the BIMO reviewer guide mentions a submitted dataset for the OSI Part 3 request, it is only the efficacy dataset and not the dataset that can be used to load the site selection tool. We did not identify a dataset for tool load in this application. Therefore, we are requesting that you submit the dataset that can be used to load the site selection tool to the NDA. If this information was already submitted to the NDA please let us know the location.

Please confirm receipt of this email.

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
11/09/2015

From: Tilley, Amy
To: "Yu-Kite, Michelle"
Subject: RE: IBRANCE (palbociclib) - PRO IR
Date: Wednesday, November 04, 2015 4:27:41 PM

Michelle, you can lump the PRO response, other clinical response, and the programming response in the same submission.
Regards.

Amy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Wednesday, November 04, 2015 3:18 PM
To: Tilley, Amy
Subject: IBRANCE (palbociclib) - PRO IR

Hi Amy,

Please find our responses for the PRO queries asked during the AOM general meeting.

I am planning to send our clinical IR and programming IR this Friday.

I will also submit these officially to the NDA – can I lump all three IRs in the same submission or would you like them separated?

Thanks,
Michelle

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/s/

AMY R TILLEY
11/04/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207103/S-002

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Pfizer Inc.
Attention: Michelle Y. Kite
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Ms. Kite:

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

NDA NUMBER: 207103

SUPPLEMENT NUMBER: 002

PRODUCT NAME: Ibrance (palbociclib) Capsules; 75 mg, 100 mg, and 125 mg

DATE OF SUBMISSION: October 15, 2015

DATE OF RECEIPT: October 15, 2015

This supplemental application proposes the following change to the indication from in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease to (b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 14, 2015, in accordance with 21 CFR 314.101(a) .

If the application is filed, the user fee goal date will be April 15, 2016.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by

Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, contact me at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Amy R. Tilley
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

AMY R TILLEY
10/30/2015

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Spillman, Dianne D; Gallauresi, Beverly; Lincoln, Christine; Viesulas, Jura
Subject:	CORRECTION re URGENT REQUEST re sNDA 207103/002 Ibrance - AOM
Date:	Thursday, October 29, 2015 10:18:19 AM
Importance:	High

Michelle,

My apologies as Pfizer must provide the WebEx information and a call in number that we will patch in when we are ready to begin your AOM.

Please confirm receipt of this email.

Amy

From: Tilley, Amy
Sent: Thursday, October 29, 2015 10:07 AM
To: 'Yu-Kite, Michelle'
Subject: URGENT REQUEST re sNDA 207103/002 Ibrance - AOM
Importance: High

Michelle,

Regarding your Application Orientation Meeting (AOM) for sNDA 207103/002 Ibrance (palbociclib) you must email your slides to me **no later than 1 pm on Friday, October 30, 2015.**

I will send you the call in information and the WebEx link prior to the meeting.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
10/29/2015

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Spillman, Dianne D; Gallauresi, Beverly; Lincoln, Christine; Viesulas, Jura
Subject:	URGENT REQUEST re sNDA 207103/002 Ibrance - AOM
Date:	Thursday, October 29, 2015 10:07:12 AM
Importance:	High

Michelle,

Regarding your Application Orientation Meeting (AOM) for sNDA 207103/002 Ibrance (palbociclib) you must email your slides to me **no later than 1 pm on Friday, October 30, 2015.**

I will send you the call in information and the WebEx link prior to the meeting.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
10/29/2015

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Kacuba, Alice
Subject:	RE: IBRANCE (palbociclib) Orientation Meetings on Nov 2
Date:	Thursday, October 22, 2015 2:01:07 PM

Michelle, sorry as I forgot this would be an international call. I will have to check with the Office folks if they can patch in an international call during this mtg.

Also, will your international colleague be expecting to see the screen/slides? If so, I will also have to check with the Office folks about this as well.

I will get back to you soon.

Amy

From: Tilley, Amy
Sent: Thursday, October 22, 2015 1:51 PM
To: 'Yu-Kite, Michelle'
Subject: RE: IBRANCE (palbociclib) Orientation Meetings on Nov 2

Michelle, yes your colleague from Italy can call into both meetings. Please send me the call in information.

As for our attendees you will meet them the day of the meetings.

Amy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Thursday, October 22, 2015 1:26 PM
To: Tilley, Amy
Subject: IBRANCE (palbociclib) Orientation Meetings on Nov 2

Hi Amy,

For our upcoming Orientation meetings on Nov 2 (10:45-noon for General and noon-1pm for Dataset), is it possible to have a teleconference line for both meetings? We have a clinical colleague from Italy that I'd like to join via teleconference please.

Also, do you mind sending me a list of the FDA reviewers? The team would like to understand if there are any new reviewers different from the initial NDA.

Thanks,
Michelle

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/s/

AMY R TILLEY
10/22/2015

From:	Tilley, Amy
To:	"Yu-Kite, Michelle"
Bcc:	Tang, Shenghui; Bloomquist, Erik; Amiri Kordestani, Laleh (FDA)
Subject:	Time Sensitive Stat IR re sNDA 207103/2 Ibrance
Date:	Monday, October 19, 2015 10:58:58 AM

Michelle, please respond to this email **by 11:00 am tomorrow, Oct 20, 2015 or sooner.**

In the analysis dataset section, there are two folders, one titled "datasets-co" and the other titled "datasets-csr." Can you explain the difference between these two folders?

Regards.

Amy Tilley

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

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/s/

AMY R TILLEY
10/19/2015

From: Tilley, Amy
To: "Yu-Kite, Michelle"
Subject: RE: IBRANCE (palbociclib) NDA 207103 - Request for Orientation Meetings
Date: Friday, October 16, 2015 8:38:48 AM
Attachments: Template Foreign Visitor Form.doc

Michelle, thanks for confirming this date. Should you have a foreign visitor I will need the attached form completed and sent back to me asap in order for the visitor to be cleared.

Thanks.

Amy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Thursday, October 15, 2015 9:07 PM
To: Tilley, Amy
Subject: RE: IBRANCE (palbociclib) NDA 207103 - Request for Orientation Meetings

Hi Amy,

Pfizer would very much like to accept the Nov 2 meeting for the orientation meetings. I believe you mentioned 10:45-noon for the general meeting and noon-1pm for the dataset meeting.

I will send you complete list of attendees later today or early next week at the latest. We may have one foreign visitor.

Thanks,

Michelle

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Thursday, October 15, 2015 11:45 AM
To: Yu-Kite, Michelle
Subject: RE: IBRANCE (palbociclib) NDA 207103 - Request for Orientation Meetings

Michelle, our calendars are booked solid but I was able to find a Nov 2nd Office Mtg from ~10:30 – 12 noon that is available for the Orientation Meetings.

Does this work for Pfizer? I hope so because then it is back to the drawing board.

Please let me know Pfizer's availability for the above mentioned date/time as soon as possible.

Thanks.

Amy

From: Yu-Kite, Michelle [mailto:michelle.y.kite@pfizer.com]
Sent: Thursday, October 15, 2015 12:00 PM
To: Tilley, Amy
Subject: IBRANCE (palbociclib) NDA 207103 - Request for Orientation Meetings

Importance: High

Hello Amy,

For some reason, we experienced issues with the gateway system yesterday so the supplemental NDA 207103 (sequence 00099) and the Postmarketing Commitment Final Report were not received until very early this morning.

Now that the sNDA has been submitted, we would like to request two Face-to-Face Orientation Meetings with FDA (1) General – to provide a brief overview of the supplement to the FDA reviewers (2) Dataset – to provide an overview of the format and content of the datasets/programs to the relevant clinical and statistic reviewers.

Thanks,
Michelle

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	November 2, 2015 10:30 am
MEETING ENDING DATE AND TIME	November 2, 2015 1:00 pm
PURPOSE OF MEETING	Application Orientation Meeting
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	WO22 2205 and 2201
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	Amy Tilley, RPM, OHOP/WO22 Rm 2108 301-796-3994
ESCORT INFORMATION (If different from Hosting Official)	Same

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/s/

AMY R TILLEY
10/16/2015