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*APPLICATION NUMBER:*

**207103Orig1s000**

**OFFICE DIRECTOR MEMO**

### Office Director Decisional Memo for Regulatory Action

<b>Date</b>	Electronic stamp date
<b>From</b>	Richard Pazdur, MD
<b>Subject</b>	Office Director Decisional Memo
<b>NDA</b>	207103
<b>Applicant</b>	Pfizer
<b>Date of Submission</b>	Rolling Submission: Part 1 June 30, 2014 Part 2 August 13, 2014
<b>PDUFA Goal Date</b>	April 13, 2015
<b>Proprietary Name / Established (USAN) names</b>	lbrance/palbociclib
<b>Dosage forms / Strength</b>	Capsules: 125 mg, 100 mg, and 75 mg
<b>Proposed Indication(s)</b>	In combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.
<b>Recommended:</b>	<i>Accelerated Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers/ Team Leaders
Division Director	Amna Ibrahim, MD
CDTL	Patricia Cortazar, MD
Regulatory Project Manager	Amy Tilley/Alice Kacuba
Medical Officer Reviewers	Julia Beaver, MD (efficacy)/Patricia Cortazar, MD Laleh Amiri-Kordestani, MD (safety)/Patricia Cortazar, MD
Statistical Review	Erik W Bloomquist/ Shenghui Tang
Pharmacology Toxicology Review	Wei Chen/ Todd Palmby
CMC Review	Joyce Crich PhD (Drug Product)/Ali Hakim, PhD (Branch Chief) Xiao Chen PhD (Drug Substance)/Ali Hakim, PhD (Branch Chief) Minerva Hughes PhD (Biopharm)/Angelica Dorantes PhD
Microbiology Review	Jessica G Cole/Bryan Riley
Clinical Pharmacology Review	Jeanne Fournie Zirkelbach PhD/Qi Liu PhD
Pharmacometrics Review	Jingyu (Jerry) Yu, PhD/Liang Zhao, PhD
Genomics Review	Rosane Charlab Orbach, PhD/Michael Pacanowski, PharmD
DMPP/OPDP	Morgan Walker, PharmD/Jessica Cleck Derenick, PhD
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OSE/DRM Consult	Mona Patel/Naomi Redd
Maternal Health Team Consult	Carrie Ceresa, PharmD/Tamara Johnson, MD

DMPP= Division of Medical Policy Programs  
 OPDP= Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRM= Division of Risk Management

## 1. Introduction

On August 13, 2014, Pfizer completed the rolling submission of a New Drug Application (NDA) for Ibrance (palbociclib) in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

Metastatic breast cancer is incurable and is considered a serious and life-threatening condition. In 2014, it is estimated that 40,000 women will die of breast cancer. Despite the availability of hormone directed therapies for treatment of first-line HR-positive metastatic breast cancer, patients ultimately develop resistance and disease progression and receive multiple subsequent therapies, including many lines of toxic chemotherapies. There is a clear medical need to develop new therapies for the treatment of advanced breast cancer in order to extend life, delay disease progression and/or lessen breast cancer-related symptoms.

Palbociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. In vitro palbociclib reduced cellular proliferation of ER-positive breast cancer cell lines by blocking progression of cells from G1 into S phase of the cell cycle. On April 1, 2013, FDA granted breakthrough therapy designation for palbociclib based on the preliminary clinical evidence submitted for the Phase 1/2 trial which supports this NDA that appeared to demonstrate substantial improvement in progression-free survival when compared to existing therapies.

## 2. CMC/Device

There are no issues that would preclude approval of this application from a CMC perspective.

Drug substance stability studies showed that palbociclib is stable under long term (12 months) 25°C/60%RH and accelerated (6 months) 40°C/75%RH conditions.

The stability data for the drug product support the proposed 24 months shelf-life for the drug product packaged in HDPE bottles and stored at controlled room temperature.

The microbiology review concluded that the drug product is acceptable from the microbiology perspective. In addition, the Office of Compliance issued an overall "acceptable" recommendation on November 30, 2014, for all facilities used for manufacturing and control of the drug substance.

## 3. Nonclinical Pharmacology/Toxicology

There are no issues that would preclude approval of this application from a nonclinical perspective. The following summary of nonclinical pharmacology and toxicology assessments are excerpted from reviews:

- Major adverse effects findings from toxicology studies conducted with oral palbociclib administration (27 weeks in rats and 39 weeks in dogs) at clinically relevant exposures were in the bone marrow/hematolymphoid system and male reproductive organs. Additional target organs of toxicity included the gastrointestinal tract, liver, kidney, endocrine/metabolic system, respiratory system and adrenal glands in rats or dogs.
- Altered glucose metabolism associated with changes in the pancreas (islet cell vacuolation), eye (cataracts, lens degeneration), teeth (degeneration/necrosis of ameloblasts in actively growing teeth), kidney (tubule vacuolation, chronic progressive nephropathy), and adipose tissue (atrophy) were identified in rats at doses approximately 11 times the human exposure (AUC) at the recommended dose. Hyperglycemia was not observed in clinical trials. The Applicant has incorporated appropriate monitoring in their ongoing and planned clinical trials with palbociclib, so no additional nonclinical studies are necessary at this time.
- A numerically higher number of pulmonary embolisms were observed in patients receiving palbociclib and letrozole in clinical trials. There were limited findings of thrombosis in repeat-dose toxicology studies

conducted with palbociclib. However, based on available literature, venous thrombosis is enhanced by overexpression of p16(Ink4) in mice overexpressing p16(Ink4) (Cardenas, Owens, et al. 2011). Since pulmonary embolism has been included as a Warning in the lbrance label, no additional nonclinical studies further assessing the potential for palbociclib to induce thrombosis are required at this time

- Palbociclib was clastogenic in an in vitro micronucleus assay in Chinese Hamster Ovary cells and in vivo in the bone marrow of male rats. Palbociclib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay and did not induce structural chromosomal aberrations in the in vitro human lymphocyte chromosome aberration assay.
- No adverse effects on mating and fertility rates or embryonic development were found in treated female rats at exposures above the human exposure at the recommended dose. Testicular degeneration was observed at exposures (AUC) higher than human exposure in rats and at exposures lower than human exposure in dogs, which was partially reversible.
- 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. Although, knockout mouse data may not be predictive of effects in humans due to differences in degree of target inhibition.

#### 4. Clinical Pharmacology/Biopharmaceutics

There are no issues that would preclude approval of this application from a clinical pharmacology perspective. The following is a summary of the clinical pharmacology review:

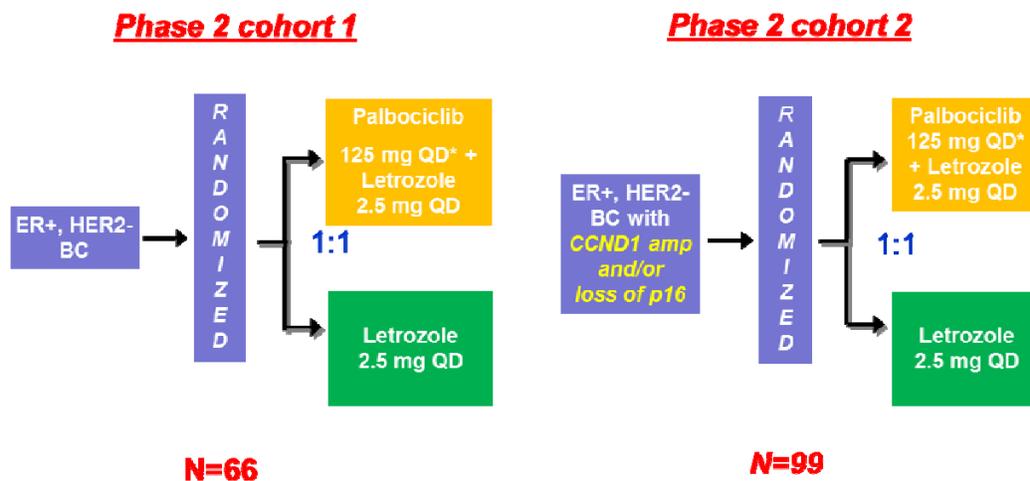
- There is insufficient clinical and PK data to determine if a starting dose adjustment is needed for patients with pre-existing moderate or severe hepatic impairment or patients with co-medications. Therefore, postmarketing studies addressing this issue will be required.
- A definitive conclusion regarding an exposure-response relationship for PFS could not be made due to the limited data at a fixed dose of 125 mg from trial 1003. A greater reduction in absolute neutrophil count appeared to be associated with increased palbociclib exposure. No clinically significant change in the QTc interval was detected when palbociclib was administered to steady state.
- Palbociclib should be administered with food. The palbociclib absorption/exposure of the commercial freebase formulation was low in approximately 13% of the population under a 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. As a result, food intake reduced the inter-subject variability in palbociclib exposure for the commercial freebase formulation, compared to the overnight fasted condition, which supports the recommended administration of palbociclib with food.
- Based on the human mass balance trial, palbociclib is primarily eliminated by hepatic metabolism. Based on the population PK analysis, a dose reduction is not needed in patients with mild or moderate renal impairment, or mild hepatic impairment.
- Palbociclib is primarily metabolized by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. In vivo, palbociclib is a time-dependent inhibitor of CYP3A.
  - *Agents That May Increase Palbociclib Plasma Concentrations:* Coadministration of a strong CYP3A inhibitor (itraconazole) increased the plasma exposure of palbociclib in healthy subjects by 87%. The concomitant use of strong CYP3A inhibitors should be avoided. Grapefruit or grapefruit juice during palbociclib treatment should also be avoided. If coadministration of palbociclib with a strong CYP3A inhibitor cannot be avoided, the dose of palbociclib should be reduced.
  - *Agents That May Decrease Palbociclib Plasma Concentrations:* Coadministration of a strong CYP3A inducer (rifampin) decreased the plasma exposure of palbociclib in healthy subjects by 85%. The concomitant use of strong and moderate CYP3A inducers should be avoided.

- *Drugs That May Have Their Plasma Concentrations Altered by Palbociclib:* Coadministration of midazolam with multiple doses of palbociclib increased the midazolam plasma exposure by 61%, in healthy subjects, compared with administration of midazolam alone. The dose of the sensitive CYP3A substrate with a narrow therapeutic index may need to be reduced as palbociclib may increase their exposure.

## 5. Clinical/Statistical- Efficacy

This NDA is primarily supported by results from PALOMA-1, which was a randomized, open-label, multicenter study of palbociclib plus letrozole versus letrozole alone conducted in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. The trial enrolled 165 patients randomly allocated to receive either palbociclib (125 mg orally daily for 21 consecutive days, followed by 7 days off treatment) plus letrozole (2.5 mg daily continuously throughout the 28-day cycle) or letrozole alone. The trial was divided into two parts: Part 1 enrolled 66 biomarker-unselected patients and Part 2 enrolled 99 biomarker-positive demonstrating CCND1 gene amplification (CCND1/CEP11 ratio > 1.5) and/or loss of CDKN2A/p16 gene (CDKN2A/CEP9 ratio < 0.8).

**Figure 1 PALOMA 1 Trial Design**



Among the 165 patients, 43% had received chemotherapy and 33% had received anti-hormonal therapy as a neoadjuvant or adjuvant treatment. Forty-nine percent of patients had no prior systemic therapy in the neoadjuvant or adjuvant setting. The majority of patients (98%) had metastatic disease; 48% had visceral disease, 75% had bone disease and 19% had bone only disease.

The major efficacy outcome measure was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors Version 1.0 (RECIST). Median investigator-assessed PFS was 20.2 months (95% CI 13.8, 27.5) in the palbociclib plus letrozole arm and 10.2 months (95% CI 5.7, 12.6) in the letrozole alone arm [Hazard Ratio (HR) 0.488 (95% CI 0.319, 0.748)]. The treatment effect of the combination on PFS was also supported by a retrospective radiographic independent review [HR 0.621 (95% CI: 0.378, 1.019).] Overall response rate in patients with measurable disease (investigator assessment) was higher in the palbociclib plus letrozole compared to the letrozole alone arm (55.4% versus 39.4%).

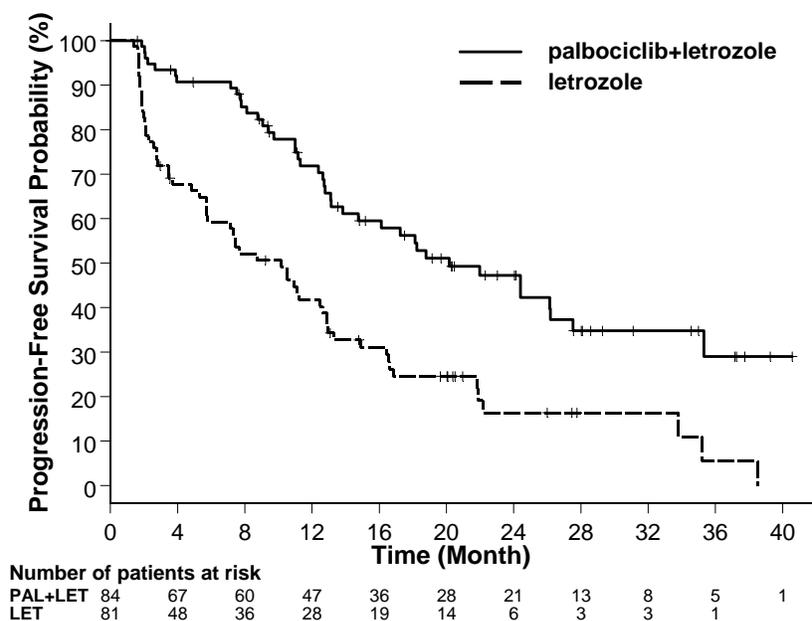
**Table 1 Efficacy Results – PFS (Investigator Assessment, Intent-to-Treat Population) Table**

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

CI=confidence interval; N=number of patients.

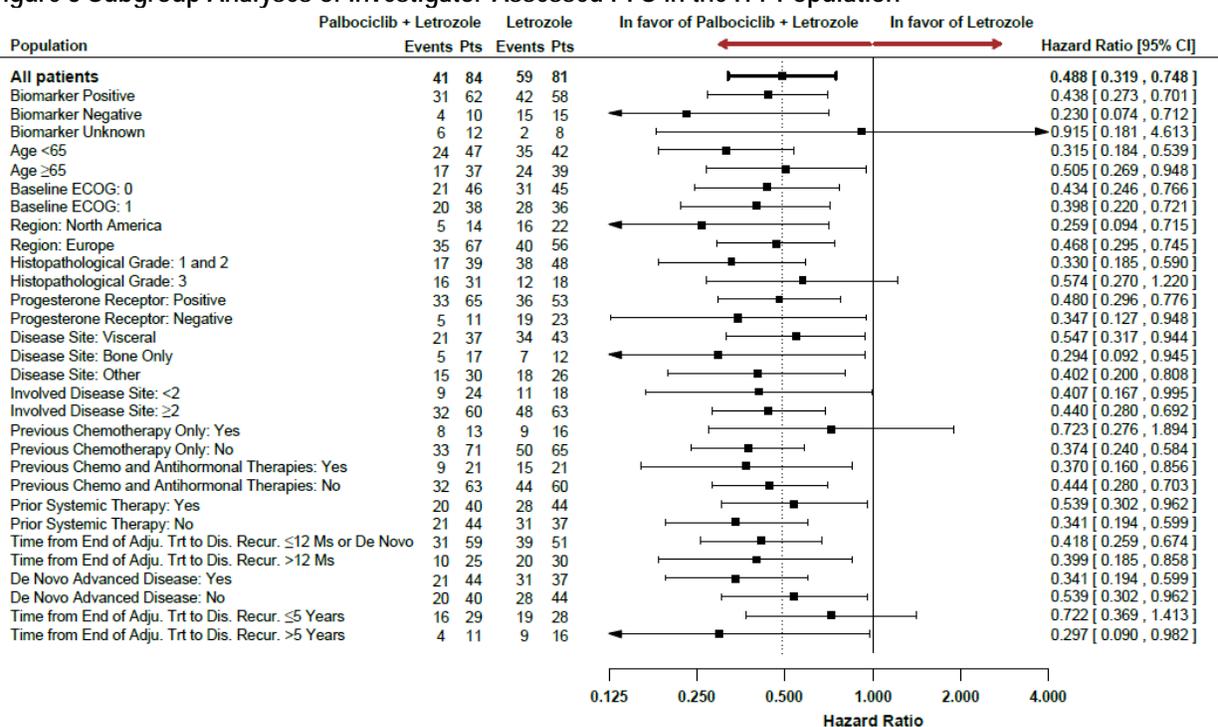
\*Nominal p-value <0.001

**Figure 2 Kaplan-Meier Curves of Progression-Free Survival (Investigator Assessment, Intent to Treat Population) KM curves**



Consistent results were observed across patient subgroups including age, disease-free interval, disease site and prior therapy (Figure 3).

Figure 3 Subgroup Analyses of Investigator-Assessed PFS in the ITT Population



**Overall Survival**

At the data cut off in November 29, 2013, 61 patients had died; 30 death events in the palbociclib plus letrozole arm and 31 death events in the letrozole arm. There is a longer survival, by 4 months in the palbociclib plus letrozole treatment arm [HR 0.813 (95% CI: 0.492, 1.345)]. However, the survival data is not mature at this time.

**Main issues with this application**

The PALOMA-1 trial (A5481003) was not designed to support the marketing authorization of palbociclib, and there were data-driven changes to the statistical analysis plan, as well as protocol deviations which are addressed below.

- Three data driven amendments were incorporated in the protocol and statistical analysis plan as the trial was ongoing. Initially, the protocol planned to enroll 150 biomarker unselected patients. Based on pre-clinical data indicating a potential effect in the biomarker enriched population, the Phase 2 study was amended to include a biomarker selected population based on CCND1 gene amplification and/or loss of CDKN2A/p16 gene. Part 1 of the study included an unselected patient population (N=66) and Part 2 included a biomarker selected population (N=99). After an interim analysis of Part 1 showed a preliminary benefit, enrollment to the Part 2 cohort was halted and the analysis plan for the primary endpoint (PFS) was changed to include the combination of Part 1 and Part 2. These data driven amendments to the statistical analysis plan preclude the interpretation of p-values, (b) (4).
- While the Blinded Independent Central Review (BICR) analysis supported the primary endpoint of PFS (Part 1 and Part 2), the BICR analysis of Part 1 did not support the corresponding investigator-assessed PFS results. This discrepancy likely resulted from disagreements of progression events and high censoring which could indicate a level of investigator bias. Despite these concerns and uncertainties, multiple sensitivity analyses conducted by Pfizer and FDA, supported the finding of clinical benefit.
- The study had a high number of protocol deviations. However, the clinical review team thoroughly reviewed all of the protocol deviations in both treatment arms and concluded that these deviations did not impact the overall efficacy results. An additional concern was that eight investigators had financial information to disclose (see clinical review for additional information). FDA conducted a sensitivity analysis removing the conflicted investigator clinical sites. This sensitivity analysis showed that the PFS effect remained in favor of

the palbociclib plus letrozole arm reassuring there was no bias by leaving these clinical sites in the primary analysis of PFS.

In conclusion, palbociclib in combination with letrozole for the treatment of postmenopausal women with (b)  
(4)-positive HER2-negative advanced breast cancer demonstrates a favorable risk-benefit.

## 6. Safety

Safety data from 458 patients with malignant disease and 297 healthy subjects constitute the safety database for this application. The clinical safety data supporting this NDA is primarily derived from the PALOMA-1 trial (A5481003), (Phase 1, N=12, Phase 2, N=83). The median duration of treatment for palbociclib was 13.8 months while the median duration of treatment for letrozole on the letrozole monotherapy arm was 7.6 months.

The most common adverse reactions (greater than or equal to 10%) were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis. The most frequently reported serious adverse reactions in patients receiving palbociclib plus letrozole were pulmonary embolism (3 of 83; 4%) and diarrhea (2 of 83; 2%).

## 7. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because outside expertise was not necessary.

## 8. Pediatrics

A full waiver in pediatric patients will be granted because the disease/condition does not exist in the pediatric population.

## 9. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Accelerated approval.
- Risk Benefit Assessment  
The assessment of benefit for this NDA is based on a 10-month improvement in median PFS observed in patients receiving palbociclib plus letrozole compared to those receiving letrozole [HR 0.488 (95% CI 0.319, 0.748)]. The improvement in PFS is clinically meaningful, represents an improvement over current therapy, and demonstrates a positive risk-benefit. Consistent results were observed across patient subgroups of disease-free interval, disease site and prior therapy. The treatment effect of the combination on PFS was also supported by a retrospective radiographic independent review [HR 0.621 (95% CI: 0.378, 1.019)]. These results are supported by a higher overall response rate in patients with measurable disease (investigator assessment) in the palbociclib plus letrozole compared to the letrozole alone arm (55.4% versus 39.4%). To address concerns regarding changes to the statistical analysis plan and protocol deviations, multiple sensitivity analyses were performed and supported the finding of clinical benefit for palbociclib.

Overall, the safety profile of palbociclib appeared to be acceptable relative to the benefit. Palbociclib did increase the incidence of cytopenias (particularly neutropenia), infections, diarrhea, nausea, eye disorders, and pulmonary embolisms.

In conclusion, palbociclib in combination with letrozole for the first-line treatment of advanced breast cancer in postmenopausal patients with <sup>(b)</sup><sub>(4)</sub>-positive HER2-negative disease demonstrates a favorable risk-benefit profile. The risk-benefit profile was also acceptable for Drs. Ibrahim, Cortazar, Amiri-Kordestani and Beaver. In addition, the review team recommends approval of this NDA, and I concur. Granting accelerated approval to palbociclib is justified due to the positive benefit risk. Withholding palbociclib from patients while awaiting results from the confirmatory trial would not be appropriate. However, continued approval for this indication may be contingent upon verification and description of clinical benefit in the Phase 3 trial PALOMA-2.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies  
A REMS is not necessary.
- Recommendation for other Postmarketing Requirements and Commitments  
See action letter.

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/s/  
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02/03/2015

RICHARD PAZDUR  
02/03/2015