

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

207103Orig1s008

Trade Name: IBRANCE

Generic or Proper Name: palbociclib

Sponsor: Pfizer, Inc.

Approval Date: April 4, 2019

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

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

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207103Orig1s008

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Officer/Employee List	
Multidiscipline Review(s) <ul style="list-style-type: none">• Summary Review• Office Director• Cross Discipline Team Leader• Clinical• Non-Clinical• Statistical• Clinical Pharmacology	X
Product Quality Review(s)	X
Clinical Microbiology / Virology Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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APPROVAL LETTER



NDA 207103/S-008

SUPPLEMENT APPROVAL

Pfizer, Inc.
Attention: Michelle Kite, MS, RAC
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 June 15, 2018, received June 15, 2018, and your amendments, 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.

This Prior Approval supplemental new drug application expands the approved indications for palbociclib in combination with an aromatase inhibitor, and for palbociclib in combination with fulvestrant, to include male patients with advanced or metastatic breast cancer.

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 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 Prescribing Information and Patient Package Insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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).

REQUIRED PEDIATRIC ASSESSMENTS

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

Because none of these criteria apply to your application, you are exempt from this requirement.

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, call Amy Tilley, Regulatory Project Manager, at 301-796-3994.

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Supervisory Associate 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LALEH AMIRI KORDESTANI
04/04/2019 12:37:55 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207103Orig1s008

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) 4/2019

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

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: 4/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Schedule

2.2 Dose Modification

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

5.2 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Agents That May Increase Palbociclib Plasma Concentrations

7.2 Agents That May Decrease Palbociclib Plasma Concentrations

7.3 Drugs That May Have Their Plasma Concentrations Altered by Palbociclib

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

8.7 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Schedule

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

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

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

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

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

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

For men treated with combination IBRANCE plus aromatase inhibitor therapy, consider treatment with an LHRH agonist 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 15 of the first 2 cycles, and as clinically indicated.	
For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated.	
CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3	<p><u>Day 1 of cycle:</u> Withhold IBRANCE, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤ 2, start the next cycle at the <i>same dose</i>.</p> <p><u>Day 15 of first 2 cycles:</u> If Grade 3 on Day 15, continue IBRANCE at current dose to complete cycle and repeat complete blood count on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below.</p> <p>Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.</p>
Grade 3 neutropenia ^b with fever ≥ 38.5 °C and/or infection	<p><u>At any time:</u> Withhold IBRANCE until recovery to Grade ≤ 2. Resume at the <i>next lower dose</i>.</p>
Grade 4	<p><u>At any time:</u> Withhold IBRANCE until recovery to Grade ≤ 2. Resume at the <i>next lower dose</i>.</p>

Grading according to CTCAE 4.0.

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

^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/mm³; Grade 2: ANC 1000 - <1500/mm³; Grade 3: ANC 500 - <1000/mm³; Grade 4: ANC <500/mm³.

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)	<p>Withhold until symptoms resolve to:</p> <ul style="list-style-type: none"> • Grade ≤ 1; • Grade ≤ 2 (if not considered a safety risk for the patient) <p>Resume at the <i>next lower dose</i>.</p>

Grading according to CTCAE 4.0.

CTCAE=Common Terminology Criteria for Adverse Events.

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

Dose Modifications for Use With Strong CYP3A Inhibitors

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

Dose Modifications for Hepatic Impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

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

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

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

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

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

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

5.2 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at maternal exposures that were ≥ 4 times the human clinical exposure based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 weeks after the last dose [see *Use in Specific Populations (8.1 and 8.3) and Clinical Pharmacology (12.1)*].

6 ADVERSE REACTIONS

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

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

6.1 Clinical Studies Experience

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

Study 1: IBRANCE plus Letrozole

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

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

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

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

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

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

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

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

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

Grading according to CTCAE 4.0.

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

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

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

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

^d Grade 1 events – 30%; Grade 2 events – 3%.

^e Grade 1 events – 15%; Grade 2 events – 1%.

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

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

Table 5. Laboratory Abnormalities in Study 1

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

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

Study 2: IBRANCE plus Fulvestrant

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

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

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

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

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

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

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

Table 6. Adverse Reactions (≥10%) in Study 2						
Adverse Reaction	IBRANCE plus Fulvestrant (N=345)			Placebo plus Fulvestrant (N=172)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	%	%	%	%	%	%
Infections and infestations						
Infections ^a	47 ^b	3	1	31	3	0
Blood and lymphatic system disorders						
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	4	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	8	1	0
Gastrointestinal disorders						
Nausea	34	0	0	28	1	0
Stomatitis ^c	28	1	0	13	0	0
Diarrhea	24	0	0	19	1	0
Vomiting	19	1	0	15	1	0
Skin and subcutaneous tissue disorders						
Alopecia	18 ^d	N/A	N/A	6 ^e	N/A	N/A
Rash ^f	17	1	0	6	0	0
General disorders and administration site conditions						
Fatigue	41	2	0	29	1	0
Pyrexia	13	<1	0	5	0	0

Grading according to CTCAE 4.0.

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

- ^a Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.
- ^b Most common infections (≥1%) include: nasopharyngitis, upper respiratory infection, urinary tract infection, bronchitis, rhinitis, influenza, conjunctivitis, sinusitis, pneumonia, cystitis, oral herpes, respiratory tract infection, gastroenteritis, tooth infection, pharyngitis, eye infection, herpes simplex, and paronychia.
- ^c Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.
- ^d Grade 1 events – 17%; Grade 2 events – 1%.
- ^e Grade 1 events – 6%.
- ^f Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.

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

Table 7. Laboratory Abnormalities in Study 2

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

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of IBRANCE. 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.

Respiratory disorders: Interstitial lung disease (ILD)/non-infectious pneumonitis.

Male patients with HR-positive, HER2-negative advanced or metastatic breast cancer

Based on limited data from postmarketing reports and electronic health records, the safety profile for men treated with IBRANCE is consistent with the safety profile in women treated with IBRANCE.

7 DRUG INTERACTIONS

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

7.1 Agents That May Increase Palbociclib Plasma Concentrations

Effect of CYP3A Inhibitors

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

7.2 Agents That May Decrease Palbociclib Plasma Concentrations

Effect of CYP3A Inducers

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

7.3 Drugs That May Have Their Plasma Concentrations Altered by Palbociclib

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal 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 of palbociclib up to 300 mg/kg/day and 20 mg/kg/day, respectively, during the period of organogenesis. The maternally toxic dose of 300 mg/kg/day was fetotoxic in rats, resulting in reduced fetal body weights. At doses ≥ 100 mg/kg/day in rats, there was an increased incidence of a skeletal variation (increased incidence of a rib present at the seventh cervical vertebra). At the maternally toxic dose of 20 mg/kg/day in rabbits, there was an increased incidence of skeletal variations, including small phalanges in the forelimb. At 300 mg/kg/day in rats and 20 mg/kg/day in rabbits, the maternal systemic exposures were approximately 4 and 9 times the human exposure (AUC) at the recommended dose, respectively.

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

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

Males

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

Infertility

Males

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

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days [see *Dosage and Administration (2.2)*]. Based on a pharmacokinetic trial in subjects with varying degrees of hepatic function, the palbociclib unbound exposure (unbound AUC_{INF}) decreased by 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure (unbound C_{max}) increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function [see *Clinical Pharmacology (12.3)*].

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

8.7 Renal Impairment

No dose adjustment is required in patients with mild, moderate, or severe renal impairment ($CrCl > 15$ mL/min). Based on a pharmacokinetic trial in subjects with varying degrees of renal function, the total palbociclib exposure (AUC_{INF}) increased by 39%, 42%, and 31% with mild ($60 \text{ mL/min} \leq CrCl < 90 \text{ mL/min}$), moderate ($30 \text{ mL/min} \leq CrCl < 60 \text{ mL/min}$), and severe ($CrCl < 30 \text{ mL/min}$) renal impairment, respectively, relative to subjects with normal renal function. Peak palbociclib exposure (C_{max}) increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis [see *Clinical Pharmacology (12.3)*].

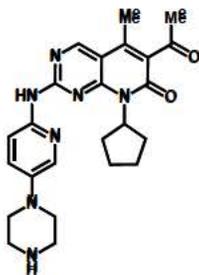
10 OVERDOSAGE

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; the printing ink contains shellac, titanium dioxide, ammonium hydroxide, propylene glycol, and simethicone.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of palbociclib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with breast cancer. Palbociclib had no large effect on QTc (i.e., >20 ms) at 125 mg once daily for 21 consecutive days followed by 7 days off treatment 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 maximum observed concentration (C_{\max}) of palbociclib is generally observed between 6 to 12 hours (time to reach maximum concentration, T_{\max}) following oral administration. The mean absolute bioavailability of IBRANCE after an oral 125 mg dose is 46%. In the dosing range of 25 mg to 225 mg, the AUC and C_{\max} increased proportionally with dose in general. Steady state was achieved within 8 days following repeated once daily dosing. With repeated once daily administration, palbociclib accumulated with a median accumulation ratio of 2.4 (range 1.5 to 4.2).

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

Distribution

Binding of palbociclib to human plasma proteins in vitro was approximately 85%, with no concentration dependence over the concentration range of 500 ng/mL to 5000 ng/mL. The mean fraction unbound (f_u) of palbociclib in human plasma in vivo increased incrementally with worsening hepatic function. There was no obvious trend in the mean palbociclib f_u in human plasma in vivo with worsening renal function. The geometric mean apparent volume of distribution (V_z/F) was 2583 L with a coefficient of variation (CV) of 26%.

Metabolism

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

Elimination

The geometric mean apparent oral clearance (CL/F) of palbociclib was 63.1 L/hr (29% CV), and the mean (\pm standard deviation) plasma elimination half-life was 29 (± 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.

Hepatic Impairment

Data from a pharmacokinetic trial in subjects with varying degrees of hepatic impairment indicate that palbociclib unbound AUC_{INF} decreased 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Palbociclib unbound C_{max} increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function. In addition, based on a population pharmacokinetic analysis that included 183 patients, where 40 patients had mild hepatic impairment based on National Cancer Institute (NCI) classification (total bilirubin \leq ULN and AST $>$ ULN, or total bilirubin >1.0 to $1.5 \times$ ULN and any AST), mild hepatic impairment had no effect on the exposure of palbociclib, further supporting the findings from the dedicated hepatic impairment study.

Renal Impairment

Data from a pharmacokinetic trial in subjects with varying degrees of renal impairment indicate that palbociclib AUC_{INF} increased by 39%, 42%, and 31% with mild ($60 \text{ mL/min} \leq \text{CrCl} < 90 \text{ mL/min}$), moderate ($30 \text{ mL/min} \leq \text{CrCl} < 60 \text{ mL/min}$), and severe ($\text{CrCl} < 30 \text{ mL/min}$) renal impairment, respectively, relative to subjects with normal renal function. Peak palbociclib exposure (C_{max}) increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. In addition, based on a population pharmacokinetic analysis that included 183 patients where 73 patients had mild renal impairment and 29 patients had moderate renal impairment, mild and moderate renal impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis.

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 to administration of midazolam alone [see *Drug Interactions (7.3)*].

Gastric pH Elevating Medications: In a drug interaction trial in healthy subjects, coadministration of a single 125 mg dose of IBRANCE with multiple doses of the proton pump inhibitor (PPI) rabeprazole under fed conditions decreased palbociclib C_{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.

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

Effect of Palbociclib on Transporters: In vitro evaluations indicated that palbociclib has a low potential to inhibit the activities of drug transporters organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, and organic anion transporting polypeptide (OATP)1B1, OATP1B3 at clinically relevant concentrations. In vitro, palbociclib has the potential to inhibit OCT1 at clinically relevant concentrations, as well as the potential to inhibit P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) in the gastrointestinal tract at the proposed dose.

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

Palbociclib was assessed for carcinogenicity in a 6-month transgenic mouse study and in a 2-year rat study. Oral administration of palbociclib for 2 years resulted in an increased incidence of microglial cell tumors in the central nervous system of male rats at a dose of 30 mg/kg/day (approximately 8 times the human clinical exposure based on AUC). There were no neoplastic findings in female rats at doses up to 200 mg/kg/day (approximately 5 times the human clinical exposure based on AUC). Oral administration of palbociclib to male and female rasH2 transgenic mice for 6 months did not result in increased incidence of neoplasms at doses up to 60 mg/kg/day.

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, 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 in association with lower sperm motility and density at 100 mg/kg/day with projected exposure levels [AUC] of 20 times the exposure in humans at the recommended dose.

14 CLINICAL STUDIES

Study 1: IBRANCE plus Letrozole

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

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

progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST).

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

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

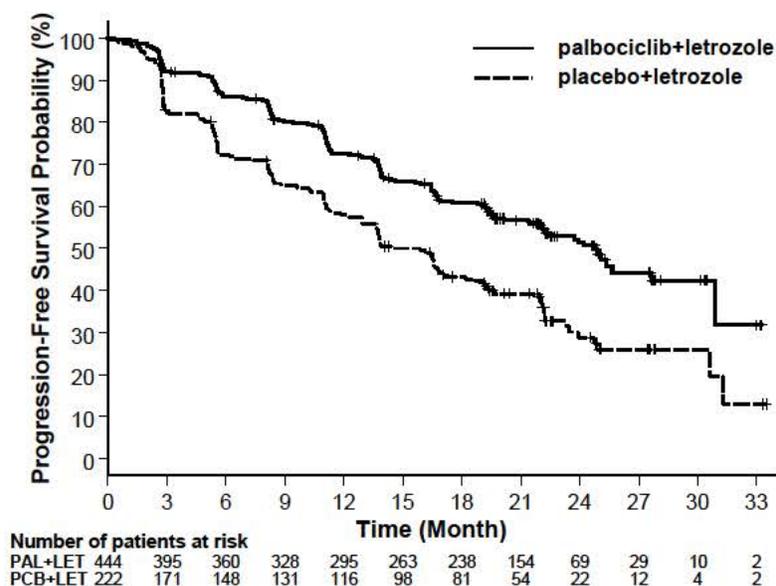
Table 8. Efficacy Results – Study 1 (Investigator Assessment, Intent-to-Treat Population)

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

*Response based on confirmed responses.

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

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



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

Study 2: IBRANCE plus Fulvestrant

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

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

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

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

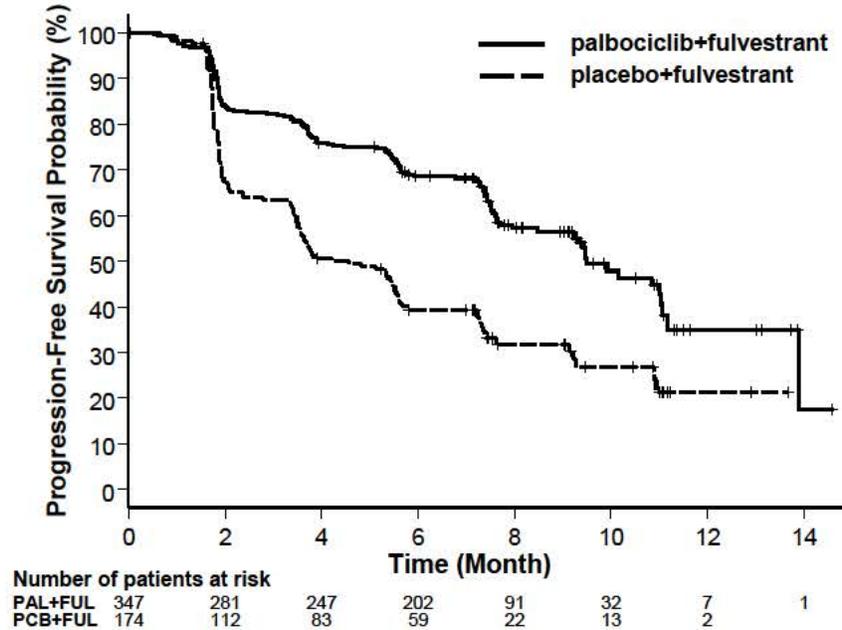
Table 9. Efficacy Results – Study 2 (Investigator Assessment, Intent-to-Treat Population)

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

* Response based on confirmed responses.

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

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



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 °C to 25 °C (68 °F to 77 °F); excursions permitted between 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Myelosuppression/Infection

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

Drug Interactions

- Grapefruit may interact with IBRANCE. Patients should not consume grapefruit products while on treatment with IBRANCE.
- Inform patients to avoid strong CYP3A inhibitors and strong CYP3A inducers.
- Advise patients to inform their healthcare 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.
- Pre/perimenopausal women treated with IBRANCE should also be treated with LHRH agonists [see Dosage and Administration (2.1)].

Pregnancy, Lactation, and Infertility

- Embryo-Fetal Toxicity
 - Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with IBRANCE therapy and for at least 3 weeks after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.2) and Use in Specific Populations (8.1 and 8.3)*].
 - Advise male patients with female partners of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 months after the last dose [*see Use in Specific Populations (8.3)*].
- Lactation: Advise women not to breastfeed during treatment with IBRANCE and for 3 weeks after the last dose [*see Use in Specific Populations (8.2)*].
- Infertility: Inform males of reproductive potential that IBRANCE may cause infertility and to consider sperm preservation before taking IBRANCE [*see Use in Specific Populations (8.3)*].

This product's label may have been updated. For full prescribing information, please visit www.IBRANCE.com.



LAB-0723-6.3

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

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

IBRANCE may cause serious side effects, including:

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

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

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

What is IBRANCE?

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

- an aromatase inhibitor as the first hormonal based therapy in postmenopausal women or in men, **or**
- fulvestrant 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 should use effective birth control during treatment and for at least 3 weeks after the last dose of IBRANCE.
 - **Males** with female partners who can become pregnant should use effective birth control during treatment with IBRANCE for at least 3 months after the last 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. Do not breastfeed during treatment with IBRANCE and for 3 weeks after the last dose.

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.
- IBRANCE should be taken at about the same time each day.
- Swallow IBRANCE capsules whole. Do not chew, crush or open IBRANCE capsules before swallowing them.
- Do not take any IBRANCE capsules that are broken, cracked, or that look damaged.
- Avoid grapefruit and grapefruit products during treatment with IBRANCE. Grapefruit may increase the amount of IBRANCE in your blood.
- Do not change your dose or stop taking IBRANCE unless your healthcare provider tells you.

- If you miss a dose of IBRANCE or vomit after taking a dose of IBRANCE, do not take another dose on that day. Take your next dose at your regular time.
- If you take too much IBRANCE, call your healthcare provider right away or go to the nearest hospital emergency room.

What are the possible side effects of IBRANCE?

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

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

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

IBRANCE may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider about family planning options before starting IBRANCE 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.

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.

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.

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

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



LAB-0724-3.4

For more information, go to www.IBRANCE.com or call 1-800-438-1985.

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

Revised: April 2019

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207103Orig1s008

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	207103-S-008
Priority or Standard	Standard
Submit Date(s)	June 15, 2018
Received Date(s)	June 15, 2018
PDUFA Goal Date	April 15, 2019
Division/Office	DOP1
Review Completion Date	<i>Electronic Stamp Date</i>
Established Name	Palbociclib
(Proposed) Trade Name	IBRANCE®
Pharmacologic Class	Cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor
Code name	N/A
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	<i>Regular Approval</i>
Recommended Indication(s)/Population(s) (if applicable)	<p>IBRANCE is indicated for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with:</p> <ul style="list-style-type: none"> • an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men; or • fulvestrant in patients with disease progression following endocrine therapy.

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation	7
Additional Reviewers of Application.....	7
Glossary.....	8
1 Executive Summary	10
1.1. Product Introduction.....	10
1.2. Conclusions on the Substantial Evidence of Effectiveness	11
1.3. Benefit-Risk Assessment	12
1.4. Patient Experience Data.....	15
2 Therapeutic Context	17
2.1. Analysis of Condition.....	17
2.2. Analysis of Current Treatment Options	17
3 Regulatory Background	21
3.1. U.S. Regulatory Actions and Marketing History.....	21
3.2. Summary of Presubmission/Submission Regulatory Activity	21
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	23
4.1. Office of Scientific Investigations (OSI)	23
4.2. Product Quality	23
4.3. Clinical Microbiology	23
4.4. Devices and Companion Diagnostic Issues	23
5 Nonclinical Pharmacology/Toxicology.....	24
5.1. Executive Summary	24
5.2. Referenced NDAs, BLAs, DMFs.....	24
5.3. Pharmacology.....	24
5.4. ADME/PK	24
5.5. Toxicology.....	24
5.5.1. General Toxicology.....	24
5.5.2. Genetic Toxicology.....	24
5.5.3. Carcinogenicity.....	25

5.5.4. Reproductive and Developmental Toxicology	29
5.5.5. Other Toxicology Studies	29
6 Clinical Pharmacology.....	30
7 Sources of Clinical Data and Review Strategy	31
7.1. Table of Clinical Studies.....	31
7.2. Review Strategy.....	34
8 Statistical and Clinical and Evaluation	35
8.1. Review of Relevant Individual Trials Used to Support Efficacy.....	35
8.1.1. Study 1008 (PALOMA-2)	35
8.1.2. Study Results.....	39
8.1.3. Real -World Data Analysis – Flatiron Health.....	45
8.1.4. Study Design.....	45
8.1.5. Study Results.....	51
8.2. Study A5481097 (IQVIA).....	60
8.2.1. Study Design.....	60
8.2.2. Assessment of Efficacy Across Trials.....	67
8.2.3. Integrated Assessment of Effectiveness.....	68
8.3. Review of Safety.....	68
8.3.1. Safety Review Approach	69
8.3.2. Review of the Safety Database	69
8.3.3. Adequacy of Applicant’s Clinical Safety Assessments	69
8.3.4. Safety Results.....	70
8.3.5. Analysis of Submission-Specific Safety Issues.....	72
8.3.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability.....	72
8.3.7. Safety Analyses by Demographic Subgroups.....	73
8.3.8. Specific Safety Studies/Clinical Trials.....	73
8.3.9. Additional Safety Explorations.....	73
8.3.10. Safety in the Postmarket Setting.....	73
8.3.11. Integrated Assessment of Safety.....	75
SUMMARY AND CONCLUSIONS	75
8.4. Statistical Issues	75

Multi-disciplinary Review and Evaluation
sNDA 207103/008 IBRANCE® (Palbociclib)

8.5.	Conclusions and Recommendations	75
9	Advisory Committee Meeting and Other External Consultations.....	77
10	Pediatrics	78
11	Labeling Recommendations	78
11.1.	Prescription Drug Labeling	78
11.2.	Patient Labeling	81
12	Risk Evaluation and Mitigation Strategies (REMS)	81
13	Postmarketing Requirements and Commitment	82
14	Division Director (OB)	83
15	Division Director (Clinical) (or designated signatory authority)	84
16	Appendices	85
16.1.	References	85
16.2.	Financial Disclosure	85
16.3.	Nonclinical Pharmacology/Toxicology.....	86
16.4.	OCP Appendices (Technical documents supporting OCP recommendations)	88

Table of Tables

Table 1: Available Endocrine (or Endocrine Combination) Therapies for Patients with HR-positive/HER2-negative Locally Advanced or Metastatic Breast Cancer	18
Table 2: OSI Findings.....	23
Table 3: Listing of Clinical Trials Relevant to this sNDA	32
Table 4: Study PALOMA-2 Patient Disposition	40
Table 5: Demographic Characteristics for Study PALOMA-2.....	40
Table 6: Baseline Disease Characteristics for Study PALOMA-2.....	41
Table 7: Primary Endpoint Results, Updated (Progression Free Survival Study PALOMA-2)	43
Table 8: Primary Endpoint Results, Original Approval (Progression Free Survival Study PALOMA-2)	43
Table 9: Demographic Characteristics (Real -World Data Analysis – Flatiron Health)	52
Table 10: Baseline Disease Characteristics (Real -World Data Analysis – Flatiron Health)	53
Table 11: Demographic Characteristics of Analysis Cohorts A, B (Real -World Data Analysis – Flatiron Health)	54
Table 12: Baseline Disease Characteristics of Analysis Cohorts A, B (Real -World Data Analysis – Flatiron Health)	55
Table 13: FDA Analysis of Real-World Response Rate (Real -World Data Analysis – Flatiron Health).....	55
Table 14: Study 1097 Patient Demographics.....	65
Table 15: Study 1097 Duration of Prescription Order	66

Table of Figures

Figure 1: Primary Endpoint Results (Progression Free Survival Study PALOMA-2)..... 44
Figure 2: Cohort Selection and Attrition..... 48
Figure 3: Analysis Cohort A Duration of real-world Response 57
Figure 4: Analysis Cohort B Duration of real-world Response..... 59
Figure 5: IQVIA Line Advancement Determination 63
Figure 6: Study 1097 First-Line Prescription Order Duration 66

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OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
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
DHOT	Division of Hematology Oncology Toxicology
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
GPP	Good Pharmacoepidemiology Practices
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
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

Multi-disciplinary Review and Evaluation
sNDA 207103/008 IBRANCE® (Palbociclib)

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
PhRMA	Pharmaceutical Research and Manufacturers Association
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

IBRANCE® (palbociclib) Capsules, an inhibitor of cyclin-dependent kinases (CDK) 4 and 6, was approved on February 3, 2015, under the provisions of accelerated approval regulations (21 CFR 314.500). The initial approval was for use in combination with letrozole for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy in postmenopausal women. Regular approval was granted on February 19, 2016, for palbociclib in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. On March 31, 2017, regular approval for palbociclib as initial endocrine-based therapy was granted and the indication was expanded from allowing palbociclib in combination with only letrozole to allowing it in combination with any aromatase inhibitor.

The proposed indication for palbociclib is:



The recommended indication for palbociclib is:

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

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

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

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

This approval is based upon FDA’s previous finding of the effectiveness of palbociclib in combination with an aromatase inhibitor as an initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, and of palbociclib in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease has progressed following endocrine therapy. The applicant provided updated results from the randomized, double-blind, placebo-controlled phase 3 trial (Study PALOMA-2) in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease was not previously treated. The results of this trial continue to demonstrate that treatment with palbociclib in combination with letrozole results in clinically meaningful benefit characterized by a median PFS in the palbociclib plus letrozole arm of 27.6 months (95% CI = 22.4, 30.3) compared to 14.5 months (95% CI: 12.3, 17.1) in the placebo plus letrozole arm (HR = 0.563 95% CI: 0.461, 0.687; $p < 0.001$).

Male patients with breast cancer were ineligible in studies that provided the data to demonstrate the clinical benefit to support prior approvals of palbociclib (IBRANCE®). According to the current clinical practice standards, in the absence of safety and efficacy data from adequate and well-controlled studies, male patients with breast cancer are treated similarly to women with breast cancer. In this submission, the applicant provided the results of an analysis of real-world data (RWD) from electronic health records (EHRs) as additional supportive data to characterize the use of palbociclib in combination with endocrine therapy (aromatase inhibitor or fulvestrant) in male patients with breast cancer based on observed tumor responses in this rare subset of patients with breast cancer.

1.3. **Benefit-Risk Assessment**

Breast cancer is the second leading cause of cancer death among women and the fourth leading cause of cancer death overall. In 2019, it is estimated that there will be 271,270 newly diagnosed breast cancer cases in the United States, and that 42,260 people will die from breast cancer. Breast cancer is rare in males, with only 2670 cases of male breast cancer estimated in 2019. The majority of breast tumors in male patients express hormone receptors. Men are more likely to be diagnosed at an older age, with a more advanced stage of disease, and are more likely to have lymph node involvement. The prognosis for men with breast cancer is similar to that for women with comparable stage of disease.

Metastatic breast cancer (MBC) is incurable. Thus, the treatment of patients with MBC is palliative in nature. Endocrine therapy is preferable to chemotherapy for patients with hormone receptor (HR)-positive metastatic breast cancer (MBC), provided there is no visceral crisis. Other treatment options for patients with HR-positive MBC include endocrine therapy in combination with CDK 4/6 inhibitors. Most patients with HR-positive MBC will eventually require cytotoxic chemotherapy either as initial treatment or following endocrine therapy (ies). FDA-approved endocrine therapies available for HR-positive MBC include tamoxifen, anastrozole, letrozole, toremifene, exemestane, and fulvestrant. In addition, everolimus has been approved in combination with exemestane, palbociclib has been approved in combination with letrozole or fulvestrant, abemaciclib has been approved in combination with fulvestrant and ribociclib has been approved in combination with letrozole.

Tamoxifen and single agent abemaciclib are approved for all patients (males and females). All other hormonal and targeted agents for HR-positive MBC are currently approved only for females; although, they are often prescribed for male patients. According to current clinical practice standards, in the absence of safety and efficacy data from adequate and well-controlled studies, male patients with breast cancer are treated similarly to women with breast cancer.

The applicant submitted a supplemental new drug application (sNDA) application to expand the proposed indication of palbociclib (b) (4) with HR-positive, HER2-negative advanced or metastatic breast cancer. Palbociclib (IBRANCE®) is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Palbociclib was originally granted accelerated approval on February 3, 2015, for use in combination with letrozole for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy in postmenopausal women. Regular approval was granted in February 19, 2016, for palbociclib in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. On March 31, 2017, regular approval for palbociclib as initial endocrine-based therapy was granted and the indication was expanded from allowing

palbociclib in combination with only letrozole to allowing it in combination with any aromatase inhibitor. None of the studies leading to these approvals included male patients in the inclusion criteria and therefore did not enroll male patients on to study. Although the mechanism of action for palbociclib alone is not expected to be different in males compared to females, data for the combination of palbociclib plus endocrine therapy (aromatase inhibitors or fulvestrant) was necessary prior to expanding the indication to male patients as it was not clear whether manipulation of the hormonal axis would affect results in male patients.

The basis for this recommendation is a favorable benefit-risk profile for palbociclib when added to aromatase inhibitors or fulvestrant in male patients with HR-positive, HER2- negative advanced or metastatic breast cancer as supported by the known efficacy in female patients and supportive real-world data (RWD) along with safety information from review of two phase 1 studies, the Pfizer global database and postmarketing reports. Updated results from the randomized, double-blind, placebo-controlled phase 3 trial (Study PALOMA-2) in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease was not previously treated were submitted with this sNDA and continue to demonstrate a clinically meaningful benefit with the addition of palbociclib to letrozole therapy. The estimated median PFS in the palbociclib plus letrozole arm was 27.6 months (95% CI = 22.4, 30.3) compared to 14.5 months (95% CI: 12.3, 17.1) in the placebo plus letrozole arm (HR = 0.563 95% CI: 0.461, 0.687; p<0.001). RWE from the Flatiron Health Study reviewing electronic health records (EHRs) provide additional support for the use of palbociclib in combination with endocrine therapy (aromatase inhibitor or fulvestrant) in male patients with breast cancer based on observed tumor responses.

Review of two phase 1 studies with single agent palbociclib, the Pfizer global database and postmarketing reports revealed no new safety signals in male breast cancer patients and in general, the adverse event (AE) profile for male patients appears to be consistent with the known AE profile of palbociclib. The known safety profile for palbociclib is acceptable for this patient population with a serious and life-threatening disease.

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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
-----------	----------------------------	-------------------------

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<ul style="list-style-type: none"> • In 2019, it is estimated that there will be 271,270 newly diagnosed breast cancer cases in the United States, and that 42,260 people will die from breast cancer. • Breast cancer is rare in males, with only 2670 cases of male breast cancer estimated in 2019. It is estimated that 500 men will die from breast cancer. 	<ul style="list-style-type: none"> • Metastatic breast cancer is incurable. • Male breast cancer is a serious and life-threatening condition. • There is an unmet medical need to develop therapies for patients with HR-positive, HER2-negative advanced or metastatic breast cancer, including in rare demographic subgroups such as males with this disease.
<p>Current Treatment Options</p>	<ul style="list-style-type: none"> • The treatment of patients with MBC is intended to be palliative, prolong survival, and/or improve disease-related symptoms. • In patients with hormone receptor (HR)-positive metastatic breast cancer (MBC), treatment with endocrine therapy (ET) is preferable to chemotherapy; tamoxifen, toremifene, exemestane fulvestrant, letrozole, anastrozole, letrozole are FDA-approved for treatment of HR+ MBC. Other treatment options for these patients include endocrine therapy in combination with mTOR inhibitors (everolimus) or CDK 4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib. • Patients with HR-positive MBC may require cytotoxic chemotherapy either as initial treatment or following treatment with endocrine therapy. • There are no therapies approved specifically for the treatment of male patients with MBC. Tamoxifen and single agent abemaciclib are approved for all patients (males and females). All other hormonal and targeted agents for HR-positive MBC are currently approved only for females. Some cytotoxic agents for the treatment of MBC are approved for use in both females and males. According 	<ul style="list-style-type: none"> • Endocrine therapy represents the main initial therapeutic strategy for patients with HR-positive, HER2-negative MBC. • Although current clinical practice standards for the treatment of male patients with breast cancer mirror those for women with breast cancer, the indications for most FDA approved therapies for the treatment of BC do not include males.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>to current clinical practice standards, male patients with breast cancer are treated similarly to premenopausal women and recommend the concomitant use of AIs with an LHRH agonist or orchiectomy for the treatment of breast cancer in men.</p>	
<p>Benefit</p>	<ul style="list-style-type: none"> Based upon results from Study PALOMA-2 in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease was not previously treated, the estimated median PFS in the palbociclib plus letrozole arm was 27.6 months (95% CI = 22.4, 30.3) compared to 14.5 months (95% CI: 12.3, 17.1) in the placebo plus letrozole arm (HR = 0.563 95% CI: 0.461, 0.687; p< 0.001). Based upon the results of the Flatiron Health Study, male patients with breast cancer who received palbociclib in combination with endocrine therapy (aromatase inhibitors or fulvestrant) tolerated this therapy and experienced tumor responses. 	<ul style="list-style-type: none"> Treatment with palbociclib plus letrozole demonstrates a statistically significant and clinically meaningful improvement in PFS. Updated results based upon additional follow-up in the PALOMA-2 trial show persistent benefit of treatment with palbociclib plus letrozole therapy. Electronic health record data provide supportive evidence of the use and activity of palbociclib in male patients with breast cancers.
<p>Risk and Risk Management</p>	<ul style="list-style-type: none"> Limited data were provided for support a comprehensive evaluation of safety in male patients with breast cancer. However, no new safety signals have been identified in this population based upon review of postmarketing reports, the review of cases in Pfizer global safety database and in two phase 1 studies with palbociclib monotherapy which enrolled male patients with solid tumor malignancies and mantle cell lymphoma. 	<ul style="list-style-type: none"> The safety profile of palbociclib is acceptable for the intended population, and manageable with current labeling and routine oncology care. No new safety signals have been identified in male patients receiving palbociclib.

1.4. Patient Experience Data

Multi-disciplinary Review and Evaluation
 sNDA 207103/008 IBRANCE® (Palbociclib)

Patient Experience Data Relevant to this Application (check all that apply): **Not applicable for this sNDA**

<input type="checkbox"/>	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
<input type="checkbox"/>	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
<input type="checkbox"/>	<input type="checkbox"/> Patient reported outcome (PRO)	
<input type="checkbox"/>	<input type="checkbox"/> Observer reported outcome (ObsRO)	
<input type="checkbox"/>	<input type="checkbox"/> Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	<input type="checkbox"/> Performance outcome (PerFO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that was not submitted in the application, but was considered in this review.	

‘Lola Fashoyin-Aje, MD, MPH

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Breast cancer is the second leading cause of cancer death among women and the fourth leading cause of cancer death overall. In 2019, it is estimated that there will be 271,270 newly diagnosed breast cancer cases in the United States, and that 42,260 people will die from breast cancer. Breast cancer is rare in males, with only 2670 cases of male breast cancer estimated in 2019. The majority of breast tumors in male patients express hormone receptors. Men are more likely to be diagnosed at an older age, with a more advanced stage of disease, and are more likely to have lymph node involvement. The prognosis for men with breast cancer is similar to that for women with comparable stage of disease.

Metastatic breast cancer (MBC) is incurable. Thus, the treatment of patients with MBC is palliative in nature. Endocrine therapy is preferable to chemotherapy for patients with hormone receptor (HR)-positive metastatic breast cancer (MBC), provided there is no visceral crisis. Other treatment options for patients with HR-positive MBC include endocrine therapy in combination with CDK 4/6 inhibitors. Most patients with HR-positive MBC will eventually require cytotoxic chemotherapy either as initial treatment or following endocrine therapy (ies). FDA-approved endocrine therapies available for HR-positive MBC include tamoxifen, anastrozole, letrozole, toremifene, exemestane, and fulvestrant. In addition, everolimus has been approved in combination with exemestane, palbociclib has been approved in combination with letrozole or fulvestrant, abemaciclib has been approved in combination with fulvestrant and ribociclib has been approved in combination with letrozole.

Tamoxifen and single agent abemaciclib are approved for all patients (males and females). All other hormonal and targeted agents for HR-positive MBC are currently approved only for females; although, they are often prescribed for male patients. Some cytotoxic agents for the treatment of MBC are approved for use in both females and males. According to current clinical practice standards, male patients with breast cancer are treated similarly to premenopausal women and recommend the concomitant use of AIs with an LHRH agonist or orchiectomy for the treatment of breast cancer in men.

2.2. Analysis of Current Treatment Options

Listed in Table 1 are FDA-approved endocrine (or endocrine combination) treatment options for patients with HR-positive, HER2-negative MBC. Male patients are included as part of the indication for tamoxifen and single agent abemaciclib.

Table 1: Available Endocrine (or Endocrine Combination) Therapies for Patients with HR-positive/HER2-negative Locally Advanced or Metastatic Breast Cancer

Product (s) Name/ Approval Year(s)	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Drug Class
Palbociclib 2014, 2015, 2016	For the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with: an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women; or fulvestrant in women with disease progression following endocrine therapy.	25 mg once daily for 21 days followed by 7 days off treatment	Palbociclib+letrozole vs. letrozole alone: Median PFS: 24.8 mos vs. 14.5 mos ORR: 55.3% vs. 44.4% Palbociclib+fulvestrant vs. fulvestrant: Median PFS: 9.5 mos vs. 4.6 mos ORR: 24.6% vs. 10.9%	Myelosuppression, fatigue	CDK 4/6 inhibitor
Abemaciclib 2017, 2018	In combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy OR as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior	in combination with fulvestrant: 150 mg orally twice daily as monotherapy: 200 mg orally twice daily	Abemaciclib+fulvestrant vs. fulvestrant: Median PFS: 16.4 vs. 9.3 mos ORR: 48.1% vs. 21.3% Monotherapy single arm study: ORR: 17.4% by independent review and 19.7% by investigator assessment Abemaciclib+anastrozole or letrozole vs.	Diarrhea, myelosuppression, hepatotoxicity, venous thromboembolism	CDK 4/6 inhibitor

Multi-disciplinary Review and Evaluation
sNDA 207103/008 IBRANCE® (Palbociclib)

	chemotherapy in the metastatic setting OR in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer		placebo+anastrozole or letrozole: Median PFS: 28.2 vs. 14.8 mos ORR: 55.4% vs. 40.2%		
Ribociclib 2017	In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer	600mg daily by mouth, 21 days on/7 days off	Ribociclib+letrozole vs. placebo+letrozole PFS: NR vs. 14.7 months, HR 0.556 (95% CI: 0.429, 0.720; p<0.0001)	Myelosuppression, abnormal liver function tests, vomiting, QT prolongation	CDK 4/6 inhibitor
Letrozole 1997	First and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer	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
Anastrozole 1995	First-line treatment of postmenopausal women with HR-positive or unknown locally advanced or metastatic breast cancer	1mg daily by mouth	Vs. tamoxifen TTP: 11.1 vs. 5.6 months (p=0.006) and 8.2 vs. 8.3 months (p=0.92)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor
Tamoxifen 1977	In the treatment of metastatic breast cancer in women and men. Patients whose tumors are estrogen receptor positive are more likely to benefit.	20mg daily by mouth	Response rate in 14 phase 2 studies and nine literature reports. The overall database included 1164 patients.	Uterine malignancies, stroke, pulmonary embolism and hot flashes	Selective estrogen receptor modulator
Exemestane 1999	Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy	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

Multi-disciplinary Review and Evaluation
sNDA 207103/008 IBRANCE® (Palbociclib)

Fulvestrant 2002	Indicated for the treatment of: HR-positive, HER2-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.	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	Selective estrogen receptor degrader
2010	OR HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.	500mg on days 1, 15, 29 and once monthly thereafter intramuscularly	vs. fulvestrant 250mg		
Everolimus 2012	Postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole	10 mg orally once daily	Combination vs placebo+exemestane: Median PFS: 7.8 mos vs. 3.2 mos ORR: 12.6% vs. 1.7%	Pneumonitis, infections, stomatitis, angioedema	mTOR inhibitor

CDK=cyclin dependent kinase; mTOR=mammalian target of rapamycin

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Palbociclib was originally granted accelerated approval by the US FDA on February 3, 2015, for use in combination with letrozole for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy in postmenopausal women. Regular approval was granted in February 19, 2016, for palbociclib in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. On March 31, 2017, regular approval for palbociclib as initial endocrine-based therapy was granted and the indication was expanded to allow its use in combination with any aromatase inhibitor.

As of March 2018, palbociclib has been approved in 79 countries and is marketed in 51 countries worldwide.

3.2. Summary of Presubmission/Submission Regulatory Activity

Oct 4, 2016: Type C meeting to discuss the inclusion of real-world experience data with palbociclib in several proposals outlined by the Sponsor.

- *The Agency provided the following comments:*
 - *Provide a separate protocol for each proposal along with the regulatory intent*
 - *Fully outline analyses in a statistical analysis plan for each proposal*
 - *Provide detailed descriptions of algorithms of patient capture (ensure that patients are not double counted)*

Integrity of the data should be described in protocol (i.e., how data entered at point of care and transmitted to the respective database)

Multi-disciplinary Review and Evaluation
sNDA 207103/008 IBRANCE® (Palbociclib)

(b) (4)

Jan 23, 2018 – Type B pre-sNDA meeting to discuss preliminary real-world data with palbociclib in male breast cancer (b) (4)

- *The agency stated that the real-world data should be submitted in a format to support evidence of activity*
- (b) (4)

Jun 15, 2018: sNDA 207103/008 was submitted to FDA.

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) was consulted to perform site inspections as part of review of this sNDA. Reference is made to the Clinical Inspection Summary by Lauren Iacono-Connors, Ph.D. The preliminary classification given to the three sites inspected are given in Table 2.

Table 2: OSI Findings

Inspection	# of Subjects	Inspection Date	Final Classification
Flatiron Health, Inc. 200 Fifth Avenue, 8th Floor New York, NY 10010 United States Parent protocol (#15-159) and substudy #19	25 patients in palbociclib cohort and 34 patients in non-palbociclib cohort	November 5-8, 2018	NAI
IQVIA, Inc. 4820 Emperor Blvd. Durham, NC 27703 United States Protocol A5481097	147 patients in palbociclib cohort and 992 patients in non-palbociclib cohort (retrospective study)	November 6-8, 2018	NAI
Pfizer, Inc Location of master files	NA	October 2-5, 2018	NAI

NA=Not applicable; NAI=No deviation from regulations.

Reviewer Comment: According to the OSI review, no study deviations or discrepancies were noted in the clinical inspection of the three sites listed above.

4.2. Product Quality

Not applicable to this sNDA.

4.3. Clinical Microbiology

Not applicable to this sNDA.

4.4. Devices and Companion Diagnostic Issues

Not applicable to this sNDA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

In this sNDA submission, the Applicant submitted the final study reports for a 6-month carcinogenicity study in Tg.rasH2 mice and a 2-year carcinogenicity study in rats to support the proposed labeling changes in section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) of the PI for Ibrance. The 6-month carcinogenicity study did not show any drug-related neoplasms in palbociclib-treated groups in male or female mice at doses up to 60 mg/kg. The 2-year carcinogenicity study showed a statistically significant increased incidence of microglial cell tumors in brain combined with spinal cord in males at the high dose (30 mg/kg/day) when compared with the vehicle control group. There was a statistically significant dose-response relationship in male rats in the incidence of microglial cell tumors in brain and brain combined with spinal cord. The AUC at 30 mg/kg in male rats was 8.0x the exposure at the clinical recommended dose of 125 mg/day. There were no neoplastic findings in female rats at doses up to 200 mg/kg/day (high dose), 4.8x the exposure at the recommended clinical dose of 125 mg/day based on AUC. In summary, the data provided in this sNDA submission support the proposed labeling changes. This efficacy sNDA for Ibrance is recommended for approval from the perspective of the Pharmacology/Toxicology discipline. For final agreed upon changes to the Ibrance label, refer to the approved package insert.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Not conducted or required to support the labeling changes in this sNDA submission.

5.4. ADME/PK

Not conducted or required to support the labeling changes in this sNDA submission.

5.5. Toxicology

5.5.1. General Toxicology

Not conducted or required to support the labeling changes in this sNDA submission.

5.5.2. Genetic Toxicology

Not conducted or required to support the labeling changes in this sNDA submission.

5.5.3. Carcinogenicity

Study title/ number: A 6-Month Oral Carcinogenicity Study of PD-0332991 in CByB6F1/Tg rasH2 Hemizygous Mice/ Study 20066483

Key Study Findings

Non- Neoplastic Findings

No treatment-related mortalities or severe adverse effects were observed in mice administered PD-0332991 at doses up to 60 mg/kg.

Neoplastic Finding

Oral daily administration of PD-0332991 at doses up to 60 mg/kg/day was not carcinogenic in CByB6F1/Tg rasH2 hemizygous mice. NOAEL was 60 mg/kg (HD) in mice, corresponding with a male and female combined C_{max} of 1840 ng/mL and an AUC_{24} of 20500 ng·h/mL in Week 26.

Multi-disciplinary Review and Evaluation
sNDA 207103/008 IBRANCE® (Palbociclib)

Conducting laboratory and location



GLP compliance:

Yes

Doses: 0 (vehicle), 6, 20, or 60 mg/kg/day

Frequency of dosing: Daily, 28 days/cycle

Dose volume: 10 mL/kg

Route of administration: oral gavage

Formulation/Vehicle: 0.5% (w/v) methylcellulose 4000 cps in reverse osmosis deionized (RODI) water

Basis of dose selection: The high dose was based on decreased white blood cell counts and lower spleen, thymus and testis weights at 100 mg/kg/day in the GLP 1-month study in non-transgenic littermates of CByB6F1/Tg rasH2 mice. The dose spacing for mid and low doses was based on the AUC values

Species/Strain: CByB6F1-Tg(HRAS)2Jic Hemizygous mice

Number/Sex/Group: 25/sex/group

Age: 10 weeks old

Animal housing: Individual

Dual control employed: No

Interim sacrifice: No

Satellite groups: TK, 18/sex/group for LD, MD, HD, 9/sex for control
Positive control (N-nitrosomethylurea, NMU), 15/sex

Deviation from study protocol: None

ECAC protocol concurrence: Yes (ECAC minutes dated January 3, 2019)

Study title/ number: A 2-year Carcinogenicity Study of PD-0332991 by Oral Gavage in Rats/
Study 20066483

Key Study Findings

Non- Neoplastic Findings

- There was no PD-0332991-related mortality compared with control.
- PD-0332991-related mean lower body weight gain beginning approximately Week 6 was observed in males administered ≥ 3 mg/kg/day and females administered 200 mg/kg/day.
- Treatment-related toxicities involved the eyes (degeneration in lens), pancreas (decreased Islet cells), spleen and bone marrow (increased hematopoiesis), kidney

(tubular vacuolar changes and chronic progressive nephropathy), and adrenal glands (atrophy and vacuolar degeneration).

Neoplastic Finding

- The higher incidence of microglial cell tumors in brain combined with spinal cord was statistically significant in males at the high dose (30 mg/kg/day) when compared with the vehicle control group (p-value of 0.0273 for pairwise comparison).
- Dose response relationships were statistically significant in male rats for the incidence of microglial cell tumors in brain and brain combined with spinal cord (p-value = 0.0110, and 0.0039, respectively).
- The no-observed-adverse-effect level (NOAEL) for neoplastic findings in males and females was 10 mg/kg/day and 200 mg/kg/day (HD), respectively.
- The NOAEL for neoplastic findings in males at 10 mg/kg/day and females at 200 mg/kg/day corresponded with an overall PD-0332991 C_{max} of 546 ng/mL and 1240 ng/mL and an AUC_{0-24} of 5400 ng•h/mL and 8980 hr•ng/mL, respectively.

Maximum Clinical Exposure:

- The AUCs at NOAEL in male and female rats for neoplastic findings were about 3 and 5 folds of human exposure at the recommended dose, respectively. The calculation was based on the AUC of 1863 ng•h/mL in human at the recommended daily dose of 125 mg.

Multi-disciplinary Review and Evaluation
sNDA 207103/008 IBRANCE® (Palbociclib)

Conducting laboratory and location



GLP compliance:

Yes

Doses: Male: 0 (vehicle), 3, 10, or 30 mg/kg/day
Female: 0 (vehicle), 25, 75, or 200 mg/kg/day

Frequency of dosing: Daily x21, 28 days/cycle

Dose volume: 10 mL/kg

Route of administration: oral gavage

Formulation/Vehicle: 0.5% (w/v) methylcellulose 4000 cps in reverse osmosis deionized (RODI) water

Basis of dose selection: The basis for the dose selection is the maximum tolerated dose, based on the mortality, treatment-related toxicities, and on body weight decrement observed in the 13-week and 27-week studies

Species/Strain: Sprague Dawley Crl:CD(SD) rats

Number/Sex/Group: 70/sex/group

Age: 7 weeks old

Animal housing: Individual

Dual control employed: No

Interim sacrifice: The Group 1 females reached 20 animals due to age-related mortality as of Week 94, Day 652, and all remaining females within the study (Groups 1, 2, 3, and 4) were terminated as soon as practical beginning on Day 653 (Week 94 through Week 95). Similarly, Group 1 males reached 20 animals due to age-related mortality as of Week 98, Day 686, and all remaining males within the study were also terminated as soon as practical beginning on Day 687 (Week 99 through Week 100).

Satellite groups: TK, 5/sex/group for LD, MD, HD, 4/sex for control

Deviation from study protocol: None

ECAC protocol concurrence: Yes (ECAC minutes dated January 3, 2019)

Observations and Results Refer to section 19.3 (Nonclinical Pharmacology/Toxicology) in this review

5.5.4. **Reproductive and Developmental Toxicology**

Not conducted or required to support the labeling changes in this sNDA submission

5.5.5. **Other Toxicology Studies**

None

Wei Chen, PhD

Primary Reviewer

Tiffany K. Ricks, PhD

Team Leader

6 Clinical Pharmacology

No new clinical pharmacology data were included in this supplemental NDA. Refer to previous reviews of the palbociclib clinical pharmacology data and FDA's assessments.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 3: Listing of Clinical Trials Relevant to this sNDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Trials to Support Efficacy and Safety</i>								
PALOMA-2,	NCT01740427	Prospective, randomized, double blind phase 3 study	Palbociclib 125mg daily for 3 weeks on 1 week off with letrozole vs. placebo plus letrozole	Investigator assessed PFS	Median days on treatment: palbociclib-603, letrozole-618 vs letrozole-413, placebo-420	666	Women with newly diagnosed ER+, HER2-negative advanced breast cancer	186 centers in 17 countries
<i>Studies to Support Efficacy</i>								
Real-World Analysis of Males Treated for Metastatic Breast Cancer in the US (Flatiron Health)	NA	Detailed retrospective male patient information from electronic health records (EHRs)	NA	Real world treatment response	NA	25 with palbociclib therapy and 34 with endocrine therapy alone	Males with HR-positive, HER2-negative metastatic breast cancer	NA
<i>Trials to Support Safety</i>								
1001	Not provided	Open-label, dose-finding study	Palbociclib single agent on 3 weeks on/1 week off or 2 weeks	Not provided	Not provided	36 male patients (15 on 3weeks on/1	Patients with advanced cancer	Not provided

Multi-disciplinary Review and Evaluation
sNDA 207103/008 IBRANCE® (Palbociclib)

			on/1 week off schedule			week off)		
1002	Not provided	Open label phase 1 study to evaluate and compare biomarkers of CDK4/6 inhibition in tumor biopsies with changes in positron emission tomography (PET)	Not provided	Not provided	Not provided	14 male patients	Patients with mantle cell lymphoma	Not provided
Other Study								
A5481097 (Study 1097, "IQVIA")	NA	Retrospective analysis of claims data	NA	NA	NA		Male patients with metastatic breast cancer	NA

NA=Not applicable

7.2. Review Strategy

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

1. Literature review of breast cancer in males.
2. Research of the FDA data base for regulatory history of the palbociclib IND 69324, and review of minutes summarizing key interactions between FDA and the Applicant prior to- and after the initial approval of palbociclib.
3. Review of FDA review documents for NDA 207103 (supplemental NDAs) documenting FDA's previous findings of safety and effectiveness for palbociclib.
4. Review of the protocol and protocol amendments, the Clinical Study Report and selected datasets for Study 1008 (PALOMA-2).
5. Review of clinical study report and patient narratives included in the Flatiron Health Study.
6. Review of the Applicant's responses to FDA's clinical and biostatistical requests for information during the review of the sNDA.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 1008 (PALOMA-2)

Overview and Objective

PALOMA-2 was reviewed as part of sNDA 207103/4 with a data cutoff date of February 26, 2016. The current submission includes an updated analysis for the primary endpoint of PFS with a data cutoff date of May 31, 2017. The Sponsor stated that the data cutoff date for the updated analysis was chosen based on the projection that the percentage of progression free survival (PFS) events would reach 60% of the total population (400/666) at the time of analysis, which would give a more precise and robust estimation of the treatment effect in terms of hazard ratio (HR), median PFS, and their corresponding 95% confidence intervals (CIs). After the primary analysis, the investigators and patients remained blinded to treatment assignments. The key design features of PALOMA-2 are summarized below. Refer to the multidiscipline review document for sNDA 207103/4 for a more detailed review of this study.

Trial Design

PALOMA-2 is entitled “A Randomized, Multicenter, Double-Blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo plus Letrozole for the Treatment of Postmenopausal Women with ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti-Cancer Treatment for Advanced Disease”. Patients were treated with either palbociclib 125 mg/day or placebo orally for 3 of 4 weeks. Patients also received letrozole 2.5mg orally continuously. The primary objective was to demonstrate an improvement in investigator-assessed PFS with palbociclib plus letrozole over placebo plus letrozole. Key secondary objectives include overall survival (OS), objective response rate (ORR), duration of response (DOR), and clinical benefit response defined as complete response (CR) or partial response (PR) or stable disease (SD) of ≥ 24 weeks.

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

Study Endpoints

The primary endpoint of Study PALOMA-2 was investigator-assessed PFS, defined as the time from the date of randomization to the date of the first documentation of objective PD or death due to any cause in the absence of documented PD, whichever occurs first. PFS data was planned to be censored on the date of the last tumor assessment on study for patients who do not have objective tumor progression and who do not die while on study.

Patients lacking an evaluation of tumor response after randomization would have their PFS time censored on the date of randomization with duration of 1 day. Additionally, patients who start a new anti-cancer therapy prior to documented PD would be censored at the date of the last tumor assessment prior to the start of the new therapy. Patients with documentation of PD or death after an unacceptably long interval (i.e., 2 or more incomplete or non-evaluable assessments) since the last tumor assessment were censored at the time of last objective assessment that did not show PD. The primary analysis was performed in the ITT population.

Secondary Endpoints include:

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

Refer to the review of NDA 207103-supplement 4 for the inclusion/exclusion criteria for PALOMA-2.

Allocation to Treatment

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

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

The Interactive Randomization Technology (IRT) assigned a unique patient identification

number. The IRT system was also used to assign study medication.

Study Treatments

Arm A (experimental arm):

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

Arm B (control arm):

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

Concomitant Radiotherapy or Surgery

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

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

Subject completion, discontinuation, or withdrawal

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

Tumor Assessments

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

Statistical Analysis Plan

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

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

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

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

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

analysis (0.0001). The final OS analysis is to occur when 347 deaths have happened.

8.1.2. Study Results

Compliance with Good Clinical Practices

Study PALOMA-2 was conducted according to the ethical principles originating from the Declaration of Helsinki and in compliance with the International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines. Each investigational center obtained approval from their IRB or Independent Ethics Committee. All patients gave informed written consent before entering the studies. In addition, all local regulatory requirements were followed.

Financial Disclosure

See review for sNDA 207103/004.

Patient Disposition

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

As of the data cutoff date, May 31, 2017, 69.8% of patients in the palbociclib plus letrozole arm and 86.0% of patients in the placebo plus letrozole arm had discontinued study treatment, while 30.2% of patients in the palbociclib plus letrozole arm and 14.0% of patients in the placebo plus letrozole arm were still on study treatment (Table 4). For the purpose of treatment, patients continuing on study with letrozole monotherapy following palbociclib/placebo discontinuation were still considered “on treatment”.

Table 4: Study PALOMA-2 Patient Disposition

	Palbociclib plus Letrozole N=444 n (%)	Placebo plus Letrozole N=222 n (%)	Total N=666 n (%)
Randomized to study treatment	444	222	666
Randomized and not treated	0	0	0
Randomized and treated	444 (100)	222 (100)	666 (100)
Discontinued	310 (69.8)	191 (86.0)	501 (75.2)
Ongoing at data cutoff date	134 (30.2)	31 (14.0)	165 (24.8)
Adverse Event			
Global deterioration of health status	24 (5.4)	12 (5.4)	36 (5.4)
Lost to Follow-Up	2 (<1.0)	0	2 (<1.0)
Medication error without associated AE	0	0	0
Objective progression or relapse plus progressive disease	217 (48.9)	150 (67.6)	367 (55.1)
Protocol violation	5 (1.1)	3 (1.4)	8 (1.2)
Study terminated by the sponsor	1 (<1.0)	0	1.0 (<1.0)
Patient died	6 (1.4)	2 (<1.0)	8 (1.2)
Patient refused to continue treatment for reason other than AE	19 (4.3)	10 (4.5)	29 (4.4)

Source: Modified from Study PALOMA-2 CSR Table 12 and Table 13; discon.xpt. Data cutoff May 31, 2017.

Protocol Violations/Deviations

The protocol violations/deviations for PALOMA-2 can be found in the original review of the sNDA 207103/4.

Table 5: Demographic Characteristics for Study PALOMA-2

Demographic Parameters	Palbociclib plus Letrozole N=444 N (%)	Placebo plus Letrozole N=222 N (%)	Total N=666 N (%)
Sex			
Female	444 (100)	222 (100)	666 (100)
Age			
Mean years (SD)	61.7	60.6	61.3
Median (years)	62	61	62
Age Group			
≥ 17 - < 65 years	263 (59.2)	141 (63.5)	404 (60.7)
≥ 65 - < 75 years	133 (30.0)	62 (27.9)	195 (29.3)

Multi-disciplinary Review and Evaluation
sNDA 207103/008 IBRANCE® (Palbociclib)

≥ 75 years	48 (10.8)	19 (8.6)	67 (10.1)
Race			
White	344 (77.5)	172 (77.5)	516 (77.5)
Black or African American	8 (1.8)	3 (1.4)	11 (1.7)
Asian	65 (14.6)	30 (13.5)	95 (14.3)
Other	27 (6.1)	17 (7.7)	44 (6.8)
Ethnicity			
Hispanic or Latino	39 (8.8)	15 (6.8)	54 (8.1)
Not Hispanic or Latino	386 (86.9)	193 (86.9)	576 (86.5)
Missing/Not reported	19 (4.3)	14 (6.3)	33 (5.0)

Source: Modified from Study PALOMA-2 CSR Table 17 and demog.xpt

Table 6: Baseline Disease Characteristics for Study PALOMA-2

	Palbociclib plus Letrozole N=444 N (%)	Placebo plus Letrozole N=222 N (%)	Total N=666 N (%)
Measurable disease			
Yes	338 (76.1)	171 (77.0)	509 (76.4)
No	106 (23.9)	51 (23.0)	157 (23.6)
Adequate baseline assessment			
Yes	444 (100)	222 (100)	666 (100)
No	0	0	0
Bone Only Disease			
Yes	103 (23.2)	48 (21.6)	151 (22.7)
ER Status			
Positive	443 (99.8)	222 (100)	665 (99.8)
Negative	0	0	0
Missing	1 (0.2)	0	1 (0.2)
HER2 status			
Positive	0	0	0
Negative	444 (100)	222 (100)	666 (100)
Equivocal	0	0	0
Histopathologic classification			
Ductal	313 (70.5)	158 (71.2)	471 (70.7)
Lobular	68 (15.3)	30 (13.5)	98 (14.7)
Other	63 (14.2)	34 (15.3)	97 (14.6)
Histologic Grade			
1	52 (11.7)	18 (8.1)	70 (10.5)
2	205 (46.2)	108 (48.6)	313 (47.0)
3	100 (22.5)	49 (22.1)	149 (22.4)
Stage at Initial Diagnosis			
I	51 (11.5)	30 (13.5)	81 (12.2)
II	137 (30.9)	68 (30.6)	205 (30.8)
III	72 (16.2)	39 (17.6)	111 (16.7)

IV	138 (31.1)	72 (32.4)	210 (31.5)
Other/Unknown	46 (12.6)	13 (10.4)	59 (8.9)
ECOG Performance Status			
0	257 (57.8)	102 (45.9)	359 (53.9)
1	178 (40.1)	117 (52.7)	295 (44.3)
Involved Disease Sites			
Bone	325 (73.2)	162 (73.0)	487 (73.1)
Breast	137 (30.9)	74 (33.3)	211 (31.7)
Liver	75 (16.9)	46 (20.7)	121 (18.2)
Lung	150 (33.8)	71 (32.0)	221 (33.2)
Lymph Node	212 (47.7)	110 (49.5)	322 (48.3)
Other	115 (25.9)	64 (28.8)	179 (26.9)

Source: Modified from Study PALOMA-2 CSR Table 18, demog.xpt, and Table 14.1.2.5

Efficacy Results – Primary Endpoint

The primary endpoint was reviewed as part of sNDA 207103/4. An update to the primary endpoint of PFS was provided by the applicant as part of this sNDA. There were no updates to the overall survival data and follow-up for this endpoint is continuing to occur.

Data Quality and Integrity

The data are of good quality and integrity; the same quality as previous supplements.

Efficacy Results – Secondary and other relevant endpoints

The updated results for PFS in Study PALOMA-2 are shown in Table 7 and Figure 1. The final PFS analysis from the original supplemental application are shown in Table 8. With approximately 15 months of additional follow-up, the updated results are very similar with those seen in original supplemental application (sNDA 207103/4). The primary difference is an increase of 3 months for the median in the treatment arm.

Reviewers Comment: *The updated information is very consistent with that in the original supplemental application and the conclusions remain the same.*

(b) (4)

The applicant did not request a labeling change based upon the updated information.

Table 7: Primary Endpoint Results, Updated (Progression Free Survival Study PALOMA-2)

	May 31, 2017 cutoff	
	Letrozole + Palbociclib N = 444	Letrozole + Placebo N = 222
Events	245 (55.2%)	160 (72.1%)
Median (months)	27.6 [22.4, 30.3]	14.5 [12.3, 17.1]
Hazard Ratio	0.563 (0.461, 0.687)	
Nominal p-value	< 0.0001	

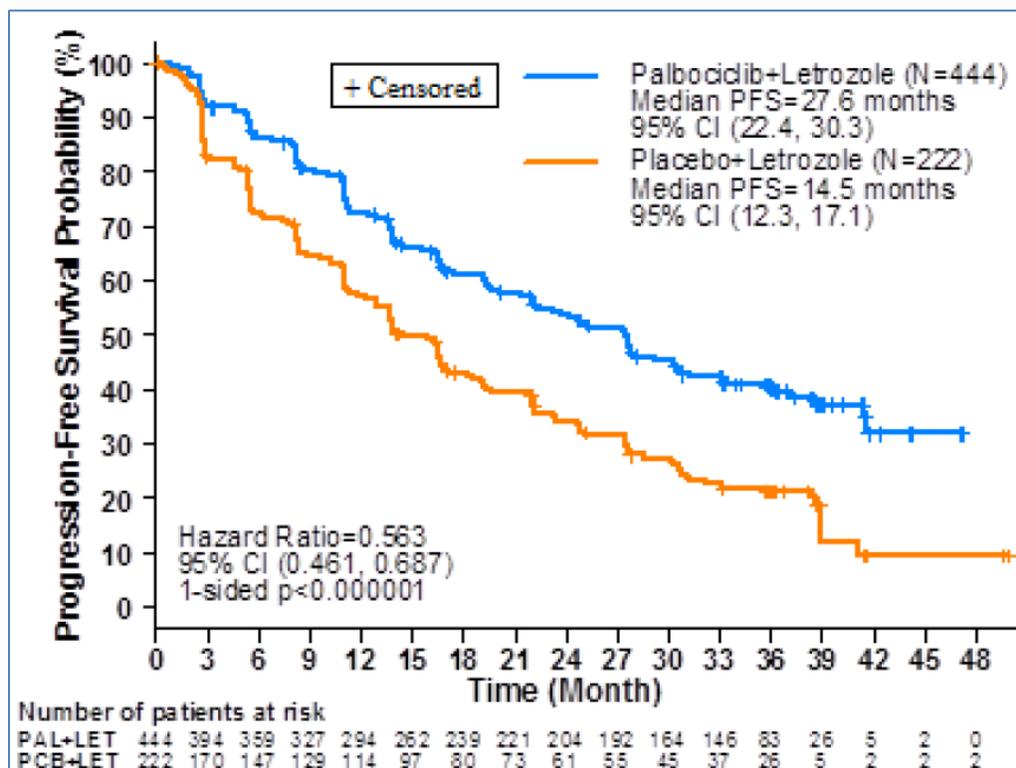
Source: Study PALOMA-2 PFS Update Report, reviewer's analysis

Table 8: Primary Endpoint Results, Original Approval (Progression Free Survival Study PALOMA-2)

	February 26, 2016 cutoff	
	Letrozole + Palbociclib N = 444	Letrozole + Placebo N = 222
Events	194 (43.7%)	137 (61.7%)
Median (months)	24.8 [22.1, NE]	14.5 [12.9, 17.1]
Hazard Ratio	0.576 (0.463, 0.718)	
p-value	< 0.0001	

Source: Study PALOMA-2 Final PFS Analysis, reviewer's analysis

Figure 1: Primary Endpoint Results (Progression Free Survival Study PALOMA-2)



Source: Study PALOMA-2 PFS Update Report, reviewer's analysis

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. Additional details on durability of response can be found in the review for sNDA 207103/004.

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.

In the updated results, the palbociclib plus letrozole had a total of 7 additional confirmed responders in the measurable disease population for a ORR of 57.4% (95% CI: 51.9, 62.7). The placebo + letrozole population had no additional confirmed responders in the measurable disease population and the ORR remained the same, 44.4% (95% CI: 36.9, 52.2).

There are updates for the duration or response data with the additional responders and follow-up. The duration of response (confirmed response) for those with measurable disease was 27.7 months (95% CI: 24.7, 36.1) in the palbociclib + letrozole arm and 20.9 months (95% CI: 16.5, 27.6) in the letrozole only arm. In the original supplemental application, the duration of response (confirmed response) for those with measurable disease was 22.5 months (95% CI: 19.8, 28.0) in the palbociclib + letrozole arm and 16.8 months (95% CI: 15.4, 28.5) in the letrozole only arm.

Reviewer's Analysis: The updated response and duration data are consistent with those in the original supplemental application. (b) (4)

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

See review for sNDA 207103/004

8.1.3. Real -World Data Analysis – Flatiron Health

The applicant provided a retrospective outcomes analysis that used data from electronic health records (EHR) from the Flatiron Health Analytic Database, to support the request for broadening the palbociclib indication to include male patients. According to the applicant, the Flatiron Database is generated from the EHR data that is collected within the Flatiron Provider Network of cancer care providers in the US. The Flatiron Database includes cancer patients who are actively receiving treatment. Data collection was performed by Flatiron Health Inc. in accordance with the parent protocol (#15-159), and the Retrospective Sub-Study #19 and Analytic Guide for Flatiron Health Data, both submitted to NDA as appendices.

As is standard, the EHR contains both structured and unstructured patient disease and treatment information. The structured data (e.g., laboratory test values, prescribed drugs, etc.) underwent a mapping and normalizing process, while the unstructured data (e.g., detailed biomarkers, radiology reports, therapies, etc.) was extracted via technology-enabled chart abstraction from physician notes and other documents.

8.1.4. Study Design

Overview and Objective

The objective of this retrospective analysis was to provide additional and supportive Real-World Data (RWD) on the treatment of males with MBC.

The study was designed to describe the clinical characteristics and outcomes in a cohort of male patients with HR-positive/HER2-negative MBC who either:

- received a palbociclib-based regimen in any line of therapy (LOT) (Cohort A: palbociclib treated cohort) or,
- received an endocrine therapy-based regimen in any LOT and were never treated with a palbociclib-containing regimen (Cohort B: non-palbociclib treated cohort)

Study Design

This study is a retrospective analysis with no formal hypothesis testing. The applicant submitted a study report based upon a dataset that includes patient-level data collected between January 1, 2011 and a data cutoff date of July 31, 2017. Patients with demographic and clinical characteristics which met eligibility criteria were assigned to either Cohort A or Cohort B (as outlined below).

Eligibility Criteria

Inclusion Criteria

- Male
- International Classification of Diseases (ICD)-9 (174.x, 175.x) or ICD-10 (C50. xx) diagnosis of breast cancer;
- Confirmation of metastatic disease (via review of unstructured data) on or after January 1, 2011;
- Two or more documented clinic visits on or after January 1, 2011;
- HR-positive (Estrogen Receptor [ER] positive and/or Progesterone Receptor positive), and HER2-negative disease, as confirmed through review of unstructured data:
 - HR-positive is defined as any positive test for ER or progesterone receptor before or up to 60 days after MBC diagnosis (or no test date provided)
 - HER2-negative is defined as any HER2-negative test and the absence of a positive test (immunohistochemistry [IHC] positive [3+], fluorescence in situ hybridization [FISH] positive/amplified, or positive not otherwise specified) before or up to 60 days after MBC diagnosis (or no test date provided);
- Assigned to either Cohort A or Cohort B
 - Cohort A: Initiation of a palbociclib-based regimen in any line of therapy in the metastatic breast cancer setting, as identified by a structured medication order of palbociclib and confirmed through unstructured data
 - Cohort B: No evidence of initiation of a palbociclib-based regimen in any line of therapy in the metastatic setting, as confirmed through unstructured data. Initiation of an endocrine therapy-based regimen in any line of therapy in the metastatic setting, as identified by a structured medication order of an endocrine therapy (letrozole, anastrozole, exemestane, fulvestrant, tamoxifen) and confirmed through unstructured data.

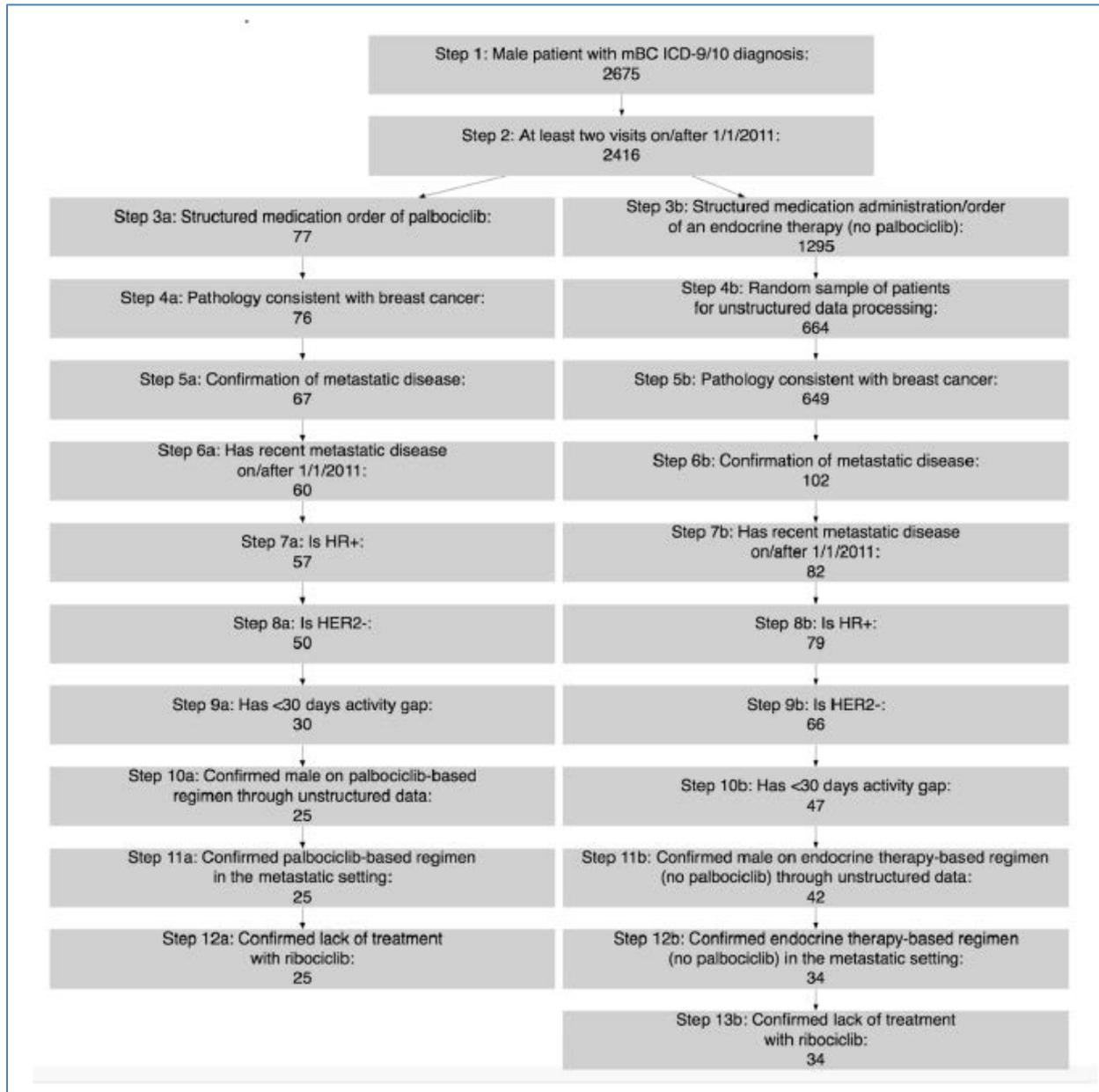
Exclusion Criteria

- Evidence of treatment with ribociclib, as confirmed through unstructured data.

- More than a 30-day gap between MBC diagnosis date and first activity.

Reviewer Comment: The criteria used to define HER2-negative disease appear adequate; however, it is difficult to know whether this followed American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines as the cutoff for FISH positivity/amplification is not known.

Figure 2: Cohort Selection and Attrition



Source: IR response dated August 15, 2018 from Sponsor for sNDA 207103/008

Reviewer’s comment: *The steps taken to identify patients for inclusion in Cohorts A and B are shown in 2. In Cohort B, step 4b used random sampling to reduce the unstructured processing size. Since the final size of Cohort B is relatively small, this random sampling step likely introduces considerable uncertainty in the data.*

An additional step of focus was step 9a for Cohort A and 9b for Cohort B, the < 30-day activity

gap. The purpose of this step was to eliminate individuals who came in for an initial consult but who eventually received therapy elsewhere; this reviewer finds this step appropriate, but also finds that the use of a 30-day cutoff may be too restrictive. An FDA analysis based upon use of a 90-day activity gap which yielded 6 additional patients with a <90-activity gap did not change the overall assessment of efficacy compared to when based upon the shorter gap

Overall, the criteria used to identify patients in the 2 cohorts do not guarantee that the 2 groups are comparable. Randomization or procedures employed to render cohorts in observational studies more comparable (e.g., matching, propensity scores, etc.) were not used in this study.

Line of Therapy (LOT)

LOT was derived based on medication orders and treatment administrations from the EHR. LOT was determined by grouping occurrences of medication(s) occurring in close proximity. The medication(s) were then summarized into LOT based on the start and end dates following an algorithm that uses a 28-day window (e.g., all medications given to treat a patient's MBC within 28 days of the initial prescription start date for palbociclib were grouped into a single LOT for that patient).

Real World Tumor Response (rwTR)

The tumor response variable was extracted from the EHR as part of routine clinical care, and the information about each response event was retrospectively collected. Response to treatment in the real-world setting (Real World Tumor Response [rwTR]) included several factors in conjunction with radiologic assessments (e.g., physical exam, symptom improvement, and pathology reports), which were used to supplement radiologic findings in the overall clinician's assessment of response. rwTR was defined as the treating clinician's assessment of radiological evidence for change in burden of disease over the course of treatment with a given LOT.

At each response assessment time point, the treating clinician's assessment or interpretation of the imaging tests were captured and mapped to 1 of the following tumor response categories:

- **Complete Response (CR)**: Complete resolution of all visible disease.
- **Partial Response (PR)**: Partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease (decrease in disease volume even though disease is still present).
- **Stable Disease (SD)**: No change in overall size of visible disease (includes cases where some lesions increased in size and some lesions decreased in size).
- **Progressive Disease (PD)**: Increase in visible disease and/or presence of any new lesions (includes cases where the clinician indicates PD or progression of disease [POD] as the overall assessment).
- **Pseudoprogression**: Clinician indicates pseudoprogression or related terminology (e.g., tumor flare).

- **Indeterminate Response:** Clinician specifically indicates that the response was “indeterminate” or “uncertain”, or if the clinician’s interpretation of the scans was documented but could not be mapped to 1 of the above assessment categories.
- **Not Documented:** Clinician’s note references the imaging test (e.g., “patient had recent scan”) but does not mention any assessment of tumor response.

Reviewer’s comment: In this study, real world tumor response data was generally available for several lines of therapy. For the primary efficacy data, the applicant’s study design focused on the first regimen containing palbociclib (Cohort A) and the first endocrine containing regimen that did not contain tamoxifen (Cohort B). Tamoxifen was excluded since it is not approved for use in combination with palbociclib and it has a different mechanism of action compared to fulvestrant or aromatase inhibitors.

Data were also presented as patient narratives consisting of prose narratives with data elements (e.g., year of birth, metastatic sites, first metastatic treatment), patient level summary tables, and patient journeys. Patient journeys were generated for visual representation of the timeline of clinic visits and treatments. Redacted, unstructured source documentation in the form of clinician assessments and/or radiology reports was also included for both cohorts.

Safety Events of Interest

Safety events were collected for Cohort A only. Details for corresponding safety events (including date of onset, where available) were abstracted from the EHR, if they were explicitly attributed by the physician to palbociclib and occurred after the start date of a palbociclib-based regimen and prior to the data cutoff date. The following 5 safety events of interest were prespecified for assessment based on the known safety profile of palbociclib:

- Fatigue
- Febrile neutropenia
- Neutropenia
- Pulmonary embolism
- Stomatitis

Reviewer’s comment: The applicant’s analysis of safety in the Flatiron study was limited to the 5 most common adverse events known to occur with palbociclib for the palbociclib containing cohort (Cohort A) only. Given this restriction, the identification of new adverse events/safety signals in male patients is limited. Additionally, comparisons of the incidence of these AEs as reported in this study versus the incidence that has been observed in clinical trials of palbociclib is limited by possible differences in AE recording practices.

Statistical Analysis Plan

This retrospective analysis is exploratory in nature and no formal statistical comparisons between groups were performed. As mentioned above, when response rate data were available for multiple lines of therapy, the efficacy data would focus on the first regimen

containing palbociclib (Cohort A) and the first endocrine containing regimen that did not contain tamoxifen (Cohort B).

The primary outcome of interest was real-world response rate. This represents the percentage of enrolled patients who achieved either a real-world partial response or a real world complete response. Patients who were eligible for study inclusion but did not have any radiological follow-up visits were excluded from the primary endpoint calculations. In addition, patients in Cohort B whose only endocrine therapy included tamoxifen, were excluded from the primary endpoint calculations.

Reviewer Comment: Given the study design, comparisons between Cohort A and Cohort B are limited and difficult to interpret; as previously described sample size was limited and no adjustments such as matching or propensity scores, were used to support comparisons across the 2 cohorts.

Protocol Amendments

No amendments were submitted for this study.

8.1.5. Study Results

Compliance with Good Clinical Practices

The applicant stated that the protocol was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and followed generally accepted research practices such as Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and similar standards. Flatiron Health collected EHR data under a parent protocol (#15-159), which was not provided to Pfizer, but is on file at Flatiron Health. The protocol included a retrospective substudy (#19) that provided a baseline description of this study and was used to outline to a central IRB the study population and research objectives. IRB approval of this retrospective substudy was obtained prior to data collection, which included a waiver of informed consent. Data were de-identified, and provisions were in place to prevent re-identification in order to protect patient confidentiality.

Financial Disclosure

Not applicable.

Patient Disposition

Not applicable.

Protocol Violations/Deviations

No protocol discrepancies were noted during clinical inspections. *See Section 4.1 Office of Scientific Investigations (OSI).*

Table of Demographic Characteristics

Baseline demographics for Cohort A (palbociclib cohort) and Cohort B (non-palbociclib cohort) are shown in Table 9 below.

Table 9: Demographic Characteristics (Real -World Data Analysis – Flatiron Health)

Demographic Parameters	Cohort A Palbociclib cohort N=25 N (%)	Cohort B Non-palbociclib cohort N=34 N (%)	Total N=59 N (%)
Sex			
Male	25 (100)	34 (100)	59 (100)
Age at diagnosis of metastatic disease			
Median (years)	64	70.5	68
Age Group			
35-49	2 (8)	3 (8.8)	5 (8.5)
50-64	12 (48.0)	8 (23.5)	20 (33.9)
64+	11 (44.0)	23 (67.6)	34 (57.6)
Race			
White	15 (60)	23 (67.6)	38 (64.4)
Black or African American	2 (8.0)	3 (8.8)	5 (8.5)
Asian	1 (4.0)	2 (5.9)	3 (5.1)
Other/unknown	7 (28)	6 (17.6)	13 (22.0)
Region within United States			
West	4 (16.0)	3 (8.8)	7 (11.9)
Midwest	5 (20.0)	8 (23.5)	13 (22.0)
South	8 (32.0)	11 (32.4)	19 (32.2)
Northeast	7 (28.0)	10 (29.4)	17 (28.8)
Other/unknown	1 (4.0)	2 (5.9)	3 (5.1)
Practice Type			
Academic	1 (4.0)	2 (5.9)	3 (5.1)
Community	24 (96.0)	32 (94.1)	56 (94.9)

Source: Flatiron Study CSR, page 12

Reviewer Comment: *This reviewer agrees with the cautionary statements stated earlier in the review above regarding the comparability of the two Cohorts as the baseline characteristics provide another example that the two cohorts were not well balanced with regards to age. Cohort B tended to be much older with 67.6% of individuals 65 years or older. Cohort A had only 44.0% aged 65 years and above. This may suggest use of palbociclib in an earlier LOT in younger patients.*

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline disease characteristics for Cohort A (palbociclib cohort) and Cohort B (non-palbociclib cohort) are shown in Table 10 below.

Table 10: Baseline Disease Characteristics (Real -World Data Analysis – Flatiron Health)

Baseline Disease Characteristics	Cohort A Palbociclib cohort N=25 N (%)	Cohort B Non-palbociclib cohort N=34 N (%)	Total N=59 N (%)
Stage and Initial Diagnosis			
I-III	20 (80)	22 (64.7)	42 (71.1)
IV	4 (16)	9 (26.5)	13 (22)
Progesterone Receptor Status			
Positive	17 (68)	26 (76.5)	43 (72.9)
Negative	5 (20)	6 (17.6)	11 (18.6)
Line Setting of Interest			
First-line	9 (36)	30 (88.2)	39 (66.1)
Second-line	5 (20)	3 (8.8)	8 (13.6)
Third or later line	11 (44)	1 (2.9)	12 (20.3)

Source: Flatiron Study CSR, page 12

Reviewer Comment: *Similar to Table 9 above, Cohort A and Cohort B were not well balanced on important baseline disease characteristics, most importantly, for the lines of therapy. The majority of patients in Cohort A had received one or more prior therapies, whereas the majority of patients in Cohort B had not received any prior therapy.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Luteinizing hormone-releasing hormone (LHRH) Agonist Use:

Seven patients (28%) in Cohort A and 5 patients (24%) in Cohort B received a LHRH agonist. In the population with on-study assessments allowing for real-world response, two patients in Cohort A and two patients in Cohort B received a LHRH agonist.

Reviewer comment: Current clinical practice recommends use of a LHRH agonist when treating a male breast cancer patient with an aromatase inhibitor. The limited reporting of LHRH agonist use does not mean that the patients didn't get it, it is just unknown, as this may have not been properly captured/reported.

Efficacy Results - Primary Endpoint

The primary outcome of interest for this study was real-world response rate. To allow for estimation of this endpoint, on-study tumor assessments (radiographic) were required to have occurred. For Cohort A (palbociclib cohort), only 12 individuals had on-study tumor assessments and for Cohort B (non-palbociclib cohort), only 29 patients had an on-study tumor assessment. Additionally, for Cohort B, patients whose endocrine therapy only included a tamoxifen agent (13 patients) were excluded from this analysis, since tamoxifen has a different mechanism of action than NSAI agents or fulvestrant. This lowered the size of Cohort B to 16 patients. For completeness, demographic and baseline disease characteristics are shown in Table 11 and Table 12 for this reduced Analysis Cohort.

Table 11: Demographic Characteristics of Analysis Cohorts A, B (Real -World Data Analysis – Flatiron Health)

Demographic Parameters	Analysis Cohort A Palbociclib cohort N=12 N (%)	Analysis Cohort B Non-palbociclib cohort N=16 N (%)	Total N=28 N (%)
Sex			
Male	12 (100)	16 (100)	28 (100)
Age at diagnosis of metastatic disease			
Median (years)	62.0	71.0	68.0
Age Group			
35-49	0 (0)	2 (12.5)	2 (7.1)
50-64	7 (58.3)	4 (25.0)	11 (39.3)
64+	5 (41.7)	10 (62.5)	15 (53.6)
Race			
White	7 (58.3)	11 (68.8)	18 (64.3)
Black or African American	2 (16.7)	2 (12.5)	4 (14.3)
Asian	2 (16.7)	1 (6.2)	3 (10.7)
Other/unknown	1 (8.3)	2 (12.5)	3 (10.7)
Region within United States			
West	1 (8.3)	1 (6.2)	2 (7.1)
Midwest	3 (25.0)	6 (37.5)	9 (32.1)

Multi-disciplinary Review and Evaluation
sNDA 207103/008 IBRANCE® (Palbociclib)

South	6 (50.0)	5 (31.2)	11 (39.3)
Northeast	2 (16.7)	3 (18.8)	5 (17.9)
Other/unknown	0 (0)	1 (6.2)	1 (3.6)
Practice Type			
Academic	0 (0.0)	1 (6.2)	1 (3.6)
Community	12 (100.0)	15 (93.8)	27 (96.4)

Source: Information request, 12/7/18

Table 12: Baseline Disease Characteristics of Analysis Cohorts A, B (Real -World Data Analysis – Flatiron Health)

Baseline Disease Characteristics	Analysis Cohort A Palbociclib cohort N=12 N (%)	Analysis Cohort B Non-palbociclib cohort N=16 N (%)	Total N=28 N (%)
Stage and Initial Diagnosis			
I-III	10 (83.3)	13 (81.2)	23 (82.1)
IV	1 (8.3)	3 (18.8)	4 (14.2)
Progesterone Receptor Status			
Positive	8 (66.7)	13 (81.2)	21 (75.0)
Negative	2 (16.7)	3 (18.8)	5 (17.9)
Line Setting of Interest			
First-line	6 (50.0)	13 (81.2)	19 (67.9)
Second-line	2 (16.7)	2 (12.5)	4 (14.3)
Third or later line	4 (33.3)	1 (6.2)	5 (17.9)

Source: Information request, 12/7/18

Table 13 shows the real-world response rate data for the 28 individuals (12 from Cohort A and 16 from Cohort B). The agency reviewed narratives for the 28 individuals shown below and agreed with the applicant except for 1 individual. The applicant stated that this individual had a complete response. But after review, the agency noted that the first palbociclib containing regimen was progressive disease.

Table 13: FDA Analysis of Real-World Response Rate (Real -World Data Analysis – Flatiron Health)

Real World Response Rate	Analysis Cohort A Palbociclib cohort N=12 N	Analysis Cohort B Non-palbociclib cohort N=16 N
rwORR	3	2
Complete Response	1	0
Partial Response	2	2
Stable Disease	5	8
Progressive Disease	4	6

Source: Reviewer's Analysis. rwORR = real-world overall response rate

Reviewer Comment: *The data provide limited evidence for the effectiveness of palbociclib plus endocrine therapy based on response rate due to the small sample sizes, with a response rate of 25% (3/12), or 2/16 of the non-placebo cohort.*

As shown in Table 10 in Cohort B, nearly all individuals were from a front-line setting (88.2%), while only (36.0%) of Cohort A were from the front-line setting. Given the limited sample size, the two cohorts were not matched with respect to baseline characteristics using any statistical tools and are not comparable. The palbociclib cohort tended to include later lines of therapy than the endocrine cohort; this may potentially tend to lower response rate.

Data Quality and Integrity - Reviewers' Assessment

The data appeared to be of good quality and integrity. The data were consistent across datasets and the clinical study report. In addition, detailed narratives were provided for patients. Refer to the results (Section 4.1) of FDA's Office of Scientific Investigations (OSI) inspection of Pfizer and Flatiron, which revealed no major deficiencies for clinical study conduct.

Efficacy Results - Secondary and other relevant endpoints

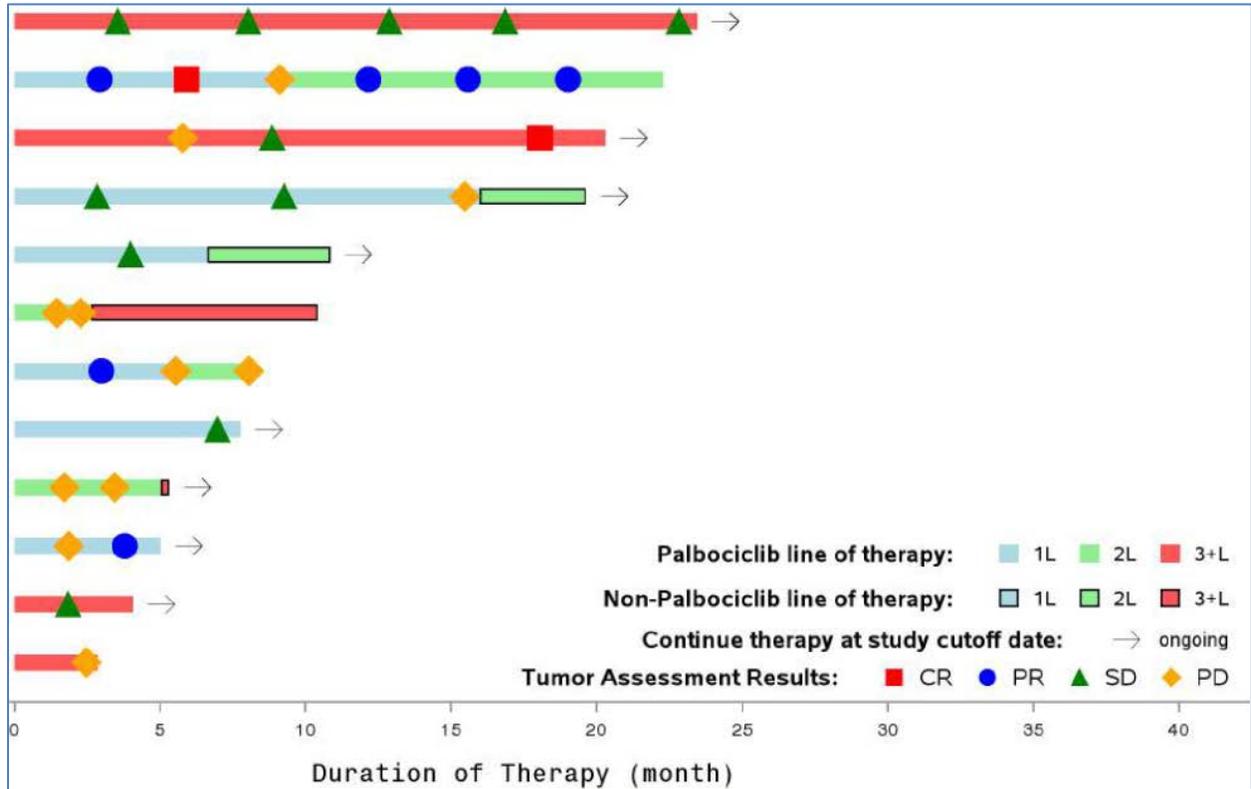
Duration of real world response is shown in Figure 3 for Analysis Cohort A and

Figure 4 for Analysis Cohort B. Responses tended to be short (range 1-3 follow-up visits) and similar between the two cohorts.

Reviewer Comment: *Due to the small number of responders (i.e., 3 in Cohort A and 2 in Cohort B), the data provide only limited information on duration of response. It should also be noted that since real-world data does not require scheduled follow-ups, those with more follow-up visits may have a shorter duration of response than those with less frequent follow-ups.*

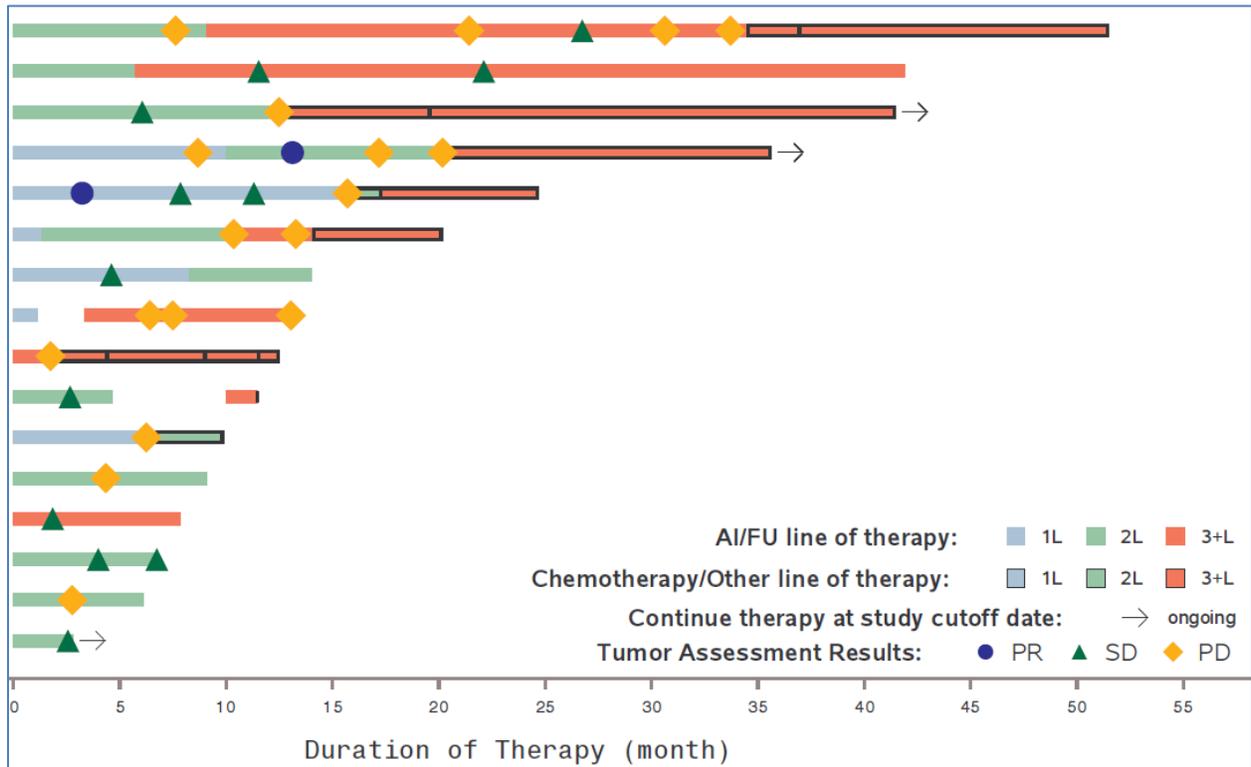
Figure 3: Analysis Cohort A Duration of real-world Response

Multi-disciplinary Review and Evaluation
sNDA 207103/008 IBRANCE® (Palbociclib)



Source: CSR, appendix 3

Figure 4: Analysis Cohort B Duration of real-world Response



Source: Applicant information request, December 2018

Dose/Dose Response

Not applicable.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

8.2. Study A5481097 (IQVIA)

The applicant submitted a study entitled, “Retrospective Claims Data Analysis of Males Treated for Metastatic Breast Cancer (MBC) in the United States” to describe patterns of palbociclib (Ibrance) use among male patients with breast cancer in the US. The study was based upon data from the Specialty Pharmacy Datamart and Pharmacy and Medical claims databases.

According to the applicant, these data are HIPAA compliant de-identified patient longitudinal data from all 50 states which represent patients regardless of age or insurance type. Patients who were identified in the Specialty Pharmacy Datamart were matched to QuintilesIMS Pharmacy and Medical claims databases using a unique identifier. Data was collected from January 1, 2010 (i.e., 5 years prior to US approval of palbociclib (Ibrance)) to April 30, 2017 to allow exploratory analysis of treatment patterns pre- and post-palbociclib approval.

8.2.1. Study Design

Overview and Objective

This study is retrospective and descriptive in design, with no formal hypothesis testing. The study objectives are listed below.

Primary Objective: Describe treatments and patterns of use in males with MBC in the US by utilizing a comprehensive data source (IQVIA Pharmacy Claims and Medical Claims databases).

Secondary Objectives:

- Describe the frequency of male patients with MBC who were prescribed palbociclib
- Describe type and frequency of specific endocrine therapies used in combination with palbociclib
- Describe line of therapy (LOT) in which palbociclib was used
- Describe how many prescriptions for palbociclib were dispensed for each patient;
- Describe proportion of patients remaining on palbociclib therapy at landmark time points (90, 180, 270, and 360 days)
- Describe MBC treatments and patterns of use in males with MBC not treated with palbociclib.

Exploratory Analysis:

- Describe time on treatment with palbociclib
- Describe frequency and reasons for rejection and reversal of palbociclib prescriptions.

Trial Design

Study 1097 was a retrospective cohort study utilizing secondary de-identified data sources that involve male patients in the United States who have been diagnosed with MBC.

This retrospective study was performed in 2 parts:

- Part 1: Matched (Linked) Pharmacy Claims and Medical Claims Analysis;
- Part 2: Palbociclib Pharmacy Adjudication Experience (FIA Data).

In Part 1, male patients with MBC were identified in the IQVIA Pharmacy Claims and Medical Claims Databases. Patients were linked to the IQVIA Pharmacy Claims and Medical Claims Databases using a unique identifier. Patients had to have a documented diagnosis of MBC at any time to be included in the analysis. These data provided information on the use and durations of prescribed endocrine agents in 2 treatment groups based on whether the patient received therapy with a palbociclib or non-palbociclib (endocrine therapy only) containing regimen.

In Part 2, FIA data, which is an IQVIA longitudinal de-identified pharmacy claims data set that tracks the claim adjudication between the retail/specialty pharmacy, payer, and patient at the point of sale, was used. As a baseline comparator, pharmacy adjudication patterns for female patients prescribed palbociclib during the same time period were assessed to identify potential differences. These data provided information as to whether the exclusion of male patients from the current approved indication is a factor in the number of males having access, and ultimately being treated with palbociclib.

Eligibility Criteria

Inclusion Criteria (Part 1)

- Male
- At least 18 years old
- Treatment for MBC during the period from January 1, 2010 to April 30, 2017
- Diagnosis of MBC reported at any time point in patient history; with breast cancer International Classification of Diseases (ICD) code and secondary (metastatic) ICD codes
- At least 1 observation in both IQVIA Medical Claims and IQVIA Medical Pharmacy Claims databases
- Patients must have received care from treating oncologists who consistently recorded prescriptions of palbociclib or non-palbociclib-containing regimens over the study period.

Inclusion Criteria (Part 2)

- Male or female
- At least 18 years old

- Treatment with palbociclib during the selection period February 1, 2015 to July 31, 2017 (the most current data available)
- No palbociclib use by the patient during the 12-month period prior to first use of palbociclib during the selection period (February 1, 2015 to July 31, 2017)

There were no exclusion criteria for either part of the study.

Reviewer's comment: The following endocrine therapy agents were allowed: letrozole, exemestane, tamoxifen, fulvestrant and anastrozole. As noted above with the Flatiron Study, since tamoxifen is not approved in combination with palbociclib, the main analyses conducted for this application excluded tamoxifen.

The data from Part 1 provides information on prescription duration with palbociclib treatment. The data from Part 1 however does not provide reasons why a prescription order was stopped, e.g. tolerability, adverse events, progressive disease, etc. Because of we do not know the reason why the prescription order was stopped, it is difficult to assess whether an improvement in average prescription order duration has a clinical benefit on time-to-death or time-to-progression.

Statistical Analysis Plan

Descriptive statistics were used to summarize basic demographic statistics and lines of therapy prescribed. Kaplan-Meier plots were used to summarize duration of prescription order. Prescription start and stop dates were known for all patients included in the study, so censoring rules were not required. Median duration of prescription order and confidence intervals were also reported.

In order to determine line of therapy the following steps were generally followed.

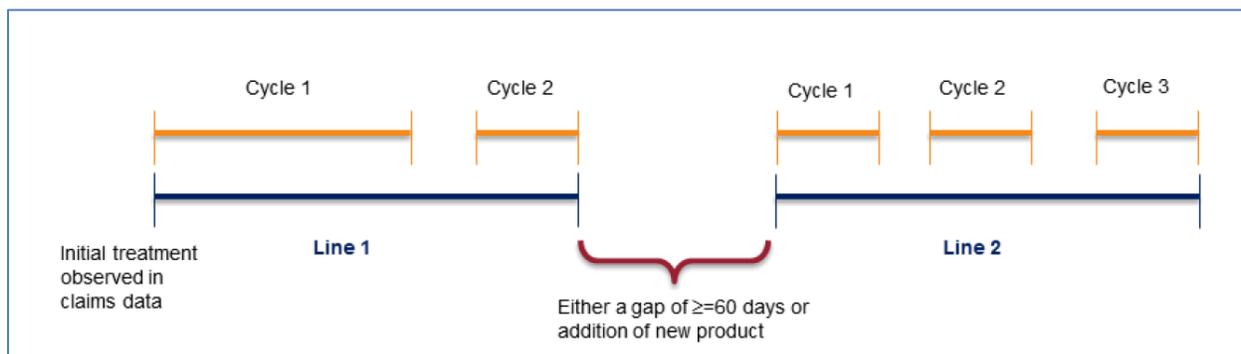
1. QuintilesIMS identifies a patient's first line of therapy for MBC by identifying monotherapy or combination therapy (endocrine therapy, chemotherapy and/or biologics) on or after initial metastatic disease diagnosis date
2. Once drug treatment is identified, QuintilesIMS builds drug cycles using a look-forward period. The look-forward period groups drugs that are administered in close time proximity as described below.
3. Once the cycles are indexed, QuintilesIMS evaluates the data for line changes

Cycles are defined, and line advancement is determined using the following steps. Once the line advancement date is known, the length of treatment (LOT) can be determined using the start date.

1. Cycle duration may range anywhere from 7 days to 28 days

2. Drug visits within a 4-, 21-, or 28-day gap (depending on the treatment regimen) would be considered as the same cycle. A new cycle starts on the next drug administration date, within the line of therapy and beyond the gap.
3. A subsequent line of therapy is noted when:
 - A gap between cycles is greater than or equal to 60 days;
 - A new drug is added after the first 28 days and 2 cycles of the existing line;
 - Otherwise, treatment(s) are considered as part of the previous line of therapy
 - An example of line advancement is shown in Figure 5.

Figure 5: IQVIA Line Advancement Determination



Source: IQVIA Protocol, page 12.

Protocol Amendments

The study was amended once in October 2017 to assess reasons for rejection and reversal of palbociclib prescriptions. This amendment had no bearing on the prescription order data that was of primary interest in the study results.

Data Quality and Integrity: Sponsor's Assurance

The applicant stated that Pfizer programmers confirmed the quantity and dataset specifications/variables (outlined in the study protocol) of the transferred files with the vendor. In addition, data were collected through a Health Insurance Portability and Accountability Act (HIPAA)-compliant process that resulted in de-identified patient data that were stored within the specific project schema on protected IQVIA servers.

Study Results

Compliance with Good Clinical Practices

The applicant stated that Study 1097 was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and followed generally accepted research practices such as GPP issued by the ISPE, the ISPOR guidance, PhRMA

guidelines and similar standards. This study was exempt from obtaining patient informed consent and IRB review and approval.

Financial Disclosure

Not applicable.

Patient Disposition

Not applicable.

Protocol Violations/Deviations

No protocol deviations were noted during clinical inspection. See Section 4.1 Office of Scientific Investigations (OSI).

Table of Demographic Characteristics

Not applicable.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The only baseline characteristic available from Part 1 was line of therapy and the agent used during that line. Table 14 below provides details on the number of patients obtained for each agent as well as the line of therapy. Note that if a patient was prescribed palbociclib + letrozole therapy in the 1st line and palbociclib + fulvestrant in the 2nd line, they are included in multiple rows of the table.

Table 14: Study 1097 Patient Demographics

Line of Therapy	Palbociclib	Non-Palbociclib				
	Palbociclib N (%)	Tamoxifen N (%)	Letrozole N (%)	Anastrozole N (%)	Exemestane N (%)	Fulvestrant N (%)
Overall	147	337	162	221	109	84
First-Line	47 (32.0)	178 (52.8)	63 (38.9)	101 (45.7)	19 (17.4)	37 (44.0)
Second-Line	45 (30.6)	112 (33.2)	55 (34.0)	77 (34.8)	31 (28.4)	24 (28.6)
≥Third-Line	72 (49.0)	79 (23.4)	55 (34.0)	60 (27.1)	64 (58.7)	36 (42.9)

Source: Table 10i

Each treatment category represents the treatment of interest-containing regimen in the specified lines of therapy (eg tamoxifen category may include tamoxifen alone or tamoxifen plus fulvestrant; letrozole category may include letrozole alone or letrozole plus fulvestrant).

Note: The counts in a column do not necessarily sum to the overall count. Patients may appear in >1 row within a column (eg, a patient who was treated in Line 1 with palbociclib and letrozole and was treated in Line 2 with palbociclib and fulvestrant appears in 2 rows under the palbociclib column. Patients who were treated with non-palbociclib-containing regimens may appear in >1 column (eg, a patient who was treated with a regimen containing letrozole and fulvestrant in Line 1 would appear in both letrozole and fulvestrant columns).

Abbreviation: N=number of patients.

Source: CSR, page 17

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

LHRH agonist use

Of the 147 patients who started palbociclib, 18 (12.2%) received an LHRH agonist from February 1, 2015 to April 1, 2017.

Reviewer comment: Current clinical practice recommends use of a LHRH agonist when treating a male breast cancer patient with an aromatase inhibitor. The limited reporting of LHRH agonist use does not mean that the patients didn't get it, it is just unknown, as this may have not been properly captured/reported.

Efficacy Results - Primary Endpoint

The primary results from Part 1, duration of prescription duration, are shown in Table 15 below. Kaplan-Meier curves for the time to prescription order stop are shown in Figure 6. The results appear to show longer prescription order duration with palbociclib therapy vs. endocrine therapy alone in the front-line setting. Nonetheless, it should be noted that these are non-randomized groups with an outcome that may not have direct clinical relevance. Therefore, one should interpret the duration of therapy results with caution.

Reviewer's comment: The data on prescription order duration should be interpreted with caution. This data does not arise from a randomized study and the groups are likely not balanced by age and stage of disease. If these confounding factors were available, they may help explain any observed difference in prescription duration between palbociclib + endocrine

therapy vs endocrine therapy alone. The usefulness of the prescription duration in evaluating efficacy is unclear.

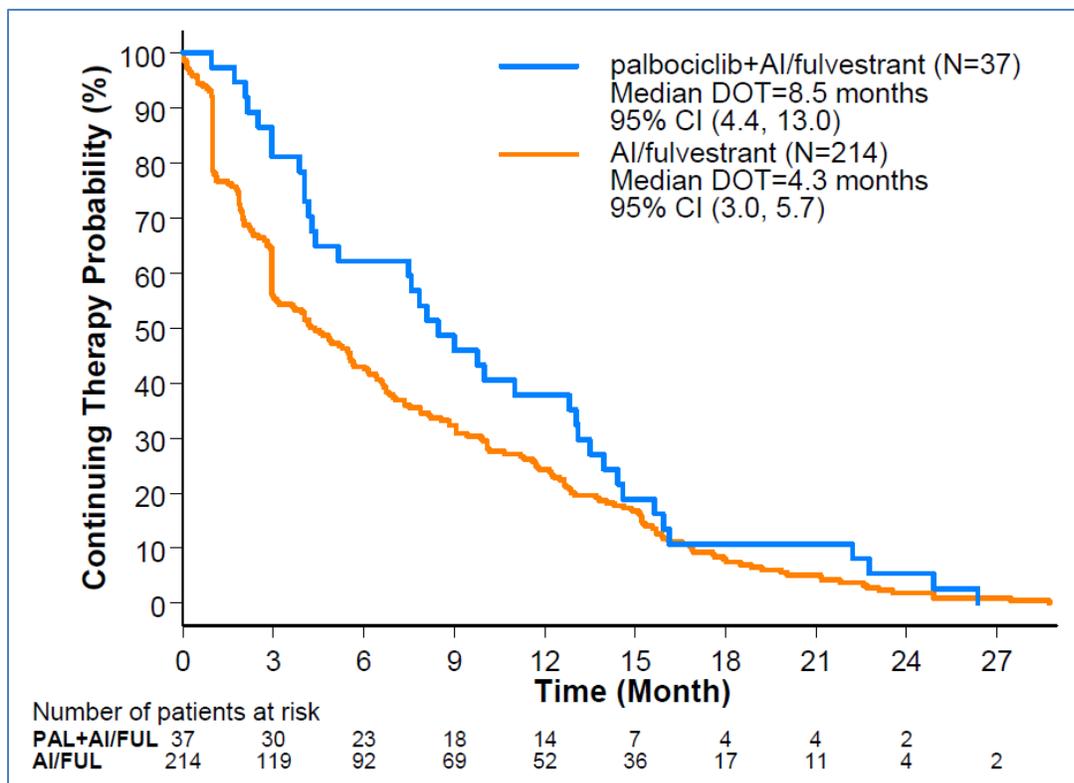
Table 15: Study 1097 Duration of Prescription Order

Therapy	Number of Patients	Median Duration of Therapy (Months [95% CI])
First-line		
Palbociclib + AI/fulvestrant	37	8.5 (4.4, 13.0)
AI/fulvestrant	214	4.3 (3.0, 5.7)
Palbociclib + letrozole	26	9.4 (4.4, 14.0)
Letrozole	63	3.0 (1.8, 4.8)
Second-line		
Palbociclib + fulvestrant	10	2.7 (0.7, 3.9)
Fulvestrant	24	1.8 (1.0, 3.7)

Source: Figures 4i, 6i and 8i.
Abbreviations: AI=aromatase inhibitor; letrozole; anastrozole; exemestane; CI=confidence interval.

Source: CSR, Page 18

Figure 6: Study 1097 First-Line Prescription Order Duration



Source: CSR, page 19

Data Quality and Integrity - Reviewers' Assessment

The data appeared to be of good quality and integrity. The data was consistent across datasets and the clinical study report. In addition, detailed narratives were provided for patients.

Efficacy Results - Secondary and other relevant endpoints

Not applicable.

Dose/Dose Response

Not applicable.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

Integrated Review of Effectiveness

8.2.2. Assessment of Efficacy Across Trials

Primary Endpoints

Not applicable.

Secondary and Other Endpoints

Not applicable.

Subpopulations

Not applicable.

Additional Efficacy Considerations

Not applicable.

8.2.3. Integrated Assessment of Effectiveness

Metastatic breast cancer in males is a very rare disease, making it difficult to conduct randomized controlled trials in this patient population. Thus, multiple sources of data are needed to evaluate efficacy. The efficacy of palbociclib in women with metastatic breast cancer has been established based on results from prospective randomized clinical trials. Updated results for one of these trials, PALOMA-2, were submitted with this sNDA. PALOMA-2 was a large, phase 3, randomized study of palbociclib plus letrozole vs letrozole alone in women with metastatic breast cancer. The updated results remain largely consistent with the previous results used to support the supplemental marketing application in women patients. The applicant provided two additional sources of clinical data (RWD from Flatiron and claims data from IQVIA) with this sNDA application to support expansion of the palbociclib indication to male patients with metastatic breast cancer.

The first study, the Flatiron study, provided some evidence, 3/12 responses, that palbociclib + endocrine therapy has anti-tumor activity (real world response rate) in men with metastatic breast cancer. There were several limitations of the Flatiron study. The study was not randomized, it included a small number of patients, and it did not employ statistical tools to balance the two cohorts (palbociclib + endocrine therapy and endocrine therapy alone).

In the second study, the IQVIA study, a longer prescription duration was observed with palbociclib + endocrine therapy compared to endocrine therapy alone. This study has several limitations. Like the Flatiron study, this was not a randomized study, there is limited information as to whether the data are confounded or balanced regarding baseline covariates. In addition, an assumption is made that prolonged prescription duration translates to prolonged treatment duration. Although this is plausible, whether this is true is not known. And whether that translates to an improvement in more clinically relevant endpoints, such as survival or progression-free survival is also not known. Due to these limitations, FDA did not consider the IQVIA study results in the benefit/risk assessment.

The effectiveness of palbociclib is expected to be the same in both women and men based on the mechanism of action for palbociclib. Given the extensive established efficacy and safety of the use of palbociclib in women observed in randomized clinical trials, the additional EHR data provided in this application for the use in men, modest as it is, does support the expansion of the palbociclib indication to provide for the treatment of men with metastatic breast cancer.

8.3. Review of Safety

8.3.1. Safety Review Approach

Safety for PALOMA-2 was reviewed in a previous supplemental review (sNDA 207103/004). No safety update was provided for this study in the current submission.

Safety information for palbociclib in male patients was provided from the following sources:

- Review of targeted prespecified adverse events (AEs) based on EHR from the Flatiron Study
- Pfizer global safety database
- 2 single-agent Phase 1 studies (Study 1001 and 1002) that enrolled male cancer patients. No male breast cancer patients were enrolled on these studies.

8.3.2. Review of the Safety Database

Overall Exposure

Not applicable.

Relevant characteristics of the safety population:

Not applicable.

Adequacy of the safety database:

Safety information for male patients with palbociclib use was available from the following sources:

- 25 patients in Cohort A of the Flatiron Health Study
- 362 cases from Pfizer Global Safety Database
- 15 patients from Study 1001 that received the approved schedule of palbociclib
- 14 patients from Study 1002

Reviewer Comment: Male breast cancer is rare; therefore, a variety of sources are necessary to obtain safety data. For this submission, information was available from real world data, claims data, phase 1 studies and the global database. The most extensive data was available from the global database.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The sNDA submission contained all required components of the eCTD. The overall quality and integrity of the application was adequate for substantive review to be completed.

Categorization of Adverse Events

Not applicable.

Routine Clinical Tests

Not applicable.

8.3.4. Safety Results

Deaths

Not applicable.

Serious Adverse Events

Not applicable.

Dropouts and/or Discontinuations Due to Adverse Effects

Not applicable.

Significant Adverse Events

Not applicable.

Treatment Emergent Adverse Events and Adverse Reactions

Pfizer global safety database:

The Pfizer global safety database was searched by the Sponsor, cumulatively through January 31, 2018 for any cases reported in male patients with breast cancer treated with palbociclib. A total of 362 cases with 752 reported AEs were identified. Of these 362 cases, 60 (17%) were serious and 302 (83%) were non-serious. Most cases were spontaneous (313), while 40 cases were derived from clinical studies, and 9 cases were solicited.

The most commonly reported Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) was Product use issue (reported 318 times), typically indicating use of palbociclib in an unapproved indication. In 216 cases, Product use issue was the only reported PT, and in 13 cases, Product use in unapproved indication was the only reported PT. Both Product use issue and Product use in unapproved indication were reported in 6 cases; in 3 of these 6 cases, these were the only PTs reported. The following PTs were reported ≥5 times: Product use issue (318), Fatigue (28), Product use in unapproved indication (24), Neoplasm progression (20), Neutropenia (17), White blood cell count decreased (15), Nausea (12), Diarrhea (10), Decreased appetite (9), Vomiting (7), Asthenia (7), Anemia (7), Neutrophil count decreased (6), Neuropathy peripheral (6), Dyspnea (6), Pruritus (5), Pain in extremity (5), Pain (5), and Constipation (5).

Study 1001:

Study 1001 was an open-label, dose-finding study conducted in patients with advanced cancer. Patients were given palbociclib treatment by repeated cycles either in accordance with dosing Schedule 3/1 or Schedule 2/1 (dosing schedule of 2 weeks on treatment/1 week off treatment) until disease progression or unacceptable toxicity occurred, or there was an investigator/patient decision to withdraw from this study. A total of 36 male patients with various solid tumors were treated with palbociclib in this study, of whom 15 received a palbociclib starting dose of 75 mg QD (3 patients), 100 mg QD (1 patient), or 125 mg QD (11 patients) on Schedule 3/1, the currently approved dosing regimens in the USPI. The remaining 21 patients received either palbociclib on Schedule 3/1 at doses other than the approved doses (25 mg [3 patients] or 150 mg QD [2 patients]) or palbociclib at various doses (100-225 mg QD) on Schedule 2/1 (16 patients).

The most common cancers in the 15 patients who received the currently approved dosing regimens were colon cancer, malignant melanoma, pancreatic carcinoma, and sarcoma (2 patients each). All AE data provided are for treatment-emergent events. The most frequently reported all-causality AEs (>25% of patients) of any grade were Fatigue (60.0%), Nausea (46.7%), Abdominal pain (33.3%), Diarrhea (33.3%), Neutropenia (33.3%), and Vomiting (33.3%) (Appendix 2 Table 1001.388.3). There were no Grade 4 or 5 AEs reported for these 15 patients. The most frequently reported treatment-related AEs (>25% of patients) of any grade were Fatigue (53.3%), Neutropenia (33.3%), Nausea (33.3%), and Diarrhea (26.7%).

Study 1002:

Study 1002 was a Phase 1 trial conducted to evaluate and compare biomarkers of CDK4/6 inhibition in tumor biopsies with changes in positron emission tomography (PET), to assess antitumor activity and safety of palbociclib in patients with mantle cell lymphoma (MCL). Eligible patients were previously treated with at least 1 prior therapy for MCL. All patients received a palbociclib starting dose of 125 mg QD dose on Schedule 3/1. A total of 14 male patients were treated with palbociclib in this study.

All AE data provided are for treatment-emergent events. The most frequently reported all-causality AEs (>25% of patients) of any grade were Fatigue (42.9%), INFECTIONS (42.9%), Neutropenia (42.9%), Rash (42.9%), and Thrombocytopenia (28.6%). There were 2 patients with Grade 4 AEs (Leukopenia, Thrombocytopenia, and Neutropenia in 1 patient and Leukopenia and Thrombocytopenia in 1 patient) and 1 patient with a Grade 5 AE (Cardiac arrest). The Grade 5 AE was not considered to be treatment-related by the investigator. The most frequently reported treatment-related AEs (>25% of patients) of any grade were Fatigue (42.9%) and Neutropenia (35.7%).

Reviewer Comment: Although it is difficult to derive any conclusions based on results from review of the Pfizer database and the phase 1 studies, in general the AE profile for male patients appears to be consistent with the known AE profile of palbociclib.

Laboratory Findings

Not applicable.

Vital Signs

Not applicable.

Electrocardiograms (ECGs)

Not applicable.

QT

Not applicable.

Immunogenicity

Not applicable.

8.3.5. Analysis of Submission-Specific Safety Issues

Targeted AE data were abstracted during the EHR chart review for Cohort A only of the Flatiron Study. The following 5 safety events of interest were prespecified for assessment based on the known safety profile of palbociclib: fatigue, febrile neutropenia, neutropenia, pulmonary embolism, and stomatitis. Details for these events were abstracted from the EHR if they were explicitly attributed by the physician to palbociclib and occurred after the start date of a palbociclib-based regimen and prior to the July 31, 2017 data cutoff date.

Overall, 11 of the 25 (44%) patients in Cohort A experienced at least 1 of the 5 prespecified AEs of interest. The AEs were neutropenia in 7 patients, fatigue in 5 patients, and stomatitis in 1 patient. One patient experienced both neutropenia and stomatitis. There were no reports of febrile neutropenia or pulmonary embolism.

Reviewer Comment: A targeted safety review was performed during the EHR chart review for Cohort A only. No safety conclusions can be drawn based on this limited AE review. As discussed in Section 8.3.10, data from the more extensive global safety database also revealed no new safety concerns.

8.3.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.3.7. Safety Analyses by Demographic Subgroups

Not applicable.

8.3.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.3.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

Human Reproduction and Pregnancy

Not applicable.

Pediatrics and Assessment of Effects on Growth

The safety and efficacy of palbociclib have not been established in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.3.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Division of Pharmacovigilance II (DPV II) conducted a review of postmarketing reports for palbociclib from the FDA Adverse Event Reporting System (FAERS), the Sponsor's latest Periodic Adverse Drug Experience Report (PADER) with reporting period between November 3, 2017 and February 2, 2018, and the literature.

The FAERS search performed on September 19, 2018 yielded a total of 23,251 reports, including 569 male reports and 21,028 female reports with palbociclib use. The gender was unknown in the remaining 1,654 reports. A majority of the top 20 reported MedRA preferred terms (PTs) for male and female patients receiving palbociclib were similar and consistent with the palbociclib product label.

Review of the latest PADER submitted by the sponsor included a total of 2506 cases, which consisted of 2326 females, 62 males, and the remaining 118 cases did not report a gender. Notably, 205 of the 2506 cases (8.2%) reported fatal events, including 11 males. In the majority of the 205 fatal cases, the cause of death was either attributed to disease progression,

unknown, or not reported. Overall, the sponsor did not identify any new significant safety issues that would alter palbociclib's safety profile.

A literature search retrieved four clinical studies of palbociclib that included both female and male patients for treatment of multiple myeloma, retinoblastoma protein (Rb)-positive germ cell tumors, liposarcoma, and Rb-positive advanced solid tumors, respectively. The most common treatment-related adverse events in these studies were thrombocytopenia, neutropenia, anemia, and fatigue. The trials did not reveal any differences in toxicities observed among male patients compared to female patients receiving palbociclib.

Reviewer Comment: DPVII did not observe any differences in the safety profile of palbociclib use based on the gender based on the review of the FAERS data, the sponsor's latest PADER, and the literature.

8.3.11. **Integrated Assessment of Safety**

Review of two phase 1 studies with single agent palbociclib, the Pfizer global database and postmarketing reports revealed no new safety signals in male breast cancer patients and in general, the AE profile for male patients appears to be consistent with the known AE profile of palbociclib. The known safety profile for palbociclib is acceptable for this patient population with a serious and life-threatening disease.

SUMMARY AND CONCLUSIONS

8.4. **Statistical Issues**

The data from this supplemental application comes from three sources. The first was an update from large clinical study of palbociclib in women with metastatic breast cancer. The second and third sources arrive from electronic health records (Flatiron) and pharmaceuticals claims databases (IQVIA). The second and third sources have several statistical limitations that limits the conclusions that can be made.

For the Flatiron study, the primary limitation is the sample size. Starting with a database of over 2,000 individuals, only a total of 28 men, with 12 taking palbociclib, could be found who met the enrollment criteria. Because this is a very limited sample, and the two analysis cohorts (palbociclib + endocrine therapy and endocrine therapy only) are not well balanced, the only reasonable conclusion to make is that palbociclib appears to have anti-tumor activity in men. While these results provided supportive evidence, the Flatiron study did not provide definitive evidence to conclude that palbociclib adds to the anti-tumor activity of endocrine therapy alone.

The IQVIA study has a larger sample size but has similar limitations. For one, the IQVIA study data does not derive from a randomized study, so we have little information whether the data is confounded or balanced on the baseline covariates. In addition, on a more basic level, it is unclear whether prolonged treatment duration translates to an improvement in more clinically relevant endpoints, such as survival or progression-free survival.

8.5. **Conclusions and Recommendations**

Although some of the data provided with this application have significant limitations, it should be noted that there is a strong mechanistic rationale why palbociclib should have the same effectiveness in men as women. Given the extensive established efficacy and safety of the use of palbociclib in women observed in randomized clinical trials and the additional EHR data provided in this application for the use in men, the reviewers believe the palbociclib indication should be expanded for the treatment of men with metastatic breast cancer in combination

Multi-disciplinary Review and Evaluation
sNDA 207103/008 IBRANCE® (Palbociclib)

with endocrine therapy.

Erik Bloomquist

Primary Statistical Reviewer

Shenghui Tang

Statistical Team Leader

Suparna Wedam

Primary Clinical Reviewer

Lola Fashoyin-Aje

Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for this sNDA.

10 Pediatrics

The safety and efficacy of palbociclib have not been established in pediatric patients.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

This submission proposed revisions to the prescribing information (PI) and patient package insert (PPI) based on real-world evidence (RWE) in male patients with BC, (b) (4) and nonclinical carcinogenicity results. *See Section 1.2 of this review for more information.*

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
Highlights of Labeling		
Indications and Usage	<i>See the revisions in the Full Prescribing information</i>	<i>See the revisions in the Full Prescribing information</i>
Use in Specific Populations	...	FDA added: <ul style="list-style-type: none"> • Males of Reproductive Potential: May impair fertility. (8.3)
Full Prescribing Information		
1. Indications and Usage	(b) (4)	FDA revised to: IBRANCE is indicated for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with: <ul style="list-style-type: none"> • an aromatase inhibitor as initial endocrine based therapy in postmenopausal women and in men; or • fulvestrant in patients with disease progression following endocrine therapy.

<p>2. Dosage and Administration</p>	<p>2.1 Recommended Dose and Schedule</p> <p>...</p> <p>Pre/perimenopausal women (b) (4) treated with the combination IBRANCE plus (b) (4) should also be treated with luteinizing hormone releasing hormone (LHRH) agonists according to current clinical practice standards</p>	<p>(b) (4)</p> <p>FDA revised to: Pre/perimenopausal women treated with the combination IBRANCE plus fulvestrant therapy should also be treated with luteinizing hormone releasing hormone (LHRH) agonists according to current clinical practice standards.</p> <p>For men treated with combination IBRANCE plus aromatase inhibitor, consider treatment with an LHRH agonist according to current clinical practice standards.</p>
<p>6. Adverse Reactions</p>	<p>6.2 Postmarketing Experience <i>(new subsection added by FDA)</i></p>	<p>FDA added: <u>Male patients with HR-positive, HER2-negative advanced or metastatic breast cancer</u></p> <p>Based on limited data from postmarketing reports and electronic health records, the safety profile for men treated with IBRANCE is consistent with the safety profile in women treated with IBRANCE.</p>
<p>8. Use in Specific Populations</p>	<p>8.3 Females and Males of Reproductive Potential</p> <p>...</p>	<p>FDA deleted the new proposed statement: (b) (4)</p>
<p>13. Nonclinical Toxicology</p>	<p>13.1 Carcinogenesis, Mutagenesis, Impairment of</p>	<p>FDA revised to: Palbociclib was assessed for</p>

	<p>Fertility Palbociclib was assessed for carcinogenicity in a 6- month transgenic mouse study and in a 2- year rat study.</p> <p>(b) (4)</p> <p>...</p>	<p>carcinogenicity in a 6-month transgenic mouse study and in a 2-year rat study. Oral administration of palbociclib for 2 years resulted in an increased incidence of microglial cell tumors in the central nervous system of male rats at a dose of 30 mg/kg/day (approximately 8 times the human clinical exposure based on AUC). There were no neoplastic findings in female rats at doses up to 200 mg/kg/day (approximately 5 times the human clinical exposure based on AUC). Oral administration of palbociclib to male and female rasH2 transgenic mice for 6 months did not result in increased incidence of neoplasms at doses up to 60 mg/kg/day.</p>
<p>14. Clinical Studies</p>	<p>(b) (4)</p>	<p>(b) (4) this data was not adequate to provide support of effectiveness in labeling.</p>

	(b) (4)	
17. Patient Counseling Information	... (b) (4)	FDA revised to: Infertility: Inform males of reproductive potential that IBRANCE may cause infertility and to consider sperm preservation before taking IBRANCE [see Use in Specific Populations (8.3)].

11.2. Patient Labeling

FDA revised the Patient Information (PPI) to be consistent with the revisions to the Indications and Usage section and the agreed to the proposed addition of (b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS was recommended for this sNDA.

13 Postmarketing Requirements and Commitment

No postmarketing requirements or commitments were required for this sNDA.

14 Division Director (OB)

Rajeshwari Sridhara, Ph.D.

15 Division Director (Clinical) (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Laleh Amiri-Kordestani
Supervisory Associate Director
Division of Oncology Products 1

16 Appendices

16.1. References

Cancer Facts and Figures 2019. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf>

NCCN guidelines. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

UpToDate. <https://www.uptodate.com/contents/breast-cancer-in-men>.
Chavez-MacGregor M, Clarke CA, Lichtensztajn D, et al. Male breast cancer according to tumor subtype and race: a population-based study. *Cancer* 2013; 119(9):1611-7.

Giordano SH, Cohen DS, Buzdar AU, et al. Breast carcinoma in men: a population-based study. *Cancer* 2004; 101(1):51-7.

Khan MH, Allerton R, Pettit L. Hormone therapy for breast cancer in men. *Clinical Breast Cancer* 2015; 15(4):245-50.

Losurdo A, Rota S, Gullo G, et al. Controversies in clinicopathological characteristics and treatment strategies of male breast cancer: a review of the literature. *Crit Rev Oncol Hemat* 2017; 113:283-91.

16.2. Financial Disclosure

Not applicable for this supplement

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (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 <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

16.3. Nonclinical Pharmacology/Toxicology

Observations and results of 2-year rat carcinogenicity study/ Study 20066483

Parameters	Major findings
Mortality	no PD-0332991-related increase of mortality
Clinical Signs	An increased incidence of ocular opacities in males administered ≥ 3 mg/kg/day and pale eyes in males administered ≥ 10 mg/kg/day. Most of the ocular opacities appeared between Days 442 to 694, were noted macroscopically and corresponded microscopically with degeneration of the lens in most animals.
Body Weights	Lower mean body weight gain beginning approximately Week 6 was observed in males administered ≥ 3 mg/kg/day and females administered 200 mg/kg/day compared with the control group. The lower body weight gain led to overall mean absolute body weights in males administered 3, 10, and 30 mg/kg/day at 0.96x, 0.96x, and 0.86x of the controls on Day 680, respectively, and overall mean absolute body weights in females administered 200 mg/kg/day at 0.91x that of the controls on Day 652.
Food Consumption	Unremarkable
Ophthalmoscopy	Unremarkable
Gross Pathology	Opacity in the eyes and discoloration in the adrenal
Histopathology	<i>Neoplastic</i>

<p>Adequate battery: Yes</p>	<p><u>Incidence of tumor findings</u> Incidence of Microglial Cell Tumors (Malignant)</p> <table border="1" data-bbox="407 302 1459 617"> <thead> <tr> <th>Sex</th> <th colspan="4">Male</th> <th colspan="4">Female</th> </tr> <tr> <th>Dose (mg/kg/day)</th> <th>0</th> <th>3</th> <th>10</th> <th>30</th> <th>0</th> <th>25</th> <th>75</th> <th>200</th> </tr> </thead> <tbody> <tr> <td>Number of animals</td> <td>70</td> <td>70</td> <td>70</td> <td>70</td> <td>70</td> <td>70</td> <td>70</td> <td>70</td> </tr> <tr> <td>Microglial cell tumors (brain)</td> <td>0</td> <td>1</td> <td>2</td> <td>5</td> <td>0</td> <td>0</td> <td>0</td> <td>1</td> </tr> <tr> <td>Microglial cell tumors (spinal cord)</td> <td>0</td> <td>0</td> <td>0</td> <td>1</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Microglial cell tumors (CNS)</td> <td>0</td> <td>1</td> <td>2</td> <td>6</td> <td>0</td> <td>0</td> <td>0</td> <td>1</td> </tr> <tr> <td>Microglial cell tumors (CNS %)</td> <td>0%</td> <td>1.4%</td> <td>2.9%</td> <td>8.6%</td> <td>0%</td> <td>0%</td> <td>0%</td> <td>1.4%</td> </tr> <tr> <td>Location with a blood-CNS barrier</td> <td>NA</td> <td>1/1</td> <td>1/2</td> <td>6/6</td> <td>NA</td> <td>NA</td> <td>NA</td> <td>1/1</td> </tr> </tbody> </table> <p><i>Non-Neoplastic</i> The target organs/tissues were bone marrow, spleen, pancreas, eye, kidney, adrenal cortex and lymph nodes. The treatment related effects were similar to the findings from the general toxicity studies.</p>	Sex	Male				Female				Dose (mg/kg/day)	0	3	10	30	0	25	75	200	Number of animals	70	70	70	70	70	70	70	70	Microglial cell tumors (brain)	0	1	2	5	0	0	0	1	Microglial cell tumors (spinal cord)	0	0	0	1	0	0	0	0	Microglial cell tumors (CNS)	0	1	2	6	0	0	0	1	Microglial cell tumors (CNS %)	0%	1.4%	2.9%	8.6%	0%	0%	0%	1.4%	Location with a blood-CNS barrier	NA	1/1	1/2	6/6	NA	NA	NA	1/1													
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Location with a blood-CNS barrier	NA	1/1	1/2	6/6	NA	NA	NA	1/1																																																																														
<p>Toxicokinetics</p>	<p>Summary Mean PD-0332991 Toxicokinetic Parameters in Male Rat Plasma Following Oral Administration of PD-0332991 on Day 1 and Day 189</p> <table border="1" data-bbox="407 884 1505 1665"> <thead> <tr> <th>Sex</th> <th>Dose mg/kg</th> <th>Study day</th> <th>C_{max} (ng/mL)</th> <th>Dose Normalized C_{max}</th> <th>AUC_{0-24h} ng.h/mL</th> <th>Dose Normalized AUC₀₋₂₄</th> </tr> </thead> <tbody> <tr> <td rowspan="6">Male</td> <td rowspan="2">3</td> <td>1</td> <td>49.6</td> <td>17</td> <td>370</td> <td>123</td> </tr> <tr> <td>189</td> <td>133</td> <td>44</td> <td>1070</td> <td>357</td> </tr> <tr> <td rowspan="2">10</td> <td>1</td> <td>386</td> <td>39</td> <td>3840</td> <td>384</td> </tr> <tr> <td>189</td> <td>546</td> <td>55</td> <td>5400</td> <td>540</td> </tr> <tr> <td rowspan="2">30</td> <td>1</td> <td>1030</td> <td>34</td> <td>14100</td> <td>470</td> </tr> <tr> <td>189</td> <td>1250</td> <td>42</td> <td>14900</td> <td>497</td> </tr> <tr> <td rowspan="9">Female</td> <td rowspan="3">25</td> <td>1</td> <td>148</td> <td>6</td> <td>789</td> <td>32</td> </tr> <tr> <td>189</td> <td>309</td> <td>12</td> <td>1360</td> <td>54</td> </tr> <tr> <td>244</td> <td>291</td> <td>12</td> <td>1410</td> <td>56</td> </tr> <tr> <td rowspan="2">75</td> <td>1</td> <td>418</td> <td>6</td> <td>3000</td> <td>40</td> </tr> <tr> <td>244</td> <td>660</td> <td>9</td> <td>4810</td> <td>64</td> </tr> <tr> <td rowspan="3">200</td> <td>1</td> <td>475</td> <td>2</td> <td>5280</td> <td>26</td> </tr> <tr> <td>189</td> <td>1240</td> <td>6</td> <td>11000</td> <td>55</td> </tr> <tr> <td>244</td> <td>1040</td> <td>5</td> <td>8980</td> <td>45</td> </tr> </tbody> </table> <p>Conclusion:</p> <ul style="list-style-type: none"> • C_{max} and AUC generally increased in a dose-dependent manner in males and females; • There was accumulation (less than 3-folds) with repeated doses; • Systemic exposures in males were generally greater than that in females. 	Sex	Dose mg/kg	Study day	C _{max} (ng/mL)	Dose Normalized C _{max}	AUC _{0-24h} ng.h/mL	Dose Normalized AUC ₀₋₂₄	Male	3	1	49.6	17	370	123	189	133	44	1070	357	10	1	386	39	3840	384	189	546	55	5400	540	30	1	1030	34	14100	470	189	1250	42	14900	497	Female	25	1	148	6	789	32	189	309	12	1360	54	244	291	12	1410	56	75	1	418	6	3000	40	244	660	9	4810	64	200	1	475	2	5280	26	189	1240	6	11000	55	244	1040	5	8980	45
Sex	Dose mg/kg	Study day	C _{max} (ng/mL)	Dose Normalized C _{max}	AUC _{0-24h} ng.h/mL	Dose Normalized AUC ₀₋₂₄																																																																																
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		244	1040	5	8980	45																																																																																

16.4. OCP Appendices (Technical documents supporting OCP recommendations)

Not applicable.

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/s/

AMY R TILLEY
04/03/2019 02:23:44 PM

WEI CHEN
04/03/2019 02:25:27 PM

TIFFANY RICKS
04/03/2019 02:27:34 PM

ERIK W BLOOMQUIST
04/03/2019 02:29:27 PM

SHENGHUI TANG
04/03/2019 02:37:35 PM

SUPARNA B WEDAM
04/03/2019 02:44:51 PM

IBILOLA A FASHOYIN-AJE
04/03/2019 02:46:37 PM

RAJESHWARI SRIDHARA
04/03/2019 02:49:18 PM

LALEH AMIRI KORDESTANI
04/03/2019 02:50:30 PM

Cross-Discipline Team Leader Memorandum
 Division of Oncology Products 1
 Office of Hematology and Oncology Products

Date	March 28, 2019
From	Lola Fashoyin-Aje, MD, MPH
NDA #	207103 s-008
Applicant	Pfizer, Inc.
Date of Submission	June 15, 2018
PDUFA Goal Date	April 15, 2019
Trade Name / Established Name	Ibrance/palbociclib
Dosing Regimen	125 mg once daily taken with food for 21 days followed by 7 days off treatment.
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommended Regulatory Action	<i>Approval</i>

The cross-discipline team leader review (CDTL) is complete and has been added to the NDA/BLA Multidisciplinary Review and Evaluation document. I agree with the review team’s recommendation to approve the Applicant’s request with the following modification to the proposed indication statement:

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

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

My recommendation for this application is based upon FDA’s previous findings a favorable benefit:risk assessment for palbociclib in combination with an aromatase inhibitor in postmenopausal women, and for palbociclib in combination with fulvestrant in women with disease progression following endocrine therapy, and supported by real-world data that characterizes the use of palbociclib in male patients with breast cancer. Refer to the NDA/BLA Multidisciplinary Review and Evaluation document for details.

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/s/

IBILOLA A FASHOYIN-AJE
03/29/2019 02:16:56 AM

**Clinical Review Memorandum
Division of Oncology Products 1
Office of Hematology and Oncology Products**

Application Type	sNDA
Application Number(s)	207103-S-008
Priority or Standard	Standard
Submit Date(s)	June 15, 2018
Received Date(s)	June 15, 2018
PDUFA Goal Date	April 15, 2019
Division/Office	DOP1
Established Name	Palbociclib
(Proposed) Trade Name	IBRANCE®
Pharmacologic Class	Cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor
Code name	N/A
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
Recommendation on Regulatory Action	<i>Regular Approval</i>

The clinical review of safety and efficacy is complete and has been included in the NDA Multidisciplinary Review and Evaluation document. See unireview for full clinical review.

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/s/

SUPARNA B WEDAM
03/27/2019 08:09:56 PM

IBILOLA A FASHOYIN-AJE
03/27/2019 08:14:18 PM

**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-08
Supporting document/s: 1
Applicant's letter date: June 15, 2018
CDER stamp date: June 15, 2018
Product: Ibrance (palbociclib)
Indication:  (b) (4)
Applicant: Pfizer Inc.
Review Division: Division of Hematology Oncology Toxicology
(for Division of Oncology Products 1)
Reviewer: Wei Chen, PhD
Supervisor/Team Leader: Tiffany Ricks, PhD
Division Director: John Leighton, PhD, DABT
(Julia Beaver, MD)
Project Manager: Amy Tilley

Comments and recommendations

The primary nonclinical Pharmacology/Toxicology review is complete and has been added to the Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-Disciplinary Review and Evaluation for additional details. My recommendation for this application is approval.

The secondary nonclinical Pharmacology/Toxicology review is complete and has been added to the Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-Disciplinary Review and Evaluation for additional details. My recommendation for this application is approval.

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/s/

WEI CHEN
03/01/2019 01:59:14 PM

TIFFANY RICKS
03/01/2019 03:03:29 PM

**CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT
AND
FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET**

P/T REVIEWER(s): Wei Chen, Ph.D.
SUPERVISOR/TL: Tiffany Ricks, Ph.D. (acting)
DATE: November 30, 2018
NDA: 207103 (IND 69324)
DRUG CODE#: PD-0332991
CAS#: 571190-30-2
DIVISION(s): Division of Hematology Oncology Toxicology
(for Division of Oncology Products 1)
DRUG NAME(s): Ibrance (palbociclib)
SPONSOR: Pfizer Inc.
LABORATORY: (b) (4)

THERAPEUTIC CATEGORY: Breast cancer

PHARMACOLOGICAL/CHEMICAL CLASSIFICATION:
Kinase inhibitor (Mechanism of action: an inhibitor of CDK 4/6)

MUTAGENIC/GENOTOXIC: yes, reviewed under NDA 207103

Palbociclib was not mutagenic in the Ames bacterial mutagenicity assay in the presence or absence of metabolic activation. Palbociclib did not induce structural or numerical chromosome aberrations in cultured human peripheral blood lymphocytes in the presence or absence of metabolic activation. Palbociclib caused micronuclei formation due to an aneugenic mechanism in CHO-WBL cells. In an in vivo rat micronucleus assay, oral daily administration of palbociclib for 21 days induced micronuclei formation in male rats at doses ≥ 100 mg/kg/day (greater than 10 times the human exposure at the therapeutic dose) but did not induce micronucleus formation in female rats at doses up to 400 mg/kg (part of 3-week toxicology study in rats). In conclusion, palbociclib is an aneugen.

MOUSE CARCINOGENICITY STUDY:**Study title: A 6-Month Oral Carcinogenicity Study of PD-0332991 in CByB6F1/Tg rasH2 Hemizygous Mice**

Study no.: 20066483
 Study report location: SDN 780, June 15, 2018
 Conducting laboratory and location: (b) (4)
 Date of study initiation: January 5, 2016
 GLP compliance: yes
 QA statement: yes
 Drug, lot #, and % purity: PD-0332991
 Batch (Lot): GR08497/E010014768
 Purity: 100.7%
 CAC concurrence: Yes (eCAC, October 27, 2015)

Key Study Findings**Non- Neoplastic Findings**

- No treatment-related mortalities or severe adverse effects were observed in mice administered PD-0332991 at doses up to 60 mg/kg.

Neoplastic Finding

Administration of PD-0332991 by once daily oral gavage at doses up to 60 mg/kg/day was not carcinogenic in CByB6F1/Tg rasH2 hemizygous mice. NOAEL was 60 mg/kg (HD) in mice, corresponding with a male and female combined C_{max} of 1840 ng/mL and an AUC_{24} of 20500 ng·h/mL in Week 26.

Adequacy of Carcinogenicity Study: yes

Appropriateness of Test Models: yes

The carcinogenicity protocol was submitted to the agency under IND 69324 and reviewed previously (November 5, 2015). The sponsor proposed to administer (b) (4) mg/kg/day of palbociclib to male and female mice. Control groups will be administered the 0.5% [w/v] methylcellulose [4000 cps] vehicle. The sponsor's proposed high dose of (b) (4) mg/kg/day for males and females was based on the results of a GLP 1-month repeat-dose toxicology study in non-transgenic littermates of CByB6F1/Tg rasH2 mice. The Executive Carcinogenicity Assessment Committee (eCAC) recommended the doses of 0 (0.5% [w/v] methylcellulose [4000 cps]), 6, 20, and 60 mg/kg/day of palbociclib by oral gavage in males and females. The high dose was based on decreased white blood cell counts and lower spleen, thymus and testis weights at 100 mg/kg/day in the GLP 1-month study in non-transgenic littermates of CByB6F1/Tg rasH2 mice. The dose spacing for mid and low doses was based on the AUC values. The study was initiated with the eCAC recommended doses. The plasma exposure (AUC) in cancer patients following continuous daily oral administration of

palbociclib with the recommended therapeutic dose of 125 mg was 1863 ng•h/mL. PD-0332991 AUC at 6, 20, and 60 mg/kg in CByB6F1/Tg rasH2 mice were 0.6x, 2.9x and 8.0x the exposures at the clinical recommended dose (AUC), and PD-0332991 AUC at 25, 75, and 200 mg/kg in female rats were 0.6x, 3 and 11x the exposure at the recommended clinical dose.

In conclusion, the test model was appropriate. The doses were selected based on agreement with the FDA Executive Carcinogenicity Assessment Committee (October 27, 2015). Animal survival was sufficient for an adequate assessment of tumorigenic potential.

Methods

Doses:	0 (vehicle), 6, 20, or 60 mg/kg/day
Frequency of dosing:	Daily, 28 days/cycle
Dose volume:	10 mL/kg
Route of administration:	oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose 4000 cps in reverse osmosis deionized (RODI) water
Basis of dose selection:	The high dose was based on decreased white blood cell counts and lower spleen, thymus and testis weights at 100 mg/kg/day in the GLP 1-month study in non-transgenic littermates of CByB6F1/Tg rasH2 mice. The dose spacing for mid and low doses was based on the AUC values..
Species/Strain:	CByB6F1-Tg(HRAS)2Jic Hemizygous mice
Number/Sex/Group:	25/sex/group
Age:	10 weeks old
Animal housing:	Individual
Dual control employed:	no
Interim sacrifice:	no
Satellite groups:	TK, 18/sex/group for LD, MD, HD, 9/sex for control Positive control (N-nitrosomethylurea, NMU), 15/sex
Deviation from study protocol:	none

Experimental Design

Group No.	Test Material	Dose Route	Dose (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Carcinogenicity Groups	
						Males (Tg)	Females (Tg)
1	Control Article	Oral	0	10	0	25	25
2	PD-0332991	Oral	6	10	0.6	25	25
3	PD-0332991	Oral	20	10	2	25	25
4	PD-0332991	Oral	60	10	6	25	25
5	Positive Control NMU ^a	Intraperitoneal Injection	75 ^a	10	7.5	15	15

Control Article = 0.5% methylcellulose; Tg = Transgenic.

^a NMU (N-nitrosomethylurea) dose only administered once on Day 1.

(Copied from the Applicant's submission)

Observations and Results

Mortality: once daily

No PD-0332991-related mortality

Clinical Signs: at least once weekly

Unremarkable

Body Weights: at least once weekly

Unremarkable

Food Consumption: weekly

Unremarkable

Clinical Pathology: Two blood smears were prepared from each hematology sample.

Slides were retained but not evaluated.

Gross Pathology: all animals at unscheduled sacrifices or on scheduled euthanasia day in Week 27

Unremarkable

Histopathology: all animals at unscheduled sacrifices or on scheduled euthanasia day in Week 27

Peer Review

Yes, a pathology peer review was conducted by a Sponsor pathologist.

Neoplastic

There were no PD-0332991-related neoplastic microscopic findings.

Note: NMU-administered positive control mice exhibited expected microscopic neoplastic findings that included malignant lymphoma ($\geq 8/15$ males, $\geq 12/15$ females); squamous cell papillomas in the skin and/or stomach (at least 1 of these tissues affected in $\geq 9/15$ males and $\geq 10/15$ females); and squamous cell carcinomas in the skin, stomach, and/or uterus (at least 1 of these tissues affected in $\geq 6/15$ males and $\geq 3/15$ females).

Non Neoplastic

Table 1 Incidence and Severity of Test Article-Related Non-Neoplastic Findings in Hematopoietic Tissues

Sex	Male				Female			
Dose (mg/kg/day)	0	6	20	60	0	6	20	60
Number of animals	25	25	25	25	25	25	25	24
Bone Marrow								
Pigmented macrophage	7	18		4	21	19	21	18
-Minimal			20	20		2	1	4
-Mild								
Liver								
Increased mitoses, hepatocellular			2	4	1	1	4	7
-Minimal			1	1				1
-Mild								

Blank: no related findings

Toxicokinetics

Sample Collection Time Points: 1, 2, 4, 7, 12, 24 hours postdose in week 26.

Note: The exposure (C_{max} and AUC_{24}) was similar between males and females; therefore, a TK assessment for sex-combined TK parameters was shown in the table below.

Table 2 Sex-Combined Mean Toxicokinetic Parameters for PD-0332991 in CByB6F1 Hybrid Mouse Plasma on Week 26

Dose mg/kg	Week	C_{max} (ng/mL)	Dose Normalized C_{max}	AUC_{0-24h} ng.h/mL	Dose Normalized AUC_{0-24}	T_{max} (hour)
6	26	177	30	1180	196	2
20		887	44	5720	286	2
60		1840	31	20500	342	2

Conclusion:

- C_{max} increased in dose-proportional manner;
- AUC increased with increasing dose in a slightly greater than dose-proportional manner;
- T_{max} was at 2 hours postdose for all dose groups on Week 26.

Dosing Solution Analysis

The Sponsor has the following statement in the submission:

- All study samples analyzed had mean concentrations within or equal to the acceptance criteria of $\pm 15\%$ (individual values within or equal to $\pm 20\%$) of their theoretical concentrations.
- For homogeneity, the relative standard deviation of concentrations for all samples in each group tested was within the acceptance criteria of $\leq 5\%$.

RAT CARCINOGENICITY STUDY:**Study title: A 2-year Carcinogenicity Study of PD-0332991 by Oral Gavage in Rats**

Study no.: 20066483
Study report location: SDN 780, June 15, 2018
Conducting laboratory and location:  (b) (4)
Date of study initiation: January 6, 2015
GLP compliance: yes
QA statement: yes
Drug, lot #, and % purity: PD-0332991
Batch (Lot) Nos.: GR08497/E010014768
GR09593/E010015337
Purity: 100.7% (E010014768)
99.7% (E010015337)
CAC concurrence: Yes (Exec. CAC meeting of 11/18/2014)

Key Study Findings

Non- Neoplastic Findings

- There was no PD-0332991-related increase in mortality compared with control.
- PD-0332991-related mean lower body weight gain beginning approximately Week 6 was observed in males administered ≥ 3 mg/kg/day and females administered 200 mg/kg/day.
- Treatment-related toxicities involved the eyes (degeneration in lens), pancreas (decreased Islet cells), spleen and bone marrow (hematopoiesis), kidney (tubular vacuolar changes and chronic progressive nephropathy), and adrenal glands (atrophy and vacuolar degeneration).

Neoplastic Finding

- The higher incidence of microglial cell tumors in brain combined with spinal cord was statistically significant in males at the high dose (30 mg/kg/day) when compared with the vehicle control group (p-value = 0.0273 for pairwise comparison).
- Statistically significant dose response relationships were noted in male rats for the incidence of microglial cell tumors in brain and brain combined with spinal cord (p-value = 0.0110, and 0.0039, respectively).
- The no-observed-adverse-effect level (NOAEL) for neoplastic findings in males and females was 10 mg/kg/day and 200 mg/kg/day (HD), respectively.
- The NOAEL for neoplastic findings in males at 10 mg/kg/day and females at 200 mg/kg/day corresponded with an overall PD-0332991 C_{max} of 546 ng/mL and 1240 ng/mL and an AUC_{0-24} of 5400 ng•h/mL and 8980 hr•ng/mL, respectively.

Maximum Clinical Exposure:

The AUCs at NOAEL in male and female rats for neoplastic findings were about 3 and 5 folds of human exposure at the recommended dose, respectively. The calculation was based on the AUC of 1863 ng•h/mL in human at the recommended daily dose of 125 mg.

Adequacy of Carcinogenicity Study: yes

Appropriateness of Test Models: yes

The carcinogenicity protocol was submitted to the agency under IND 69324 and previously reviewed(November 20, 2014). The sponsor had proposed to use 0, 3, 10 and 30 mg/kg/d for male rats and 0, (b) (4) mg/kg for female rats with one vehicle group. The dose selection by the sponsor was based on MTD achieved in the 27-week dose ranging study (Male: 10, 30, 100 mg/kg; female: 50, 100, 300 mg/kg).

The Executive Carcinogenicity Assessment Committee (eCAC) concurred with the sponsor's proposed doses of 0, 3, 10, and 30 mg/kg/day in males and recommended doses of 0, 25, 75, and 200 mg/kg/day in females, by oral gavage, based on mortality at 100 mg/kg/day in males and on body weight decrements at higher doses in females. The study was initiated with the eCAC recommended doses. Based on the Sponsor's communications with eCAC, the Group 1 females reached 20 animals due to age-related mortality as of Week 94, Day 652, and all remaining females within the study (Groups 1, 2, 3, and 4) were terminated as soon as practical beginning on Day 653 (Week 94 through Week 95). Similarly, Group 1 males reached 20 animals due to age-related mortality as of Week 98, Day 686, and all remaining males within the study were also terminated as soon as practical beginning on Day 687 (Week 99 through Week 100). The plasma exposure (AUC) in patients with cancer following continuous daily oral administration of palbociclib with the recommended therapeutic dose of 125 mg was 1863 ng•h/mL. PD-0332991 AUC at 3, 10, and 30 mg/kg in male rats were 0.6x, 2.9x and 8.0x the exposures at the clinical recommended dose (AUC), and PD-0332991 AUC at 25, 75, and 200 mg/kg in female rats were 0.8x, 2.6 and 4.8x the exposure at the recommended clinical dose.

In conclusion, the test model was appropriate. The doses were selected based on agreement with the FDA Executive Carcinogenicity Assessment Committee (11/18/2014). An MTD was reached based on decreased body weight and weight gain at HD. Animal survival was sufficient for an adequate assessment of tumorigenic potential.

Evaluation of Tumor Findings

Methods

Doses: Male: 0 (vehicle), 3, 10, or 30 mg/kg/day
 Female: 0 (vehicle), 25, 75, or 200 mg/kg/day

Frequency of dosing: Daily x21, 28 days/cycle

Dose volume: 10 mL/kg

Route of administration: oral gavage

Formulation/Vehicle: 0.5% (w/v) methylcellulose 4000 cps in reverse osmosis deionized (RODI) water

Basis of dose selection: The basis for the dose selection is the maximum tolerated dose, based on the mortality, treatment-related toxicities, and on body weight decrement observed in the 13-week and 27-week studies

Species/Strain: Sprague Dawley Crl:CD(SD) rats

Number/Sex/Group: 70/sex/group

Age: 7 weeks old

Animal housing: Individual

Dual control employed: no

Interim sacrifice: The Group 1 females reached 20 animals due to age-related mortality as of Week 94, Day 652, and all remaining females within the study (Groups 1, 2, 3, and 4) were terminated as soon as practical beginning on Day 653 (Week 94 through Week 95). Similarly, Group 1 males reached 20 animals due to age-related mortality as of Week 98, Day 686, and all remaining males within the study were also terminated as soon as practical beginning on Day 687 (Week 99 through Week 100).

Satellite groups: TK, 5/sex/group for LD, MD, HD, 4/sex for control

Deviation from study protocol: none

Experimental Design – Males

Group No.	Test Material	Dose (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Male Animals	
					Carcinogenicity Groups	Toxicokinetic Groups
1	0.5% Methylcellulose	0	10	0	70	4
2	PD-0332991	3	10	0.3	70	5
3	PD-0332991	10	10	1	70	5
4	PD-0332991	30	10	3	70	5

(copied from the Applicant's submission)

Experimental Design – Females

Group No.	Test Material	Dose (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Female Animals	
					Carcinogenicity Groups	Toxicokinetic Groups
1	0.5% Methylcellulose	0	10	0	70	4
2	PD-0332991	25	10	2.5	70	5
3	PD-0332991	75	10	7.5	70	5
4	PD-0332991	200	10	20	70	5

(Copied from the Applicant's submission)

Observations and Results

Mortality: twice daily

There was no PD-0332991-related increase in mortality in this study compared with control.

Due to reduce survival in the control group (decreased to 20 before Week 100) males and females, scheduled euthanasia in Groups 1 to 4 began on Day 687 (Week 99) for males and on Day 653 (Week 94) for females. Exec CAC concurrence was obtained prior to early termination of study groups.

Clinical Signs: at least once weekly

PD-0332991-related clinical findings were limited to an increased incidence of ocular opacities in males administered ≥ 3 mg/kg/day, pale eyes in males administered ≥ 10 mg/kg/day, and dry feces in males administered ≥ 3 mg/kg/day compared with the controls. Most of the ocular opacities appeared between Days 442 to 694, were noted macroscopically and corresponded microscopically with degeneration of the lens in most animals (e.g., microscopic degeneration of the lens consistent with "cataractous" change correlated with 16 of 18 ocular opacities observed clinically in males).

Body Weights: weekly for the first 26 weeks, and at least once every 4 weeks thereafter

PD-0332991-related mean lower body weight gain beginning approximately Week 6 was observed in males administered ≥ 3 mg/kg/day and females administered 200 mg/kg/day compared with the control group. The lower body weight gain led to overall mean absolute body weights in males administered 3, 10, and 30 mg/kg/day at 0.96x, 0.96x, and 0.86x of the controls on Day 680, respectively, and overall mean absolute body weights in females administered 200 mg/kg/day at 0.91x that of the controls on Day 652.

Food Consumption: weekly for the first 26 weeks, and once (for 1 week) every 4 weeks thereafter

Unremarkable

Ophthalmology Examinations: were performed prior to in-life initiation (Day -7) and during Week 52 (Day 364).

No test article-related differences noted in animals administered PD-0332991 compared with the control group during the Week 52 assessment.

Gross Pathology: all animals at unscheduled sacrifices or on the day of scheduled euthanasia (Week 99 to 100 for males, Week 94 to 95 for females)

Table 3 Macroscopic Pathology Observations in rats
(unscheduled or scheduled combined)

Sex	Male				Female			
Dose (mg/kg/day)	0	3	10	30	0	25	75	200
Number of animals	70	70	70	70	70	70	70	70
Eye								
Protrusion			1					
Opacity	1	2	3	6				
Focus; pale							1	
Gland, adrenal								
Enlargement	2	1	1	1	7	8	8	1
Discoloration								1
Discoloration; dark	1	1	2	1	2	3	3	3
Discoloration; mottled	1	1			3	5	2	3
Discoloration; pale					1	1		
Focus; dark		4	3	2	6	9	11	18
Focus; pale	1	4	3	2	2	10	7	14
Focus; raised			1			1	1	
Mass			1			2	1	1
Small		1		1	2	1	1	

Blank: no related findings

Histopathology: all animals at unscheduled sacrifices or on the day of scheduled euthanasia (Week 99 to 100 for males, Week 94 to 95 for females)

Peer Review: A pathology peer review, including selected microscopic findings, was conducted by the Sponsor's pathologist. The peer review consisted of an examination of all tissues from 10% of the animals randomly selected from the control and high dose groups and all proliferative lesions (neoplastic and non-neoplastic) from all animals in all groups.

Neoplastic

Incidence of tumor findings

Table 4 Incidence of Microglial Cell Tumors (Malignant)

Sex	Male				Female			
Dose (mg/kg/day)	0	3	10	30	0	25	75	200
Number of animals	70	70	70	70	70	70	70	70
Microglial cell tumors (brain)	0	1	2	5	0	0	0	1
Microglial cell tumors (spinal cord)	0	0	0	1	0	0	0	0
Microglial cell tumors (CNS)	0	1	2	6	0	0	0	1
Microglial cell tumors (CNS %)	0%	1.4%	2.9%	8.6%	0%	0%	0%	1.4%
Location with a blood-CNS barrier	NA	1/1	1/2	6/6	NA	NA	NA	1/1

Note: The Statistical review team at FDA agreed with the Applicant's tumor data analysis and concluded that the incidence of microglial cell tumors in brain and brain combined with spinal cord in male rats had statistically significant dose response relationships (p-value = 0.0110, and 0.0039, respectively) if this tumor was considered to be rare. The increased incidence of microglial cell tumors in brain combined with

spinal cord in male rats was statistically significant in the high dose when compared with the vehicle control group (p -value = 0.0273) regardless the tumor classification (rare or common).

Location of the tumor findings

Microglial cell tumors originated in various locations of the CNS including the basal ganglia (striatum), midbrain, hypothalamus, hippocampus, amygdala, brain stem, and spinal cord, and they often infiltrated adjacent brain structures, especially the cortex. Overall, 9/10 microglial cell tumors were located in areas considered to be protected by the blood-CNS barrier.

Immunohistochemistry

- 1) The definitive diagnosis of malignant microglial cell tumor, as opposed to other CNS tumors with similar morphology, was confirmed by immunohistochemical (IHC) staining procedures.
- 2) IHC staining demonstrated that all tumors suspected to be of microglial cell origin stained strongly positive with Iba-1 (a microglial cell marker), and stains for astrocytic cells (GFAP) and oligodendroglial cells (Olig-2) were negative. It was stated in the study report that IHC procedures strongly indicated that all microglial cell tumors were derived from cells of monocyte/macrophage lineage and not from the cells originating in the neuroectoderm.

Conclusion: There was a test article-related increase in the incidence of malignant microglial cell tumors in the central nervous system of males administered 30 mg/kg/day, which was characterized by a statistically significant increasing trend in the incidence of microglial cell tumor in the brain/spinal cord organ combination for males

Discussion: The pathogenesis of microglial cell tumors in CNS is unknown. A direct carcinogenic effect of the test article on the microglia is unclear, given that 1) PD-332991 was reported to have poor CNS penetration; 2) No test article-related neoplasia of similar cell populations was noted outside the CNS where exposures were presumably substantially greater; 3) the absence of genotoxic potential of the test article at the expected concentrations. Microglial cell tumors are extremely rare in humans.

Non Neoplastic

Table 5 Incidence and Severity of Test Article-Related Non-Neoplastic Findings

Sex	Male				Female			
	0	3	10	30	0	25	75	200
Dose (mg/kg/day)								
Number of animals	70	70	68	70	70	70	70	70
Bone Marrow								
Increased megakaryocytes -Minimal	3	1	2	25	5	2	4	22
Spleen								
Increased hematopoiesis -Minimal	5	4	15	17	14	12	8	19
-Mild	2	3	4	11	3	2	3	7
-Moderate		1	3	1		5	5	3
-Marked	2				4	2	4	2
-Severe					1			
Pancreas								
Decreased Islet cells -Minimal		2	1	7	12	10	11	

Sex	Male				Female			
Dose (mg/kg/day)	0	3	10	30	0	25	75	200
Number of animals	70	70	68	70	70	70	70	70
Eye	-Mild	1	1	8	2	4	3	
	-Moderate	2	2	4	1	1	2	
	-Marked		3	3			2	
Eye Degeneration, lens; bilateral	-Minimal		1					
	-Mild			4				
	-Moderate	2	3	6				
	-Marked		2	7				
	-Severe		1					
Kidney Vacuolar Change, tubular-Minimal	-Mild		4	3				
	-Moderate			1				
	-Marked							
	-Severe							
	Chronic progressive nephropathy							
Kidney Chronic progressive nephropathy	-Minimal	27	28	21	17			11
	-Mild	8	10	13	21			3
	-Moderate		2	12	11			1
	-Marked		3		1			
	-Severe	1			2			
Adrenal Cortex Atrophy bilateral	-Minimal	6	5	3	7			
	-Mild	3	1	2	11	6	2	
Adrenal Cortex Vacuolar degeneration	-Minimal	11		3	2			
	-Mild	9	11	1		2	3	1
	-Moderate		3			1	1	2
	-Marked					1		1
Adrenal Cortex Hematocyst	-Minimal	1	1		3	8	6	8
	-Mild	2	5	1	3	12	15	18
	-Moderate		1		1	19	13	26
	-Marked	1		1		3	11	6
Mesenteric lymph node Pigmentation	-Minimal	44	3	41	41	54	54	27
	-Mild	6		3	9	1	4	30
	-Moderate				1		1	9
Mesenteric lymph node Histiocytic Infiltration	-Minimal			4			1	7
	-Mild		1	2	5		1	3
Blank: no related findings								

Toxicokinetics

TK sample collection schedule-satellite TK animals

Group No.	Subgroup	No. of Males/ Females	Sample Collection Time Points (Time Postdose) on Days 1 and 189					
			1 hr	2 hr	4 hr	7 hr	12 hr	24 hr
1	A	3/3	X	X	X	-	-	-
	B ^a	1/1	-	-	-	-	-	-
2	A	4/4	X	X	X	X	X	X
	B ^a	1/1	-	-	-	-	-	-
3	A	4/4	X	X	X	X	X	X
	B ^a	1/1	-	-	-	-	-	-
4	A	4/4	X	X	X	X	X	X
	B ^a	1/1	-	-	-	-	-	-

X = sample collected; - = not applicable.

^a Animals in Subgroup B were dosed; however, blood was not collected from these animals.

(copied from the Applicant's submission)

Table 6 Summary Mean PD-0332991 Toxicokinetic Parameters in Male Rat Plasma Following Oral Administration of PD-0332991 on Day 1 and Day 189

Sex	Dose mg/kg	Study day	C _{max} (ng/mL)	Dose Normalized C _{max}	AUC _{0-24h} ng.h/mL	Dose Normalized AUC ₀₋₂₄
Male	3	1	49.6	17	370	123
		189	133	44	1070	357
	10	1	386	39	3840	384
		189	546	55	5400	540
	30	1	1030	34	14100	470
		189	1250	42	14900	497
Female	25	1	148	6	789	32
		189	309	12	1360	54
		244	291	12	1410	56
	75	1	418	6	3000	40
		189*	22.6	0.3	172	2
		244	660	9	4810	64
	200	1	475	2	5280	26
		189	1240	6	11000	55
		244	1040	5	8980	45

*Relatively low PD-0332991 concentrations were observed in all females of the 75 mg/kg/day group on Day 189. An investigation was performed but no cause for the low concentrations was found. The Sponsor stated that the exposure evaluated for the females on Day 189 for the 75 mg/kg/day group was aberrant, and the exposure on Day 244 was a more accurate evaluation of the exposure after repeated dosing at 75 mg/kg/day in female rats.

Conclusion:

- C_{max} and AUC generally increased in a dose-dependent manner in males and females;
- There was accumulation (less than 3-fold) with repeated doses;
- Systemic exposures in males were generally greater than that in females.

Dosing Solution Analysis: Dose formulation samples have been analyzed by HPLC-UV for the determination of PD-0332991.

The dose formulations were within specification. Homogeneity testing showed that the formulation technique used produced homogeneous preparations.

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

sNDA/BLA #: NDA 207103 Palbociclib
Supplement #: 8

Drug Name: Ibrance (Palbociclib)
Indication(s): Metastatic Breast Cancer
Applicant: Pfizer
Date(s): Submission date: 6/15/2018
PDUFA Goal Date: 4/15/2018

Review Priority: Priority

Biometrics Division: 5
Statistical Reviewer: Erik Bloomquist, PhD
Concurring Reviewers: Shenghui Tang, PhD
Rajeshwai Sridhara, PhD

Medical Division: OHOP/DOP1
Clinical Team: Suparna Wedam, M.D.
Lola Fashoyin-Aje, Pharm.D.
Laleh Amiri-Kordestani, M.D.
Julia Beaver, M.D.

Project Manager: Amy Tiley

Keywords: Survival analysis, Breast Cancer

The statistical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. From a statistical standpoint, the BLA is acceptable to support approval.

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Food and Drug Administration
Center for Drug Evaluation and Research
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Office of Biostatistics

Statistical Review and Evaluation
CARCINOGENICITY STUDIES

IND/NDA Number: NDA 207103/S-8
Drug Name: PD-0332991
Indication: Advanced Breast Cancer (ABC)
Studies: Carcinogenicity Studies in Rats for 104 Weeks and Mice for 26 Weeks
Applicant: Sponsor:

Pfizer Global Research & Development
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Testing Facility for Rat Study:



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Table of Contents

1.	Background.....	3
2.	Rat Study.....	3
	2.1. Sponsor's analyses.....	4
	2.1.1. Survival analysis.....	4
	Sponsor's findings.....	4
	2.1.2. Tumor data analysis.....	4
	Adjustment for multiple testing.....	5
	Sponsor's findings.....	5
	2.2. Reviewer's analyses.....	5
	2.2.1. Survival analysis.....	5
	Reviewer's findings.....	6
	2.2.2. Tumor data analysis.....	6
	Multiple testing adjustment.....	7
	Reviewer's findings.....	7
3.	Mouse Study.....	8
	3.1. Sponsor's analyses.....	8
	3.1.1. Survival analysis.....	8
	Sponsor's findings.....	9
	3.1.2. Tumor data analysis.....	9
	Sponsor's findings.....	9
	3.2. Reviewer's analyses.....	10
	3.2.1. Survival analysis.....	10
	Reviewer's findings.....	10
	3.2.2. Tumor data analysis.....	10
	Reviewer's findings.....	10
4.	Summary.....	10
5.	Appendix.....	12
	Table 1A: Intercurrent mortality rate in male rats	
	Table 1B: Intercurrent mortality rate in female rats	
	Table 2A: Tumor rates and p-values for trend and pairwise comparisons in male rats	
	Table 2B: Tumor rates and p-values for trend and pairwise comparisons in female rats	
	Table 3A: Intercurrent mortality rate in male mice	
	Table 3B: Intercurrent mortality rate in female mice	
	Table 4A: Tumor rates and p-values for trend and pairwise comparisons in male mice	
	Table 4B: Tumor rates and p-values for trend and pairwise comparisons in female mice	
	Figure 1A: Kaplan-Meier survival functions for male rats	
	Figure 1B: Kaplan-Meier survival functions for female rats	
	Figure 2A: Kaplan-Meier survival functions for male mice	
	Figure 2B: Kaplan-Meier survival functions for female mice	
6.	References.....	27

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. The objective of these studies was to determine the oncogenicity and toxicokinetics of PD-0332991, a CDK4/6 inhibitor, when administered by oral gavage (dosing cycle = 3 weeks daily dosing; 1 week nondosing) for 2 years to Sprague Dawley rats and for 6 months to CByB6F1/Tg rasH2 hemizygous (transgenic) mice. In the rat study, due to the decreased number of animals in the respective control groups, surviving males were euthanized during Weeks 99 to 100 and surviving females were euthanized during Weeks 94 to 95.

In this review the phrase "dose response relationship" refers to the linear component (trend) of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

Two separate experiments, one in male rats and one in female rats were conducted. As indicated in Table 1, in each of these two experiments there were three treated groups and one vehicle control group. Two hundred eighty Sprague Dawley rats of each sex were assigned randomly in size of 70 rats per group. The dose levels for the three treated groups were 3, 10, and 30 mg/kg/day for male rats, respectively, and 25, 75, and 200 mg/kg/day for female rats, respectively. In this review these dose groups were referred to as the low (Group 2), mid (Group 3), and high (Group 4) dose groups, respectively. The rats in the vehicle control groups (Group 1) were administered with 0.5% methylcellulose, and handled for the same duration and in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group No.	No. of Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	70	70	Vehicle Control	0	0
2	70	70	PD-0332991 Low	3	25
3	70	70	PD-0332991 Mid	10	75
4	70	70	PD-0332991 High	30	200

Based on the Sponsor's communications with the FDA Carcinogenicity Assessment Committee, if a control group (Group 1) reached ≤ 20 survivors and all other dose groups of the same sex have at least 15 survivors, all animals of that sex were euthanized as soon as feasible. Based on these recommendations, since the Group 1 females reached 20 animals due to age-related mortality as of Week 94, Day 652, all remaining females within the study (Groups 1, 2, 3, and 4) were terminated as soon as practical beginning on Day 653 (Week 94 through Week 95). Similarly, Group 1 males reached 20 animals due to age-related mortality as of Week 98, Day 686, and all remaining males within the study were also terminated as soon as practical beginning on Day 687 (Week 99 through Week 100).

A macroscopic examination was conducted for carcinogenicity animals that died on study, and specified tissues were saved. Carcinogenicity animals surviving until scheduled euthanasia were euthanized by carbon dioxide inhalation, followed by exsanguination.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor's analysis, Kaplan-Meier estimates of group survival rates were calculated, by sex, and shown graphically. A log-rank test for survival was used to make the following comparisons: 1) pairwise comparisons of each treated group with the vehicle control group and 2) trend test utilizing ordinal coefficients. All tests were 2-sided and conducted at the 0.05 significance level. Survival times in which the status of the animal's death was classified as an accidental death or terminal sacrifice were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings:

The sponsor's analysis showed that the numbers of rats surviving to their terminal necropsy were 20 (29%), 17 (24%), 27 (39%), and 45 (64%) in Groups 1, 2, 3, and 4 for male rats, respectively, and 20 (29%), 35 (50%), 32 (46%), and 39 (56%) for female rats respectively. Among male rats there was a statistically significant increasing trend, relative to dose levels, in the survival rates. Additionally, the pairwise test of each test article group compared with control was statistically significant. Among female rats there was a statistically significant increasing trend, relative to dose levels, in the survival rates. Additionally, the pairwise test of the high dose group versus control was statistically significant. There were no other statistically significant findings among male and female rats for survival rates.

2.1.2. Tumor data analysis

In the sponsor's analysis, statistical analysis of the tumor incidence data was conducted in accordance with the FDA draft Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals. The incidence of tumors was analyzed by Peto's mortality-prevalence method, without continuity correction, incorporating the context (incidental, fatal, or mortality independent) in which tumors were observed.

The following fixed intervals were used for incidental tumor analyses in Male rats: Start of Study – Day 364, Day 365 – 546, Day 547 – 644, Day 645 to End of Study (up to but not including terminal sacrifice), and terminal sacrifice. Due to early termination, the following fixed intervals were used for incidental tumor analyses in Female rats: Start of Study – Day 364, Day 365 – 546, Day 547 to End of Study (up to but not including terminal sacrifice), and terminal sacrifice. All animals that died or were sacrificed after the first animal of that sex was terminally sacrificed were included in the terminal sacrifice interval for the incidental finding analyses. For example, among male rats terminal sacrifices began on Study Day 687. All male natural deaths and sacrifices that occurred after the first male sacrifice on Study Day 687 were included in the terminal sacrifice interval. All tumors in the scheduled terminal sacrifice interval were considered incidental for the purpose of statistical analysis. Tumors classified as mortality-independent were analyzed with Peto's mortality independent method incorporating the day of detection.

Each diagnosed tumor type was analyzed separately and, at the instruction of the Study

Pathologist, and in agreement with the Study Director, analysis of combined tumor types was performed. In addition, all leukemias or other systemic tumors were grouped under “hemolymphoreticular neoplasm”. Finally, all metastases and invasive tumors were considered secondary and not included in the analyses unless the primary tumor could not be identified.

All analyses were conducted separately for each sex. For each tumor type, the following analyses were conducted: 1) 1-sided pairwise comparison of each treated group with control group and 2) 1-sided trend test with the treated groups and control group 1 utilizing ordinal coefficients. In cases with low tumor incidence (<3 total in a stratum), p-values were computed using exact permutation distributions. Otherwise, p-values were computed using standard normal approximations with a continuity correction. Statistical significance was determined according to the following guidelines: trend tests were conducted at the 0.01 and 0.05 significance levels for common and rare tumors, respectively. Pairwise comparisons of each treated group with control group 1 were conducted at the 0.05 significance level for both common and rare tumors. A rare tumor was defined as one in which the historical spontaneous tumor rate was less than 1%.

Adjustment for multiple testing:

In the sponsor’s report, statistical significance was determined according to the following guidelines: trend tests were conducted at the 0.01 and 0.05 significance levels for common and rare tumors, respectively. Pairwise comparisons of each treated group with control group 1 were conducted at the 0.05 significance level for both common and rare tumors. A rare tumor was defined as one in which the historical spontaneous tumor rate was less than 1%.

Sponsor’s findings:

In the sponsor’s report, a statistically significant increasing trend in the incidence of microglial cell tumor in the brain/spinal cord organ combination was noted in male rats. Additionally, the incidence of the tumor was significantly greater in the high dose group when compared with the control group. There were no other statistically significant tumor findings among male and female rats.

2.2. Reviewer's analyses

To verify the sponsor’s analyses and to perform additional analyses suggested by the reviewing toxicologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically.

2.2.1. Survival analysis

In the reviewer’s analysis, the survival distributions of rats in all four groups (Groups 1, 2, 3, and 4) were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested across Groups 2, 3, and 4 using the likelihood ratio test, and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for all five groups in male and female rats, respectively. The intercurrent mortality data of all four groups and the results of the tests for dose response relationship and homogeneity of survivals for Groups 2, 3, and 4 are given in Tables 1A and 1B in the appendix for male and female rats, respectively.

Reviewer's findings:

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 20 (29%), 17 (24%), 27 (39%), and 45 (64%) in Groups 1, 2, 3, and 4 for male rats, respectively, and 20 (29%), 35 (50%), 32 (46%), and 39 (56%) for female rats respectively. The reviewer's analysis also showed statistically significant dose response relationship in survival in both male and female rats (p-value = 0.0136, and <0.0001, respectively). For male rats, statistically significant increases in survival were noted in all low, mid, and high dose groups when comparing to the vehicle control group (p-value = 0.0056, 0.0485, and 0.0010, respectively); whereas for female rats, statistically significant increase in survival was noted only in the high dose groups when comparing to the vehicle control group (p-value < 0.0001). No other significant findings were noted in survival for male and female rats.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across Groups 1, 2, 3, and 4, and pairwise comparisons of each of the three treated groups (Groups 2, 3, and 4) against the vehicle control group (Group 1), using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the poly-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The number of animals at risk for the i -th treatment group R_i^* is defined as $R_i^* = \sum W_{ij}$ where w_{ij} is the weight for the j -th animal in the i -th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight w_{ij} as follows:

$w_{ij} = 1$ to animals dying with the tumor, and

$w_{ij} = (t_{ij} / tsacr)^3$ to animals dying without the tumor,

where t_{ij} is the time of death of the j -th animal in the i -th treatment group, and $tsacr$ is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date without developing any tumor will also be assigned $w_{ij} = 1$ since $t_{ij} = tsacr$. Also animals developed the tumor type being tested before the end of the study will be assigned as $w_{ij} = 1$.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the $tsacr$ should not be affected by the unplanned early terminations. The $tsacr$ should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than $tsacr$, regardless their actual terminal sacrifice time, $tsacr$ was used as their time of terminal sacrifice in the analysis.

One critical point for Poly-k test is the choice of the appropriate value of k , which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse

studies, a value of $k=3$ is suggested in the literature. Hence, this reviewer used $k=3$ for the analysis of this data.

Multiple testing adjustment:

For the adjustment of multiple testing, this reviewer used the methodologies suggested in the FDA guidance for statistical design and analysis of carcinogenicity studies (2001). For dose response relationship tests, the guidance suggests the use of test levels of $\alpha=0.01$ for common tumors and $\alpha=0.05$ for rare tumors for a submission with one two-year study in one species and one short-term study with another species, in order to keep the overall false-positive rate at the nominal level of approximately 10%. For multiple pairwise comparisons of treated group with control group, however, the guidance indicated that the corresponding multiple testing adjustment is still under development and not yet available. To be conservative, the test level of $\alpha=0.05$ was used for pairwise comparisons of treated group with control group for both rare and common tumors in this study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-k tests.

A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. However, if the background information for the common or rare tumor is not available, the number of animals bearing tumors in the vehicle control group in the present study was used to determine the common or rare tumor status in the review report. That is, if the number of animals bearing tumors in the vehicle control group is 0, then this tumor is considered as the rare tumor; otherwise, if the number of animals bearing tumors in the control group is greater than or equal to 1, then this tumor is considered as the common tumor.

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female rats, respectively. The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and vehicle control are reported in Table 2.

Table 2: Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle Control Group in Male Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
Brain	Microglial Cell Tumor	0/70 (39) 0.0110 \$	1/70 (48) 0.5517	2/70 (45) 0.2840	5/70 (50) 0.0510
Spinal Cord	Microglial Cell Tumor	0/70 (39) 0.2722	0/70 (48) NC	0/70 (44) NC	1/70 (49) 0.5568
Brain /Spinal Cord	Microglial Cell Tumor	0/70 (39) 0.0039 \$	1/70 (48) 0.5517	2/70 (45) 0.2840	6/70 (50) 0.0273 \$

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

\$ = Statistically significant at 0.05 level in rare tumor for test of dose response relationship or for pairwise comparison;

As noted in Table 2, based on the criteria of adjustment for multiple testing discussed above, statistically significant dose response relationships (p-value = 0.0110, and 0.0039, respectively) were noted for the incidence of microglial cell tumor in brain and brain combined with spinal cord in male rats if this tumor was considered to be rare. Additionally, a statistically significant increase was noted in the high dose when compared with the vehicle control group (p-value = 0.0273) for the incidence of microglial cell tumor in brain combined with spinal cord in male rats regardless the tumor classification (rare or common). No other statistically significant findings were noted in tumor data for both male and female rats.

3. Mouse Study

Two separate experiments, one in male mice and one in female mice were conducted. As indicated in Table 3, in each of these two experiments there were three treated groups, one positive control group, and one vehicle control group. One hundred and fifteen hemizygous CByB6F1/Tg rash2 hemizygous (transgenic) mice of each sex were assigned randomly in size of 25 mice per group for the vehicle control and treated groups, and 15 for the positive control group. The dose levels for the three treated groups were 6, 20, and 60 mg/kg/day for both male and female mice, respectively. In this review these dose groups were referred to as the low (Group 2), mid (Group 3), and high (Group 4) dose groups, respectively. The mice in the vehicle control group were administered with the vehicle (0.5% methylcellulose), and handled for the same duration and in the same manner as the treated groups. The mice in the positive control group were administered with NMU (N-nitrosomethylurea) dose only administered once on Day 1.

Table 3: Experimental Design in Mouse Study

Group No.	No. of Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	25	25	Vehicle Control	0	0
2	25	25	PD-0332991 Low	6	6
3	25	25	PD-0332991 Mid	20	20
4	25	25	PD-0332991 High	60	60
5	15	15	Positive Control NMU	75	75

The animals were observed for general health/mortality and moribundity twice daily, once in the morning and once in the afternoon, throughout the study. Cage side observations were performed once daily, beginning Week -1, throughout the dosing phase; the observations were performed 1 to 3 hours postdose during the dosing phase. The animals were removed from the cage and a detailed clinical observation was performed at least once weekly, beginning Week -1. For carcinogenicity group animals that died on study, a macroscopic examination was conducted and specified tissues were saved. Carcinogenicity group animals surviving until scheduled euthanasia were weighed and the animals were euthanized by isoflurane inhalation, followed by exsanguination.

3.1. Sponsor's analyses

3.1.1. Survival analysis

In the sponsor's report, Kaplan-Meier estimates of group survival rates were calculated and shown graphically. The generalized Wilcoxon test for survival was used to compare the homogeneity of survival rates across the vehicle control and test article groups at the 0.05 significance level. If the survival rates were significantly different, the generalized Wilcoxon test was used to make pairwise comparisons of each test article group with the vehicle control group. Additionally, the positive control group was compared to the vehicle control group using the generalized Wilcoxon test. Survival times in which the status of the animal's death was classified as an accidental death, planned interim sacrifice or terminal sacrifice were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings:

The sponsor's analysis showed that the numbers of mice surviving to their terminal necropsy were 24 (96%), 25 (100%), 24 (96%), and 24 (96%) in Groups 1, 2, 3, and 4 for male mice, respectively, and 24 (96%), 23 (92%), 23 (92%), and 24 (96%) for female mice, respectively. There were no statistically significant findings in survival rates noted in the sponsor's report among male or female mice.

3.1.2. Tumor data analysis

In the sponsor's report, the incidence of tumors was analyzed by Peto's mortality-prevalence method, without continuity correction, incorporating the context (incidental, fatal, or mortality independent) in which tumors were observed. All tumors in the scheduled terminal sacrifice interval were considered incidental for the purpose of statistical analysis. Tumors classified as mortality-independent were analyzed with Peto's mortality independent method incorporating the day of detection.

There were no deaths in the vehicle control group prior to study day 100 and there were no tumors in the test article animals that died prior to day 100. Therefore, the following fixed intervals were used for incidental tumor analyses: Days 1 through 100, and Days 101 through and including terminal sacrifice. A minimum exposure of 100 days was considered sufficient to be included with animals surviving through scheduled termination.

All metastases and invasive tumors were considered secondary and not statistically analyzed. A 1-sided comparison of each test article group with the vehicle control was performed. An exact permutation test was conducted for all analyses. Findings were evaluated for statistical significance at both the 0.01 and 0.05 levels and all p values were reported.

Because the positive control group was scheduled for early terminal sacrifice, tumor incidence in the positive control group was compared to the vehicle control group with a 1-sided Fisher's exact test at both the 0.01 and 0.05 significance levels and all p values were reported.

Multiple testing adjustment:

No adjustment for multiple testing was described or discussed for the mouse study in the sponsor's report.

Sponsor's findings:

In the sponsor's report, no statistically significant differences were noted when comparing treated groups with control and no significant trends with dose for tumor incidence among male or female mice administered PD-0332991.

3.2. Reviewer's analyses

Similar to the rat study, this reviewer independently performed survival and tumor data analyses of mouse data to verify sponsor's analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

For the analysis of both the survival data and the tumor data in mice, this reviewer used similar methodologies that were used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data, and the results of the tests for dose response relationship and homogeneity of survivals for the vehicle control, low, mid, and high dose groups were given in Tables 3A and 3B in the appendix for male and female mice, respectively.

Reviewer's findings:

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 24 (96%), 25 (100%), 24 (96%), and 24 (96%) in Groups 1, 2, 3, and 4 for male mice, respectively, and 24 (96%), 23 (92%), 23 (92%), and 24 (96%) for female mice, respectively. No statistically significant findings were noted in mortality for male and female mice.

3.2.2. Tumor data analysis

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 4A and Table 4B in the appendix for male and female mice, respectively. No statistically significant tumor findings were noted for male and female mice.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. The objective of these studies was to determine the oncogenicity and toxicokinetics of PD-0332991, a CDK4/6 inhibitor, when administered by oral gavage (dosing cycle = 3 weeks daily dosing; 1 week nondosing) for 2 years to Sprague Dawley rats and for 6 months to CByB6F1/Tg rasH2 hemizygous (transgenic) mice. In the rat study, due to the decreased number of animals in the respective control groups, surviving males were euthanized during Weeks 99 to 100 and surviving females were euthanized during Weeks 94 to 95.

Rat Study:

Two separate experiments, one in male rats and one in female rats were conducted. In each of

these two experiments there were three treated groups and one vehicle control group. Two hundred eighty Sprague Dawley rats of each sex were assigned randomly in size of 70 rats per group. The dose levels for the three treated groups were 3, 10, and 30 mg/kg/day for male rats, respectively, and 25, 75, and 200 mg/kg/day for female rats, respectively.

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 20 (29%), 17 (24%), 27 (39%), and 45 (64%) in Groups 1, 2, 3, and 4 for male rats, respectively, and 20 (29%), 35 (50%), 32 (46%), and 39 (56%) for female rats respectively. The reviewer's analysis also showed statistically significant dose response relationship in survival in both male and female rats (p-value = 0.0136, and <0.0001, respectively). For male rats, statistically significant increases in survival were noted in all low, mid, and high dose groups when comparing to the vehicle control group (p-value = 0.0056, 0.0485, and 0.0010, respectively); whereas for female rats, statistically significant increase in survival was noted only in the high dose groups when comparing to the vehicle control group (p-value < 0.0001). No other significant findings were noted in survival for male and female rats.

In the reviewer's analysis, statistically significant dose response relationships (p-value = 0.0106, and 0.0037, respectively) were noted for the incidence of microglial cell tumor in brain and brain combined with spinal cord in male rats if this tumor was considered to be rare. Additionally, a statistically significant increase was noted in the high dose when compared with the vehicle control group (p-value = 0.0273) for the incidence of microglial cell tumor in brain combined with spinal cord in male rats regardless the tumor classification (rare or common). No other statistically significant findings were noted in tumor data for both male and female rats.

Mouse Study:

Two separate experiments, one in male mice and one in female mice were conducted. In each of these two experiments there were three treated groups, one positive control group, and one vehicle control group. One hundred and fifteen hemizygous CByB6F1/Tg rasH2 hemizygous (transgenic) mice of each sex were assigned randomly in size of 25 mice per group for the vehicle control and treated groups, and 15 for the positive control group. The dose levels for the three treated groups were 6, 20, and 60 mg/kg/day for both male and female mice, respectively.

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 24 (96%), 25 (100%), 24 (96%), and 24 (96%) in Groups 1, 2, 3, and 4 for male mice, respectively, and 24 (96%), 23 (92%), 23 (92%), and 24 (96%) for female mice, respectively. No statistically significant findings were noted in mortality for male and female mice.

No statistically significant tumor findings were noted for male and female mice.

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Mathematical Statistician

Concur: Karl Lin, Ph.D.
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Cc: Archival NDA 207103/S-8

Dr. Wei Chen
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5. Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

Week / Type of Death	Vehicle Control		Low		Mid		High	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	4	5.71	6	8.57	4	5.71	3	4.29
53 - 78	21	35.71	5	15.71	15	27.14	8	15.71
79 - 91	18	61.43	15	37.14	12	44.29	16	38.57
92 - 100	7	71.43	9	50.00	7	54.29	4	44.29
Terminal sacrifice	20	28.57	35	50.00	32	45.71	39	55.71
Total	70		70		70		70	
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High	
Dose-Response (Likelihood Ratio)	0.0136*		0.0056**		0.0485*		0.0010**	
Homogeneity (Log-Rank)	0.0034**		0.0050**		0.0458*		0.0009**	

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

* = Significant at 5% level; ** = Significant at 1% level.

Table 1B: Intercurrent Mortality Rate in Female Rats

Week / Type of Death	Vehicle Control		Low		Mid		High	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	6	8.57	4	5.71	3	4.29	2	2.86
53 - 78	26	45.71	29	47.14	16	27.14	10	17.14
79 - 91	16	68.57	18	72.86	21	57.14	8	28.57
92 - 100	2	71.43	2	75.71	3	61.43	5	35.71
Terminal sacrifice	20	28.57	17	24.29	27	38.57	45	64.29
Total	70		70		70		70	
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High	
Dose-Response (Likelihood Ratio)	<.0001**		0.7963		0.0797		<.0001**	
Homogeneity (Log-Rank)	<.0001**		0.7927		0.0746		<.0001**	

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

** = Significant at 1% level.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
Brain	Granular Cell Tumor, Benign	0/70 (39) 0.4674	2/70 (48) 0.3015	1/70 (45) 0.5357	1/70 (49) 0.5568
	Meningioma, Benign	0/70 (39) 0.2707	0/70 (48) NC	1/70 (45) 0.5357	0/70 (49) NC
	Microglial Cell Tumor	0/70 (39) 0.0110 \$	1/70 (48) 0.5517	2/70 (45) 0.2840	5/70 (50) 0.0510
Brain/Spinal Cord	Microglial Cell Tumor	0/70 (39) 0.0039 \$	1/70 (48) 0.5517	2/70 (45) 0.2840	6/70 (50) 0.0273 \$
Epididymis	Mesothelioma, Malignant	0/70 (39) 0.2667	0/70 (48) NC	1/70 (45) 0.5357	0/69 (48) NC
Gland, Adrenal	Cortical Adenoma	0/70 (39) 0.3372	1/70 (48) 0.5517	1/69 (44) 0.5301	1/70 (49) 0.5568
	Cortical Carcinoma	0/70 (39) 0.7678	2/70 (48) 0.3015	0/69 (44) NC	0/70 (49) NC
	Cortical Adenoma/ Cortical Carcinoma	0/70 (39) 0.5741	3/70 (48) 0.1632	1/69 (44) 0.5301	1/70 (49) 0.5568
	Pheochromocytoma, Benign	6/70 (41) 0.5776	8/70 (49) 0.5308	7/69 (45) 0.5732	7/70 (50) 0.4181
	Pheochromocytoma, Malignant	0/70 (39) 0.2722	0/70 (48) NC	1/69 (44) 0.5301	0/70 (49) NC
	Pheochromocytoma, Benign/ Pheochromocytoma, Malignant	6/70 (41) 0.5851	8/70 (49) 0.5308	8/69 (45) 0.4608	7/70 (50) 0.4181
Gland, Mammary	Adenocarcinoma	1/62 (35) 0.7865	1/65 (44) 0.3070	1/66 (42) 0.2943	0/69 (48) 0.5783
	Adenoma	0/62 (35) 0.2840	0/65 (44) NC	1/66 (42) 0.5455	0/69 (48) NC
	Adenocarcinoma/Adenoma	1/62 (35) 0.7969	1/65 (44) 0.3070	2/66 (42) 0.5689	0/69 (48) 0.5783
	Fibroadenoma	1/62 (35) 0.7929	0/65 (44) 0.5570	0/66 (42) 0.5455	0/69 (48) 0.5783
Gland, Parathyroid	Adenoma	0/67 (38) 0.5089	1/66 (45) 0.5422	0/68 (43) NC	0/62 (43) NC
Gland, Pituitary	Adenoma	52/69 (61) 0.9999	47/69 (61) 0.8226	42/69 (58) 0.9325	31/70 (57) 0.9998

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
Gland, Prostate	Adenocarcinoma	0/70 (39) 0.2682	0/70 (48) NC	0/70 (44) NC	1/69 (48) 0.5517
	Adenoma	0/70 (39) 0.5140	1/70 (48) 0.5517	0/70 (44) NC	0/69 (48) NC
	Adenocarcinoma/Adenoma	0/70 (39) 0.3480	1/70 (48) 0.5517	0/70 (44) NC	1/69 (48) 0.5517
Gland, Salivary	Schwannoma, Malignant	1/70 (39) 0.7833	0/70 (48) 0.5517	0/69 (44) 0.5301	0/70 (49) 0.5568
Gland, Thyroid	C-Cell Adenoma	8/70 (41) 0.9877	14/70 (51) 0.2619	10/70 (46) 0.5049	4/70 (49) 0.8971
	Follicular Cell Adenoma	1/70 (40) 0.1850	1/70 (48) 0.2947	3/70 (45) 0.3539	3/70 (50) 0.3970
	Follicular Cell Carcinoma	1/70 (39) 0.7700	1/70 (48) 0.3015	1/70 (45) 0.2840	0/70 (49) 0.5568
	Follicular Cell Adenoma/ Follicular Cell Carcinoma	2/70 (40) 0.3984	2/70 (48) 0.3801	4/70 (45) 0.3961	3/70 (50) 0.6057
Heart	Schwannoma, Malignant	1/70 (40) 0.7790	0/70 (48) 0.5455	0/70 (44) 0.5238	0/70 (49) 0.5506
Hemolymphoreticular Tissue	Hemangiosarcoma	2/70 (40) 0.9513	1/70 (48) 0.5688	0/70 (44) 0.7762	0/70 (49) 0.8008
	Histiocytic Sarcoma	1/70 (39) 0.7833	0/70 (48) 0.5517	0/70 (44) 0.5301	0/70 (49) 0.5568
	Leukemia, Granulocytic	2/70 (40) 0.9513	1/70 (49) 0.5765	0/70 (44) 0.7762	0/70 (49) 0.8008
	Lymphoma, Malignant	0/70 (39) 0.2722	0/70 (48) NC	0/70 (44) NC	1/70 (49) 0.5568
Kidney	Amphophilic-Vacuolar Adenoma	0/70 (39) 0.5167	1/70 (48) 0.5517	0/70 (44) NC	0/70 (49) NC
	Lipoma	0/70 (39) 0.5167	1/70 (48) 0.5517	0/70 (44) NC	0/70 (49) NC
Liver	Hepatocellular Adenoma	0/70 (39) 0.2286	0/70 (48) NC	2/70 (45) 0.2840	1/70 (49) 0.5568
Lymph Node, Mesenteric	Leiomyosarcoma	1/70 (40) 0.7778	0/69 (47) 0.5402	0/69 (44) 0.5238	0/70 (49) 0.5506

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg	3 mg	10 mg	30 mg
		Vehicle (C) P - Trend	Low (L) P - C vs. L	Mid (M) P - C vs. M	High (H) P - C vs. H
Pancreas	Islet Cell Adenoma	11/70 (43) 0.9984	7/70 (50) 0.8741	2/68 (43) 0.9932	2/70 (49) 0.9966
	Islet Cell Carcinoma	0/70 (39) 0.2737	0/70 (48) NC	0/68 (43) NC	1/70 (49) 0.5568
	Islet Cell Adenoma/ Islet Cell Carcinoma	11/70 (43) 0.9932	7/70 (50) 0.8741	2/68 (43) 0.9932	3/70 (50) 0.9910
Skin	Basal Cell Tumor, Benign	2/70 (40) 0.9516	0/69 (47) 0.7915	0/70 (44) 0.7762	0/70 (49) 0.8008
	Basal Cell Tumor, Malignant	0/70 (39) 0.2722	0/69 (47) NC	1/70 (45) 0.5357	0/70 (49) NC
	Basal Cell Tumor, Benign/ Basal Cell Tumor, Malignant	2/70 (40) 0.8548	0/69 (47) 0.7915	1/70 (45) 0.5446	0/70 (49) 0.8008
	Keratoacanthoma	2/70 (40) 0.9513	1/69 (47) 0.5609	0/70 (44) 0.7762	0/70 (49) 0.8008
	Squamous Cell Carcinoma	1/70 (40) 0.8349	1/69 (47) 0.2890	0/70 (44) 0.5238	0/70 (49) 0.5506
	Keratoacanthoma/ Squamous Cell Carcinoma	3/70 (40) 0.9895	2/69 (47) 0.5769	0/70 (44) 0.8963	0/70 (49) 0.9130
	Papilloma	1/70 (40) 0.7778	0/69 (47) 0.5402	0/70 (44) 0.5238	0/70 (49) 0.5506
	Pilomatricoma	0/70 (39) 0.8911	3/69 (47) 0.1584	0/70 (44) NC	0/70 (49) NC
	Spinal Cord	Microglial Cell Tumor	0/70 (39) 0.2722	0/70 (48) NC	0/70 (44) NC
Sarcoma		0/70 (39) 0.5167	1/70 (48) 0.5517	0/69 (44) NC	0/70 (49) NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
Testis	Interstitial (Leydig) Cell Adenoma	1/70 (40) 0.1488	1/70 (48) 0.2947	2/70 (46) 0.5529	3/69 (48) 0.3801
	Seminoma, Benign	0/70 (39) 0.5140	1/70 (48) 0.5517	0/70 (44) NC	0/69 (48) NC
Thymus	Thymoma, Benign	0/68 (38) 0.3063	1/63 (43) 0.5309	1/68 (43) 0.5309	1/58 (41) 0.5190

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats

Organ name	Tumor name	0 mg	25 mg	75 mg	200 mg
		Vehicle (C) P - Trend	Low (L) P - L vs. C	Mid (M) P - M vs. C	High (H) P - H vs. C
Brain	Granular Cell Tumor, Benign	1/70 (33)	1/70 (33)	0/70 (39)	0/70 (45)
		0.8553	NC	0.5417	0.5769
	Granular Cell Tumor, Malignant	1/70 (33)	0/70 (33)	0/70 (39)	0/70 (45)
		0.7800	0.5000	0.5417	0.5769
	Granular Cell Tumor, Benign/ Granular Cell Tumor, Malignant	2/70 (33)	1/70 (33)	0/70 (39)	0/70 (45)
0.9585		0.5000	0.7934	0.8242	
Microglial Cell Tumor	0/70 (33)	0/70 (33)	0/70 (39)	1/70 (46)	
		0.3046	NC	NC	0.5823
Cervix	Granular Cell Tumor, Benign	1/70 (33)	3/70 (34)	0/70 (39)	1/70 (45)
		0.7757	0.3181	0.5417	0.3297
	Leiomyoma	1/70 (33)	0/70 (33)	0/70 (39)	0/70 (45)
		0.7800	0.5000	0.5417	0.5769
	Schwannoma, Malignant	0/70 (33)	0/70 (33)	1/70 (39)	1/70 (46)
		0.2498	NC	0.5417	0.5823
Gland, Adrenal	Cortical Adenoma	2/70 (33)	0/70 (33)	0/70 (39)	0/70 (45)
		0.9528	0.7538	0.7934	0.8242
	Pheochromocytoma, Benign	1/70 (33)	0/70 (33)	2/70 (39)	1/70 (46)
		0.4843	0.5000	0.5632	0.3359
	Pheochromocytoma, Malignant	0/70 (33)	1/70 (33)	0/70 (39)	0/70 (45)
0.5600		0.5000	NC	NC	
Pheochromocytoma, Benign/ Pheochromocytoma, Maligna	1/70 (33)	1/70 (33)	2/70 (39)	1/70 (46)	
		0.5637	NC	0.5632	0.3359
Gland, Mammary	Adenocarcinoma	27/70 (47)	26/70 (45)	16/70 (45)	18/70 (51)
		0.9936	0.5710	0.9712	0.9773
	Adenoma	2/70 (33)	1/70 (33)	3/70 (39)	5/70 (47)
		0.1372	0.5000	0.5800	0.3863
	Adenocarcinoma/Adenoma	29/70 (48)	26/70 (45)	19/70 (46)	20/70 (52)
		0.9906	0.5192	0.9504	0.9772
Adenosquamous Carcinoma	2/70 (34)	0/70 (33)	2/70 (40)	2/70 (46)	
		0.4286	0.7463	0.3714	0.4295
Fibroadenoma	26/70 (43)	23/70 (43)	28/70 (49)	26/70 (54)	
	0.8597	0.6683	0.5437	0.8422	

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	25 mg Low (L) P - L vs. C	75 mg Mid (M) P - M vs. C	200 mg High (H) P - H vs. C
Gland, Pituitary	Adenoma	63/69 (66) 0.8351	59/68 (63) 0.5260	62/70 (66) 0.5000	60/70 (66) 0.7539
	Carcinoma	0/69 (32) 0.3067	0/68 (33) NC	0/70 (39) NC	1/70 (46) 0.5897
	Adenoma/Carcinoma	63/69 (66) 0.7277	59/68 (63) 0.5260	62/70 (66) 0.5000	61/70 (66) 0.6410
Gland, Salivary	Squamous Cell Carcinoma	0/70 (33) 0.3000	0/70 (33) NC	0/70 (39) NC	1/69 (45) 0.5769
Gland, Thyroid	C-Cell Adenoma	7/70 (35) 0.5308	3/70 (34) 0.8352	10/70 (41) 0.4297	7/69 (46) 0.6082
	C-Cell Carcinoma	0/70 (33) 0.8021	2/70 (34) 0.2537	0/70 (39) NC	0/69 (44) NC
	C-Cell Adenoma/ C-Cell Carcinoma	7/70 (35) 0.6377	5/70 (35) 0.6238	10/70 (41) 0.4297	7/69 (46) 0.6082
	Follicular Cell Adenoma	1/70 (34) 0.2390	0/70 (33) 0.4925	1/70 (39) 0.2820	2/69 (45) 0.6051
	Follicular Cell Carcinoma	1/70 (33) 0.7785	0/70 (33) 0.5000	0/70 (39) 0.5417	0/69 (44) 0.5714
	Follicular Cell Adenoma/ Follicular Cell Carcinoma	2/70 (34) 0.4064	0/70 (33) 0.7463	1/70 (39) 0.5520	2/69 (45) 0.4203
Hemolymphoreticular Tissue	Hemangiosarcoma	1/70 (33) 0.6929	0/70 (33) 0.5000	1/70 (39) 0.2899	0/70 (45) 0.5769
Kidney	Amphophilic-Vacuolar Adenoma	0/70 (33) 0.6733	1/70 (34) 0.5075	2/70 (39) 0.2899	0/70 (45) NC
Liver	Hepatocellular Adenoma	1/70 (33) 0.4849	0/70 (33) 0.5000	1/70 (39) 0.2899	1/70 (45) 0.3297
Ovary	Luteoma	0/70 (33) 0.5600	1/70 (33) 0.5000	0/70 (39) NC	0/70 (45) NC
Pancreas	Islet Cell Adenoma	4/70 (34) 0.8292	2/70 (34) 0.6636	1/70 (39) 0.8611	2/70 (46) 0.7932

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	25 mg Low (L) P - L vs. C	75 mg Mid (M) P - M vs. C	200 mg High (H) P - H vs. C
Skin	Epithelioma	0/70 (33) 0.5563	1/70 (34) 0.5075	0/70 (39) NC	0/70 (45) NC
	Pilomatricoma	1/70 (33) 0.7800	0/70 (33) 0.5000	0/70 (39) 0.5417	0/70 (45) 0.5769
	Squamous Cell Carcinoma	0/70 (33) 0.3000	0/70 (33) NC	1/70 (39) 0.5417	0/70 (45) NC
Small Intestine, Jejunum	Leiomyosarcoma	1/62 (30) 0.7857	0/64 (31) 0.5082	0/63 (36) 0.5455	0/65 (43) 0.5890
Spleen	Leiomyosarcoma	0/70 (33) 0.3000	0/70 (33) NC	1/70 (39) 0.5417	0/70 (45) NC
Thymus	Thymoma, Benign	0/63 (30) 0.3147	0/66 (32) NC	0/63 (36) NC	1/69 (45) 0.6000
Uterus	Adenocarcinoma	0/70 (33) 0.3000	0/70 (33) NC	1/70 (39) 0.5417	0/70 (45) NC
	Endometrial Stromal Polyp	4/70 (35) 0.3713	4/70 (35) NC	1/70 (39) 0.8531	6/70 (47) 0.5674
Vagina	Squamous Cell Carcinoma	0/70 (33) 0.3000	0/70 (33) NC	1/70 (39) 0.5417	0/70 (45) NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

NC = Not calculable.

Table 3A: Intercurrent Mortality Rate in Male Mice

Week / Type of Death	Vehicle Control		Low		Mid		High	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13	1	4.00						
14 - 27					1	4.00	1	4.00
Terminal sacrifice	24	96.00	25	100.00	24	96.00	24	96.00
Total	25		25		25		25	
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High	
Dose-Response (Likelihood Ratio)	0.7178		0.2390		0.9885		0.9885	
Homogeneity (Log-Rank)	0.7978		0.3173		0.9885		0.9885	

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 3B: Intercurrent Mortality Rate in Female Mice

Week / Type of Death	Vehicle Control		Low		Mid		High	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13			1	4.00				
14 - 27	1	4.00	1	8.00	2	8.00	1	4.00
Terminal sacrifice	24	96.00	23	92.00	23	92.00	24	96.00
Total	25		25		25		25	
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High	
Dose-Response (Likelihood Ratio)	0.7478		0.5362		0.5521		1.0000	
Homogeneity (Log-Rank)	0.8635		0.5396		0.5557		1.0000	

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	6 mg Low (L) P - C vs. L	20 mg Mid (M) P - C vs. M	60 mg High (H) P - C vs. H
Gland, Harderian	Adenoma	4/25 (24) 0.9969	0/25 (25) 0.9498	0/25 (24) 0.9454	0/25 (24) 0.9454
Liver	Hepatocellular Adenoma	1/25 (24) 0.5446	2/25 (25) 0.5156	1/25 (24) NC	1/25 (24) NC
	Hepatocellular Carcinoma	0/25 (24) 0.2474	0/25 (25) NC	1/25 (24) 0.5000	0/25 (24) NC
	Hepatocellular Adenoma/ Hepatocellular Carcinoma	1/25 (24) 0.5500	2/25 (25) 0.5156	2/25 (24) 0.5000	1/25 (24) NC
Lung	Bronchioloalveolar Adenoma	4/25 (24) 0.3121	2/25 (25) 0.6864	1/25 (24) 0.8262	4/25 (24) NC
	Bronchioloalveolar Carcinoma	0/25 (24) 0.2551	0/25 (25) NC	0/25 (24) NC	1/25 (25) 0.5102
	Bronchioloalveolar Adenoma/ Bronchioloalveolar Carcinoma	4/25 (24) 0.1873	2/25 (25) 0.6864	1/25 (24) 0.8262	5/25 (25) 0.5275
Spleen	Hemangiosarcoma	0/25 (24) 0.4356	0/25 (25) NC	2/25 (24) 0.2447	0/25 (24) NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	6 mg Low (L) P - L vs. C	20 mg Mid (M) P - M vs. C	60 mg High (H) P - H vs. C
Gland, Harderian	Adenocarcinoma	2/25 (25) 0.2822	0/25 (24) 0.7449	0/25 (24) 0.7449	2/25 (25) NC
Lung	Bronchioloalveolar Adenoma	3/25 (25) 0.9849	0/25 (24) 0.8752	0/25 (24) 0.8752	0/25 (25) 0.8827
	Bronchioloalveolar Carcinoma	1/25 (25) 0.7449	0/25 (24) 0.4898	0/25 (24) 0.4898	0/25 (25) 0.5000
	Bronchioloalveolar Adenoma/ Bronchioloalveolar Carcinoma	4/25 (25) 0.9965	0/25 (24) 0.9403	0/25 (24) 0.9403	0/25 (25) 0.9451
Ovary	Hemangiosarcoma	1/24 (24) 0.7526	0/25 (24) 0.5000	0/25 (24) 0.5000	0/25 (25) 0.5102
Skin	Keratoacanthoma	0/25 (25) 0.2551	0/25 (24) NC	1/25 (24) 0.4898	0/25 (25) NC
Spleen	Hemangiosarcoma	2/25 (25) 0.5418	0/25 (24) 0.7449	0/25 (24) 0.7449	1/25 (25) 0.5000
Stomach	Papilloma	0/25 (25) 0.5000	1/25 (24) 0.4898	0/25 (24) NC	0/25 (25) NC
Thymus	Thymoma, Malignant	0/25 (25) 0.2500	0/25 (24) NC	1/24 (23) 0.4792	0/24 (24) NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

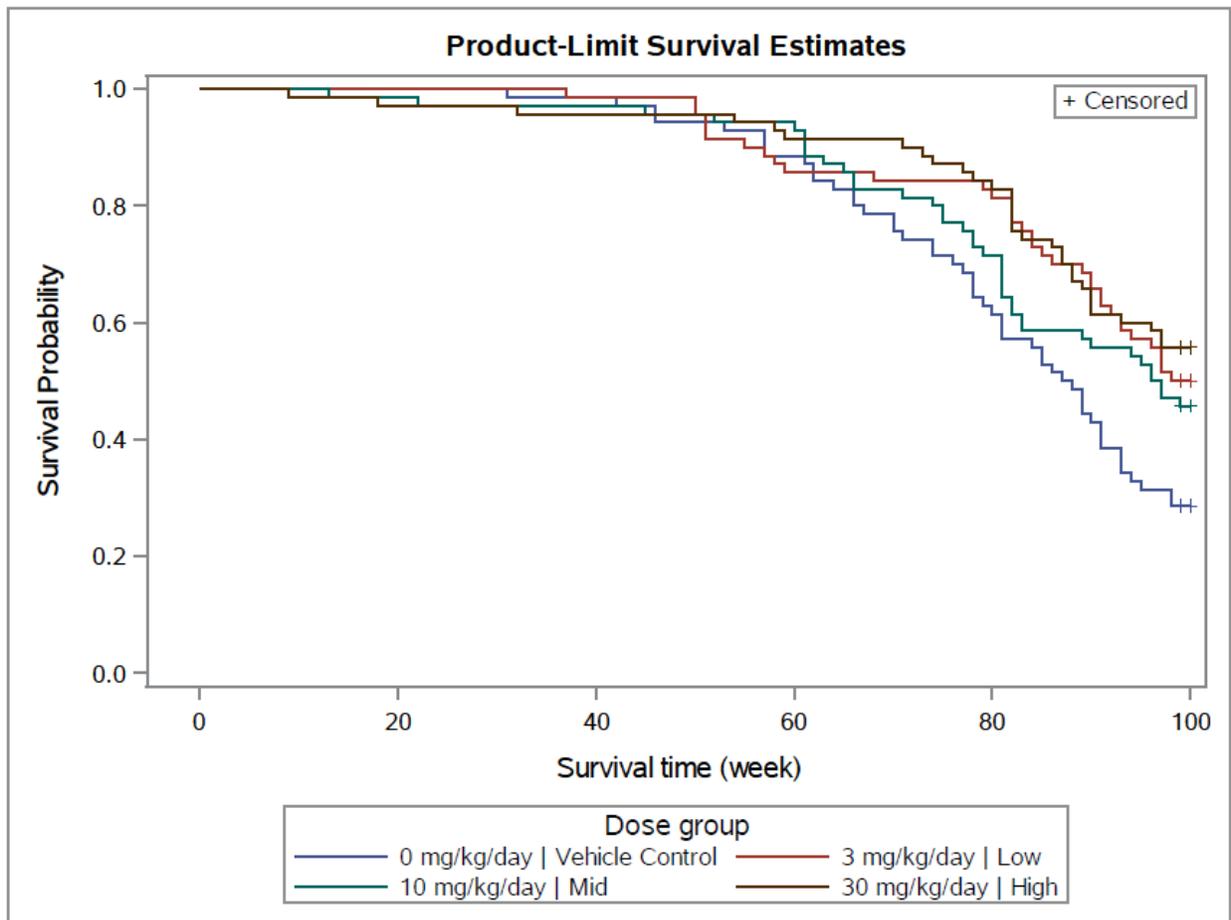


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

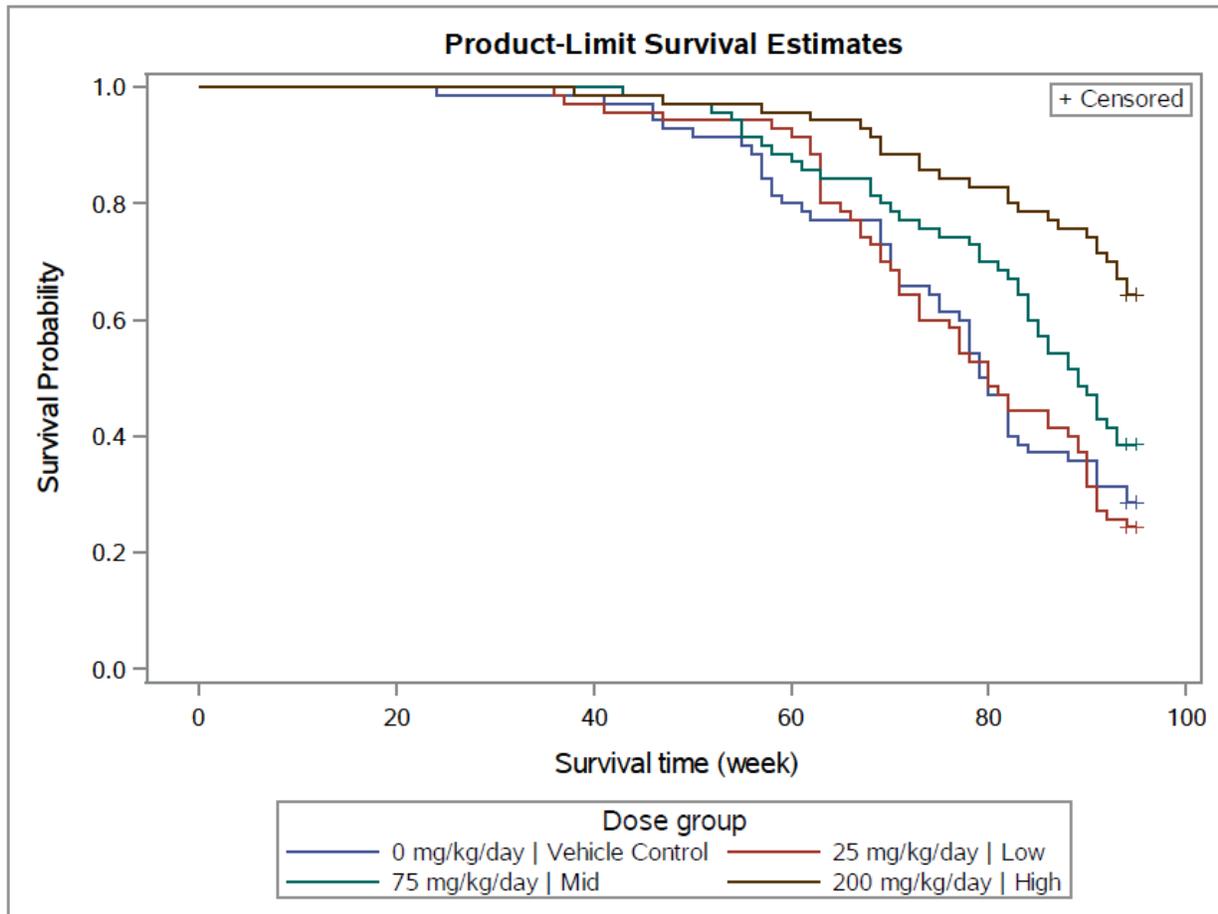


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

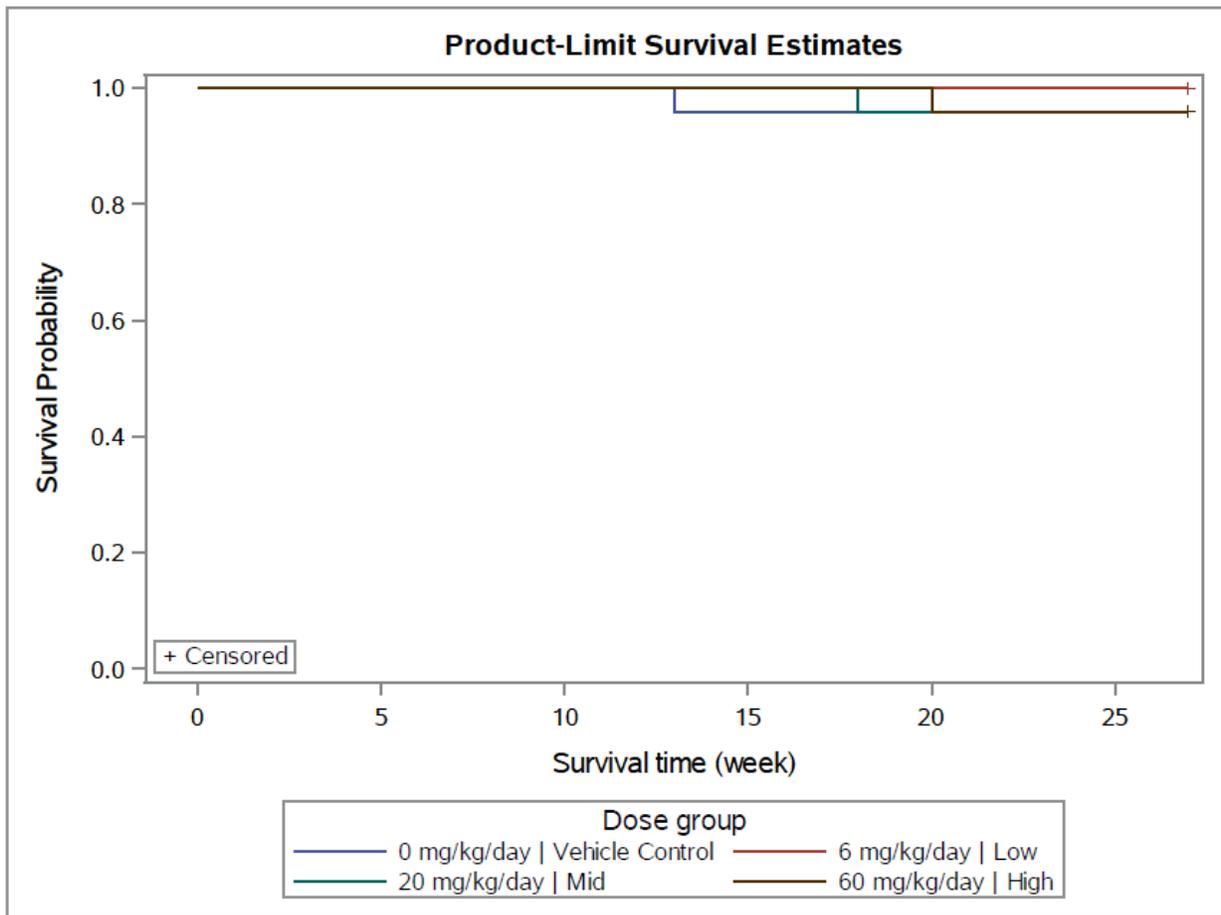
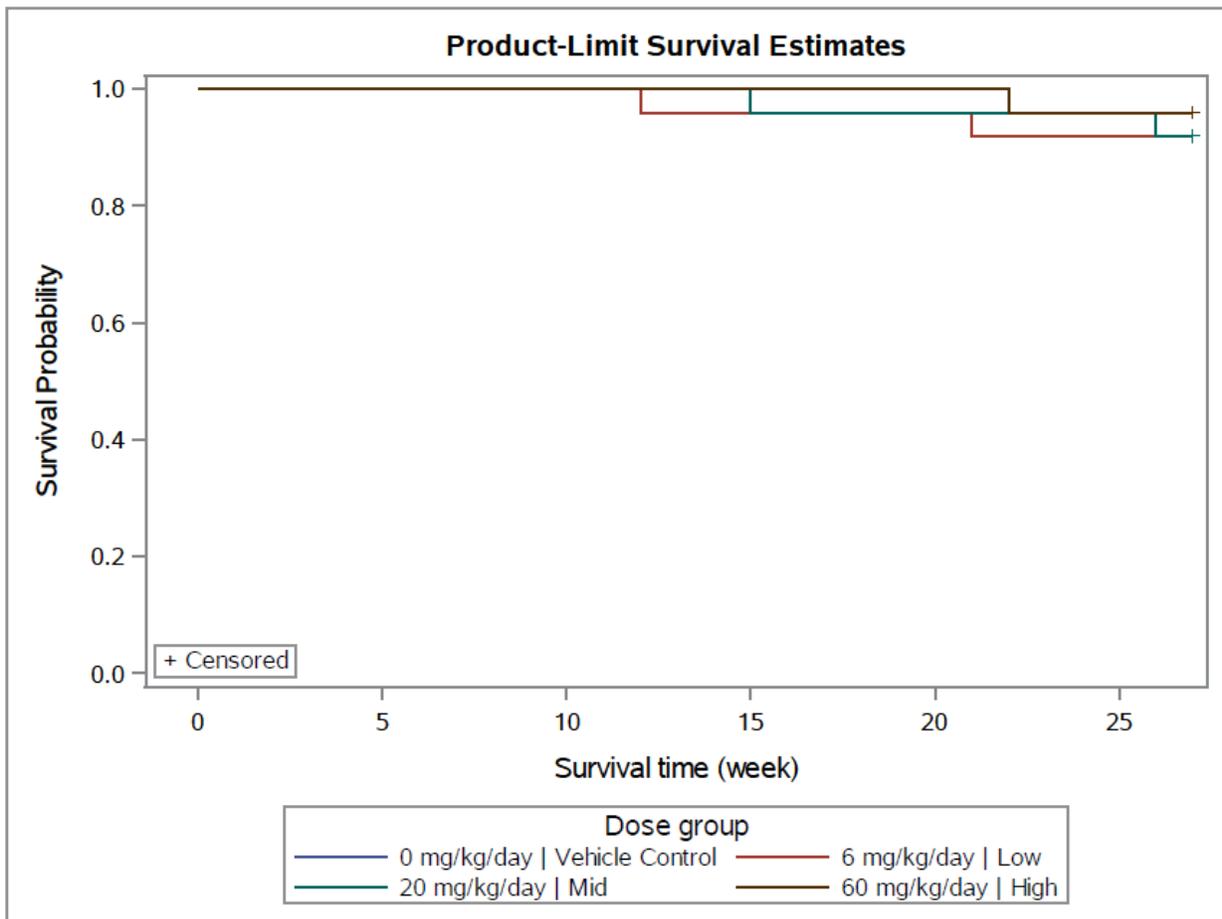


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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- Rahman, A.M., and Lin, K.K. (2008), "A Comparison of False Positive Rates of Peto and Poly-3 Methods for Long-Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman", *Journal of Biopharmaceutical Statistics*, 18:5, 849-858.
- Rahman, A.M., and Lin, K.K. (2009), "Design and Analysis of Chronic Carcinogenicity Studies of Pharmaceuticals in Rodents", in "Design and Analysis of Clinical Trials with Time-to-Event Endpoints", K.E Peace, Editor, Chapman & Hall/CRC, Taylor & Francis Group, LLC, Boca Raton, FL, London, and New York.

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/s/

HEPEI CHEN
11/21/2018

KARL K LIN
11/21/2018
Concur with review.

Clinical Pharmacology Memo

NDA	207103 S-8
Submission Date	June 15, 2018
Brand Name	Ibrance
Generic Name	Palbociclib
Dosage Form / Strength	Capsules: 125 mg, 100 mg, and 75 mg
Applicant	Pfizer
OCP Reviewer	Wentao Fu, Ph.D.
OCP Team Leader	Pengfei Song, Ph.D.
OCP Division	Division of Clinical Pharmacology V
ORM Division	Division of Oncology Products 1
Submission Type; Code	Suppl-8 Efficacy SDN 780
Dosing Regimen	125 mg once daily taken with food for 21 days followed by 7 days off treatment.

Indication



The Office of Clinical Pharmacology recommends approval of the NDA 207103 S-8 from a clinical pharmacology perspective. In the current submission, the applicant seeks the following indications expansion ^{(b) (4)}. There are no clinical pharmacology related labeling updates in this submission.



The proposed indications are supported by the following studies.

- Study A5481097: A retrospective claims data analysis of males treated for metastatic

breast cancer in the US.

- Real-World Analysis of Males Treated for Metastatic Breast Cancer in the US (Flatiron Health, US): A retrospective real-world analysis of males treated for metastatic breast cancer in the US.
- Study A5481008 is an international, multicenter, randomized, double-blind, placebo controlled, parallel-group, Phase 3 clinical trial comparing the efficacy and safety of palbociclib in combination with letrozole versus placebo in combination with letrozole in postmenopausal women with ER-positive, HER2-negative advanced breast cancer.

The first two studies provide support of efficiency for male patients. These studies contain no clinical pharmacology data and are not reviewed by the clinical pharmacology review team in this submission. Under NDA 207103 S-4, study A5481008 was accepted by clinical pharmacology review team to support of full approval of the use of palbociclib in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of women (please refer to the clinical pharmacology review dated March 27, 2017 for detail). Off note, a population PK analysis in 50 male patients and 133 female patients with cancer indicated that there was on effect of gender on the pharmacokinetics of palbociclib (please refer to the clinical pharmacology review of the original NDA 207103 dated January 15, 2015 for detail).

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/s/

WENTAO FU
03/04/2019 04:18:49 PM

PENGFEI SONG
03/06/2019 06:12:04 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207103Orig1s008

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Efficacy Supplement Number:** 207103/S008

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

Submission	Type	Sub Date	Stamp Date	Assigned Date	Goal Date	Review Date
Original Supplement	SE	15-Jun-18	15-Jun-18	19-Jun-18	15-Dec-18	13-Nov-18

3. (a) **Provides For From Cover Letter:**

- Pfizer is seeking [REDACTED] (b) (4)

(b) **Additional Change(s) Proposed in the Supplement:** none

4. **Review #:** 1

5. **Clinical Review Division:** Division of Oncology Products 1 (DOP1)

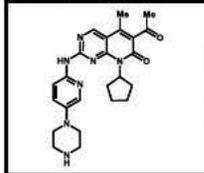
6. **Name and Address of Applicant:**

Pfizer Inc.
235 East 42nd Street
New York, NY 10017

7. **Drug Product:**

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Ibrance [®]	Capsule	75mg, 100mg & 125mg	oral	Rx	No

8. **Chemical Name and Structure of Drug Substance:**



USAN: palbociclib
Chem. 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: [REDACTED] (b) (4)₂
MW: 447.54

9. **Indication:**

Ibrance is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6, and is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with:

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

10. **Supporting/Relating Documents:** none

11. **Consults:** none

12. **Executive Summary:**

Pfizer NDA 207103 for Ibrance (palbociclib) Capsules 75, 100 & 125mg was approved 3-Feb-15.

This efficacy supplement includes real-world evidence (RWE) in male patients with breast cancer, efficacy results from the updated analyses for Study 1008 (A5481008 [PALOMA-2]) & nonclinical carcinogenicity results. Based on these data, Pfizer proposes that the Ibrance USPI be updated to include male breast cancer patients in the approved indication in order to facilitate their access to this medicine.

There are no proposed CMC changes in SE 207103/S008. Section 1.14.1 contains the PI (annotated (1.14.1.2) & clean (1.14.1.3)), which has been updated to include male breast cancer patients in the approved indication. The draft labeling (clean & redline version) show that no changes have been made to the relevant CMC sections of the PI.

Pfizer has submitted an Environmental Assessment (EA) statement (1.12.14) claiming categorical exclusion from the requirement to prepare an EA in accordance with 21 CFR 25.31(b) applicable for action on a supplement when the estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1ppb (Expected Introduction Concentration (EIC) = [REDACTED] (b) (4)) based on projected total usage at peak market [REDACTED] (b) (4). Pfizer claims that to the best of their knowledge no extraordinary circumstances exist that would significantly affect the quality of the human environment. Pfizer's claim of categorical exclusion is acceptable.

13. **Conclusions & Recommendations:** This supplement is recommended for approval from a CMC perspective.

14. **Comments/Deficiencies to be Conveyed to Applicant:** none

15. **Primary Reviewer:** Lorenzo Rocca, CMC Reviewer, Branch 1, DPMA 1, OLDP, OPQ

16. **Secondary Reviewer:** Ramesh Raghavachari, Branch Chief, Branch 1, DPMA 1, OLDP, OPQ



Lorenzo
Rocca

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Ramesh
Raghavachari

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207103Orig1s008

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: March 5, 2019

To: Julia Beaver, M.D., Director
Division of Oncology Products 1 (DOP1)

Amy Tilley, Regulatory Project Manager, DOP1

William Pierce, PharmD, Associate Director for Labeling, DOP1

From: Kevin Wright, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for Ibrance® (palbociclib) capsules, for oral use

NDA: 207103/Supplement 008

In response to DOP1 consult request dated September 11, 2018, OPDP has reviewed the proposed prescribing information (PI) and patient package insert (PPI). This supplement (S-008) includes real-world evidence of efficacy in males with breast cancer and carcinogenicity results.

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP1 (Amy Tilley) on February 26, 2019, and we do not have any comments.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on March 5, 2019.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

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/s/

KEVIN WRIGHT
03/05/2019 09:37:39 AM

**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: March 5, 2019

To: Julia Beaver, MD
Director
Division of Oncology Products 1 (DOP 1)

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

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Maria Nguyen, MSHS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kevin Wright, PharmD
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: NDA 207103

Supplement Number: S-008

Applicant: Pfizer, Inc.

1 INTRODUCTION

On June 15, 2018, Pfizer, Inc., submitted for the Agency's review a Prior Approval Supplement-Efficacy for New Drug Application (NDA) 207103/S-008 IBRANCE (palbociclib) capsules, for oral use. With this supplement, the Applicant proposes revisions to the Prescribing Information (PI) and Patient Package Insert (PPI) to include male breast cancer patients in the indication. The Applicant provides real-world evidence (RWE) in male patients with breast cancer, updated study results, and nonclinical carcinogenicity results.

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 (DOP 1) on September 11, 2018 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for IBRANCE (palbociclib) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft IBRANCE (palbociclib) capsules PPI received on June 15, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 26, 2019.
- Draft IBRANCE (palbociclib) capsules Prescribing Information (PI) received on June 15, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 26, 2019.
- Approved IBRANCE (palbociclib) capsules labeling dated February 19, 2019.

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.

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 APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
03/05/2019 10:33:29 AM
palbociclib (IBRANCE) NDA 207103 S-008 DMPP-OPDP PPI FINAL MAR 2019

KEVIN WRIGHT
03/05/2019 10:42:44 AM

BARBARA A FULLER
03/05/2019 11:04:09 AM

LASHAWN M GRIFFITHS
03/05/2019 12:07:00 PM