

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207103Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 2, 2015
DDOP Clinical Team Leader	Patricia Cortazar, M.D.
NDA	207,103
Applicant	Pfizer, Inc
Date of Submission	Rolling Submission: Part 1 June 30, 2014 Part 2 August 13, 2014
PDUFA Goal Date	April 13, 2015
Proprietary Name / Established (USAN) names	Ibrance®/ Palbociclib
Dosage forms / Strength	Capsules: 125 mg, 100 mg, and 75 mg
Proposed Indication(s)	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.
Recommended:	<i>This indication will be approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.</i>

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

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

Introduction

On August 14, 2014, Pfizer Inc. 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.

The approval of palbociclib is primarily based on data from PALOMA-1 trial (A5481003), a randomized, multicenter, open-label trial in postmenopausal women with ER-positive, HER2-negative, advanced (locally advanced or metastatic) breast cancer who had not received previous systemic treatment for 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 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 progression-free survival (PFS) in the intent to treat population (ITT) 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)]. 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%). At the time of the final analysis of PFS, overall survival (OS) data was not mature with 37% of events.

The safety profile of palbociclib when added to letrozole was acceptable and the toxicities were transient and reversible. Palbociclib did increase adverse events particularly the incidence of neutropenia, although no cases of febrile neutropenia were observed in the PALOMA-1 trial (A5481003). 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%).

This document summarizes the reviews and conclusions of each review discipline.

Main issues with this application

The PALOMA-1 trial (A5481003) was not designed to support the marketing authorization of palbociclib. As a result there were data-driven changes to the statistical analysis plan. In addition, there were protocol deviations and issues with respect to compliance and conduct of the study.

- Three data driven amendments were incorporated in the protocol and statistical analysis plan as the trial was ongoing. The initially 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 the 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. [REDACTED] (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 [REDACTED] (b) (4)-positive HER2-negative advanced breast cancer demonstrates a favorable risk-benefit profile with enough evidence to recommend accelerated approval. Despite the concerns with the supporting study and even if the magnitude in the difference in median PFS time is uncertain at this time, palbociclib has a favorable benefit risk given the life-threatening nature of metastatic breast cancer and the acceptable safety profile. Therefore, granting accelerated approval to palbociclib is justified due to the positive benefit risk and withholding palbociclib from patients while awaiting results from the confirmatory trial will not be appropriate. Continued approval for this indication will be contingent upon demonstration of a favorable benefit risk in the confirmatory trial (Phase 3 trial PALOMA-2 A5481008), which is currently fully accrued and final results are expected in the first or second quarter of 2016.

1. Background

Palbociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. In vitro studies demonstrate that 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.

Studies using a patient-derived ER-positive breast cancer xenograft model demonstrate that palbociclib in combination with letrozole inhibits Rb phosphorylation, downstream signaling and tumor growth.

Presubmission regulatory History:

- **March 9th, 2004:** IND 69324 for PD-0332991 (palbociclib) was submitted for the treatment of [REDACTED] ^{(b) (4)}.
- **April 9th, 2008:** The protocol for Study A5481003 was submitted to the IND (SN39/SN0030).
- **October 2nd, 2012:** A Type B End of Phase 2 took place to discuss the potential submission of the Phase 2 trial results to support a Subpart H approval. FDA requested a pre-specified statistical analysis plan (SAP) and detailed safety information. FDA also recommended there be a central review of the Phase 2 PFS data as soon as possible. FDA recommended incorporating an early efficacy analysis (if expecting a large effect) in the Phase 3 confirmatory.
- **April 1st, 2013:** FDA granted breakthrough therapy designation based on the preliminary clinical evidence submitted on PD-0332991 Phase 1/2 trial that appeared to demonstrate substantial improvement in progression-free survival when compared to existing therapies.
- **May 17th, 2013:** At a Type B Pre-NDA meeting, FDA agreed to accept the NDA submission based on the top line results from Study A5481003 as the results appeared to be promising. FDA stated interpretation of p-values will be difficult since there were many looks at the data making the analysis not entirely pre-specified. Pfizer proposed a gatekeeping strategy to maintain statistical rigor with a proposal to analyze the study as a whole and if positive move to individual cohort analyses. Pfizer proposed setting the final analysis of the primary endpoint PFS when approximately 90 events had occurred (instead of the 114 previously stated). The FDA did not agree with the plan to decrease the number of PFS events as the proposal was based on the observed data and was not pre-planned. FDA agreed that the estimated safety data was acceptable to support an NDA submission. FDA encouraged Pfizer to open an expanded access program for palbociclib.
- **November 14th, 2013:** A Type B Breakthrough Meeting follow-up discussed the overall development plan for palbociclib. Pfizer clarified that the interim analysis for the PALOMA-2 confirmatory A5481008 trial would not be available during the A5481003 Phase 2 based NDA review.
- **February 28, 2014:** A Type B Pre-NDA Meeting was held to discuss the Top Line Results from the PALOMA-1 A5481003 study. FDA requested an analysis of the imbalance in censoring on the two arms and reasons for censoring observations in both investigator assessments and BICR analysis. FDA expressed concern that drug administration condition for the initial approval Phase 2 PALOMA-1 A5481003 trial was

under the fasting condition and the confirmatory trial PALOMA-2 A5481008 was under the fed condition with a new free base to-be-marketed formulation. Pfizer responded they would address these issues prior to NDA submission.

- **May 6th, 2014:** A Type B Pre-NDA Meeting was held to discuss CMC issues. FDA agree that the bridging data between the capsule formulation used in fasting conditions in the Phase 2 PALOMA-1 trial with the free base capsule used in the Phase 3 PALOMA-2 trial could be adequate to support the NDA.

2. CMC/Device

The clinical CMC reviewers (Joyce Crich and Xiao Chen) and Branch Chief (Ali Al Hakim) concluded that there are no outstanding issues that preclude approval. Adequate data were provided for the manufacture and controls of the drug substance and drug product. The microbiology reviewer, Minerva Hughes and Team leader (Jessica Dorantes) determined that the drug product is acceptable from the microbiology perspective. The Office of Compliance issued an overall “acceptable” recommendation dated 30-Nov-2014 for all facilities used for manufacturing and control of the drug substance. The following summary of chemistry assessments is excerpted from the CMC reviews:

Drug Substance:

- 1) The molecular formula for palbociclib is C₂₄H₂₉N₇O₂. 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(8H)-one.
- 2) Palbociclib is manufactured by (b) (4)
Impurities are controlled using a risk based control strategy based on process knowledge and process characterization.
- 3) Drug substance specifications were proposed as per ICH guidelines when applicable. Controls of potential genotoxic impurities use a risk based approach instead of regular controls applied to the genotoxic impurities ((b) (4) µg/day), considering the API is potentially genotoxic and patient population being advanced breast cancer patients.
- 4) Drug substance stability studies demonstrated that palbociclib is physicochemically stable under both long term 25oC/60%RH (12 months) and accelerated 40°C/75%RH (6 months) conditions. No significant change or trending has been observed under either storage conditions. Photostability showed that palbociclib is not light sensitive.

Drug Product

- 1) Ibrance (palbociclib) Capsules will be supplied in the following strengths and package configuration:

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

- 2) The stability data support the proposed 24 months shelf-life for the drug product in all three strengths packaged in HDPE bottles and stored at controlled room temperature. The submitted photostability study results on the primary lots indicate that the drug product does not require protection from light.

Biopharmaceutical:

- 1) The biopharmaceutics review evaluated the bridging data linking the initial Phase 3 (free base) formulation and the final to-be-marketed formulation, data supporting the proposed drug substance particle size acceptance criteria and data investigating dissolution effects (i.e., (b) (4)) on bioavailability. These data were adequate and demonstrate the free-base formulation is bioequivalent to the proposed commercial product.

3. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewer, Dr. Chen, and the supervisory reviewers, Drs. Palmby and Leighton state that there are no outstanding clinical pharmacology issues that preclude approval and that no additional pharmacology/toxicology studies are needed. The following summary of nonclinical pharmacology and toxicology assessments are excerpted from the reviews:

1. Palbociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. In vitro, palbociclib reduced cellular proliferation of estrogen receptor (ER)-positive breast cancer cell lines by blocking progression of the cell from G1 into S phase of the cell cycle. Treatment of breast cancer cell lines with the combination of palbociclib and antiestrogens lead to decreased retinoblastoma protein (Rb) phosphorylation resulting in reduced E2F expression and signaling and increased growth arrest compared to treatment with each drug alone. In 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.

2. 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.
3. 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.
4. 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 Ibrance label, no additional nonclinical studies further assessing the potential for palbociclib to induce thrombosis are required at this time.
5. 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.
6. 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.
7. 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,

8. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology/biopharmaceutics reviewer (Jeanne Fournie Zirkelbach, PhD) and team leader (Qi Liu, PhD) concluded that there are no outstanding clinical pharmacology issues that preclude approval. The following are the most important points of the clinical pharmacology and biopharmaceutics review:

- 1) There is insufficient clinical and pharmacokinetic 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 leading to the following PMRs:
 - Submit the final study report for your ongoing clinical trial (A5481013) in subjects with normal hepatic function and pre-existing hepatic impairment to assess the effect of moderate and severe hepatic impairment on the pharmacokinetics of palbociclib.

- Submit the final study report for your ongoing drug interaction trial (A5481039) evaluating the effect of modafinil (a moderate CYP3A inducer) on the pharmacokinetics of palbociclib in healthy volunteers.
- 2) 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.
 - 3) Palbociclib should be administered with food. A bioequivalence trial showed that the commercial freebase formulation was not bioequivalent to the isethionate salt formulation used in the pivotal trial 1003 under overnight fasted conditions. Therefore, the applicant conducted a comparative bioavailability trial which showed that the exposure of the commercial freebase formulation administered with food was comparable to the isethionate salt formulation used in trial 1003, administered under a modified fasted condition similar to trial 1003.

The palbociclib absorption/exposure of the commercial freebase formulation was 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. 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.

- 4) Based on the human mass balance trial, palbociclib is primarily eliminated by hepatic metabolism. Based on the population pharmacokinetic analysis, a dose reduction is not needed in patients with mild or moderate renal impairment, or mild hepatic impairment.
- 5) 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

9. Clinical/Statistical- Efficacy

This NDA is primarily supported by results from a single industry-sponsored study, PALOMA-1 (U.S. study number A5481003), entitled:

“Phase 1/2, Open-Label, Randomized Study of the Safety, Efficacy, and Pharmacokinetics of Letrozole Plus PD 0332991 (Oral CDK 4/6 Inhibitor) and Letrozole Single Agent for the First-Line Treatment of ER Positive, HER2 Negative Advanced Breast Cancer in Postmenopausal Women”

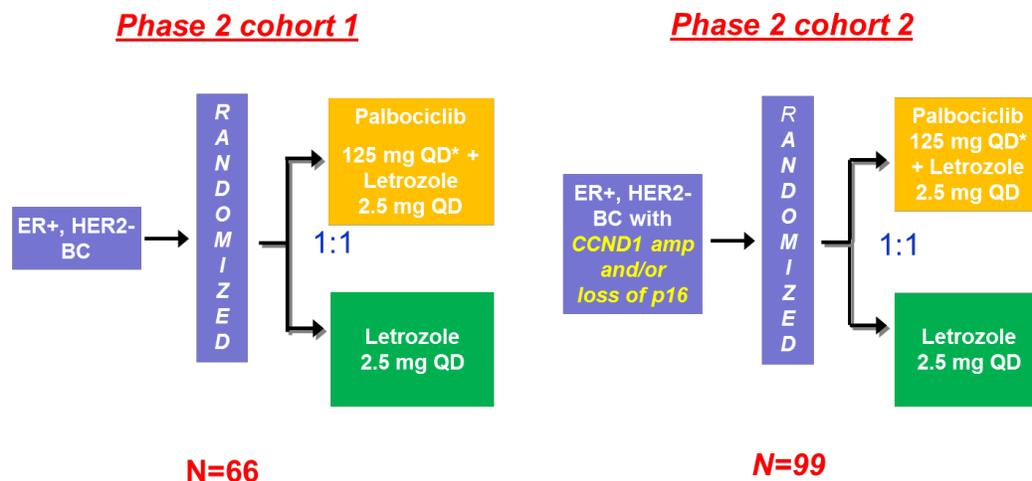
Sixteen additional studies were submitted by Pfizer to support this application: two clinical studies (A5481023, A5481004), two bioavailability (BA) studies (A5481015, A5481021), four comparative BA and bioequivalence (BE) studies (A5481009, A5481020, A5481022, A5481036), three PK and tolerability studies (A5481011, A5481001, A5481010), four extrinsic factor PK studies (A5481012, A5481017, A5481018, A5481026) and a patient PD and PK/PD study (A5481002).

Study Design:

PALOMA-1 trial (A5481003) was a Phase 1/2 randomized, open-label, multicenter study of palbociclib (isethionate salt formulation) 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. Twelve patients were enrolled in the Phase 1 section of the study, which intended to establish the Recommended Phase 2 Dose (RP2D) and to exclude a pharmacokinetic interaction with the combination of letrozole and palbociclib. The clinical efficacy analyses did not take into account the data from these 12 patients.

The Phase 2 section of 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). Randomization was stratified by disease site (visceral versus bone only versus other) and by disease-free interval (>12 months from the end of adjuvant treatment to disease recurrence versus ≤ 12 months from the end of adjuvant treatment to disease recurrence or de novo advanced disease). Patients received study treatment until progressive disease, unmanageable toxicity, or consent withdrawal.

Figure 1 PALOMA 1 Trial Design



The primary endpoint of the study was investigator-assessed PFS evaluated according to Response Evaluation Criteria in Solid Tumors Version 1.0 (RECIST). Progression-free survival (PFS) was defined as the time from randomization date to date of first documentation of progression or death due to any cause, whichever occurred first. Assessments of progressive disease were planned every 8 weeks. Key secondary endpoints included BICR assessed PFS, objective response rate, overall survival and evaluation of tissue levels of Rb, p16/INK4A, CCND1, CDK4, CKD6, and Ki67 and copy number of CCND1 and p16.

Statistical Analysis Plan (SAP):

The original protocol was finalized on March 2008 and incorporated seven protocol amendments. The following protocol data driven amendments resulted in changes to the statistical analysis plan:

- **July 2010 (Protocol Version a3):** The Phase 2 portion of the study was divided as Part 1 (unselected biomarker patient population) and Part 2 (biomarker positive patient population). An interim analysis for Phase 2 Part 2 was added.
- **June 2012 (Protocol Version a5):** The primary analysis plan of PFS was expanded from Part 2 only to include all randomized patients from Part 1 and Part 2. The formerly planned futility interim analysis was replaced by two or possibly three efficacy interim analyses.
- **November 2012 and July 2013 (Protocol Version a6):** A retrospective Blinded Independent Central Review (BICR) evaluation of tumor response based only on radiological evidence was required to all patients randomized in the Phase 2 trial. A formal hypothesis testing procedure to reflect Part 1 and Part 2 as individual cohorts/studies to be analyzed separately was added. The final analysis time of PFS was changed from 114 PFS events to 95 PFS events based upon a slower than expected event rate. The third interim analysis was removed.

The statistical analysis plan specified a sample size of 150 patients needed to detect a 50% improvement in PFS (9 months letrozole arm vs. 13.5 months median palbociclib plus letrozole; HR=0.67) at the one sided significance level of 0.10 with 80% power which required a total of 114 events. However an adjustment was made based on data from the interim analyses (the first performed at 28% of information and 31 PFS events and the second at 50% of information and

57 PFS events) demonstrating a lower event rate than expected and a larger effect size in both the biomarker enriched and the unselected population. Therefore an amendment to the final analysis plan of the primary endpoint PFS was incorporated when 95 PFS events had occurred. At 95 PFS events, there would be more than 98% power to detect a hazard ratio of 0.50 at 1-sided alpha = 0.10 or 75% power to detect a hazard ratio of 0.67.

The significance level for the final analysis was adjusted for the two interim analyses. At the final analysis of the primary endpoint PFS based on the investigator assessment, a Gate-keeping procedure was used for hypotheses testing in a hierarchical approach to control the family wise error rate. The testing started with all patients randomized to Phase 2 trial (Parts 1 and 2). If unable to reject the null hypothesis based on the combined population a Holm procedure will be used to test the same hypotheses for Part 1 and Part 2 as separate cohort.

PFS was assessed using Kaplan-Meier (KM) methods and displayed graphically with median event times and confidence intervals. In addition, the difference in PFS between the treatment and control arms was analyzed using a stratified log-rank test. Unstratified log-rank test was to be applied as a sensitivity analysis and cox regression models were used to estimate the treatment hazard ratio and the confidence intervals.

PALOMA-1 (A5481003) Efficacy Results:

The trial randomized 165 patients, 84 to the palbociclib plus letrozole arm and 81 to the letrozole arm, comprising the ITT population. Patients were recruited at 50 centers in 12 countries. Approximately 74% of the patients were from Europe, 22% from North America, and 4% from Asia. The majority of patients were Caucasian (90%). Patients enrolled in this study had a median age of 63 years (range 38 to 89) and all patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. Forty-three percent of patients had received chemotherapy and 33% had received antihormonal therapy in the neoadjuvant or adjuvant setting prior to their diagnosis of metastatic breast cancer. Forty-nine percent of patients had no prior systemic therapy in the neoadjuvant or adjuvant setting. The majority of patients (98%) had metastatic disease. Nineteen percent of patients had bone only disease, 75% of patients had bone as a site of disease, and 48% of patients had visceral disease.

Baseline demographics were well balanced between treatment arms. Stratification factors, (disease free interval: > 12 months from prior diagnosis versus \leq 12 months or de novo disease and site of disease: visceral vs. bone only vs. other) were misclassified at the time of randomization. Disease free interval was misclassified in 22 patients, although it was equally balanced in the two treatment arms. Stratification based on site of disease was misclassified in 17 (20.2%) patients in the palbociclib plus letrozole arm and 12 (14.8%) patients in the letrozole arm. These misclassification result in an imbalance of patients with visceral disease, (44%: palbociclib arm, 53%: letrozole arm) and bone disease only (21%: palbociclib arm, 15%: letrozole arm). However, as described in the clinical and statistical reviews, sensitivity analyses showed that the misclassifications of the stratification factors do not affect the study results as the PFS analyses remained in favor of the palbociclib plus letrozole arm.

Protocol Deviations:

As stated in the clinical review, there were many protocol deviations in both treatment arms. The review team thoroughly reviewed these protocol deviations and concluded that it did not impact the overall efficacy results. Missed assessments were well balanced between arms and were not followed by progression events. While eight patients were treated with bisphosphonates after enrollment which could have helped stabilize bone disease, seven of the patients that received bisphosphonate were randomized to the letrozole monotherapy arm thus not biasing the study toward palbociclib benefit.

Primary Endpoint: Investigator-Assessed Progression-Free Survival

The primary endpoint of the Phase 2 study was investigator-assessed PFS in the combined (Part 1 and Part 2) population. At the data cut-off date of November 29 2013, 100 investigator-assessed PFS events had occurred; 41 (48.8%) in the palbociclib plus letrozole arm and 59 (72.8%) in the letrozole arm. 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)] (Figure 2, Table 1). The sponsor reported a p-value of 0.0004. However, due to the data-driven changes in the SAP, the FDA statistical review team recommended (b) (4).

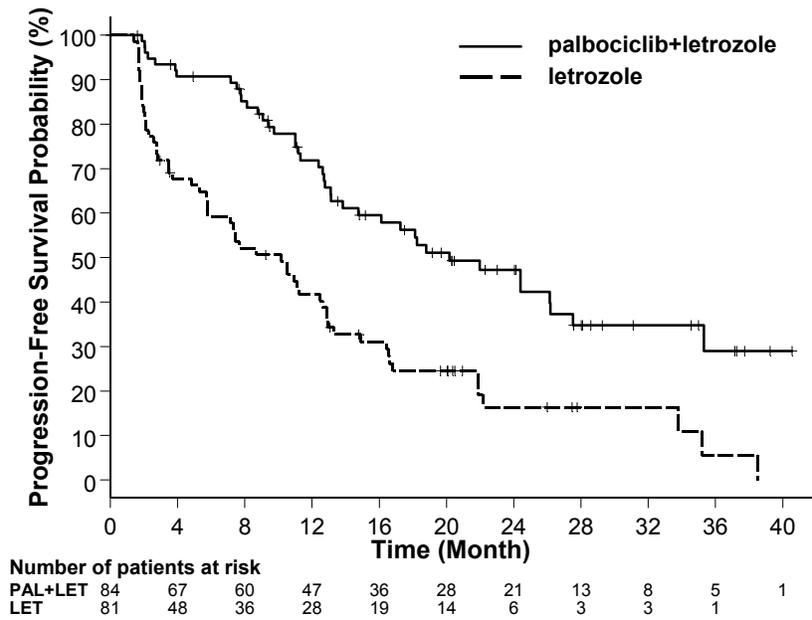
Table 1 Efficacy Results – PFS (Investigator Assessment, Intent-to-Treat Population) Sponsor Table

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

CI=confidence interval; N=number of patients.

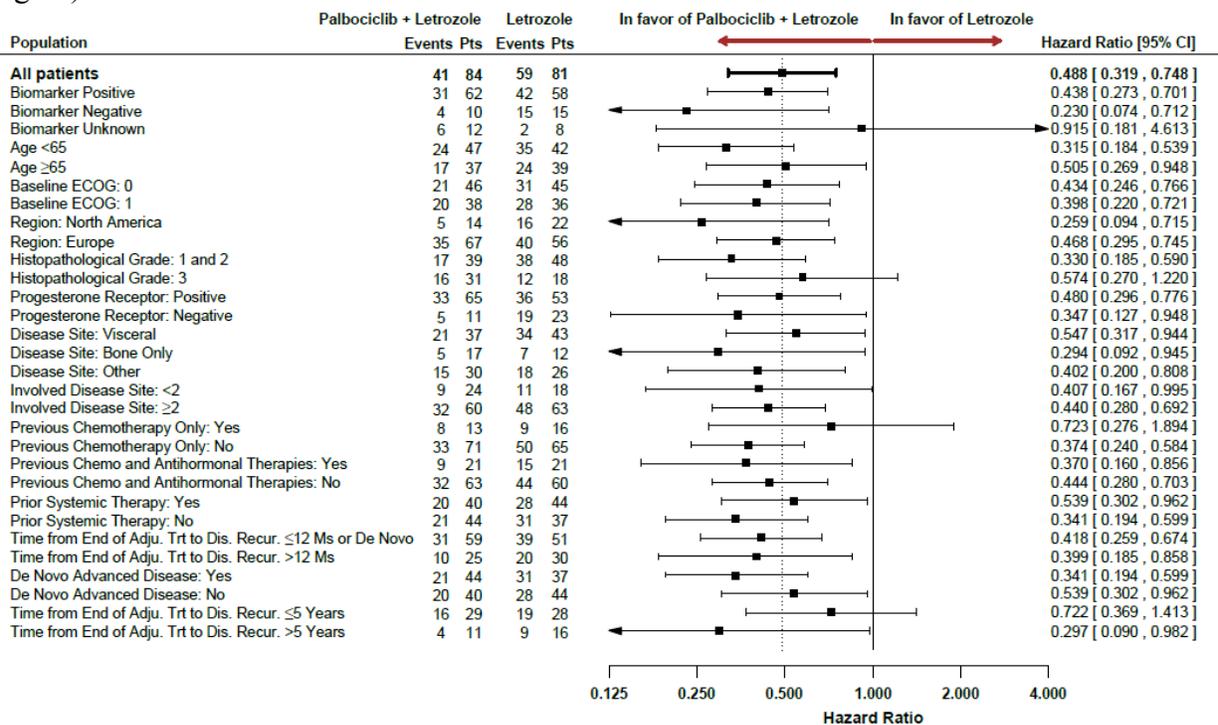
*Nominal p-value <0.001

Figure 2 Kaplan-Meier Curves of Progression-Free Survival (Investigator Assessment, Intent to Treat Population) Sponsor 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 (Applicant Figure)



An improvement in the palbociclib plus the letrozole treatment arm was also observed when the two cohorts were analyzed separately. As shown in Table 2, the magnitude of PFS improvement differs in the two cohorts. Aggressive baseline disease characteristics such as a higher number of patients with de novo disease in the letrozole arm in Part 1 (50%) compared to Part 2 (40%) may explain the lower median PFS seen in the letrozole monotherapy arm. The PFS in the palbociclib plus letrozole treatment arm was lower in Part 2 compared to Part 1. A certain level of investigator bias could be the cause of the treatment effect difference in Part 1 and Part 2.

Table 2 Investigator-assessed PFS by Part (From Reviewer 's Table)

	Part 1		Part 2		Part 1 + Part2	
	P+L N=34	L N=32	P+L N=50	L N=49	P+L N=84	L N=81
Number of events (%)	15(44.1%)	25 (78.1%)	26 (52.0%)	34 (69.4%)	41 (48.8%)	59 (72.8%)
Censored (%)	19 (55.9%)	7 (21.9%)	24 (48.0%)	15 (30.6%)	43 (51.2%)	22 (27.2%)
Median PFS (months)	26.1	5.7	18.1	11.1	20.2	10.2
95% CI	(11.2, NR)	(2.6, 10.5)	(13.1, 27.5)	(7.1, 16.4)	(13.8, 27.5)	(5.7,12.6)
Hazard Ratio	0.299		0.508		0.488	
95% CI	(0.156 – 0.572)		(0.303 – 0.853)		(0.319 – 0.748)	
p-value*	<0.01		<0.01		<0.01	

*Nominal p-value

The treatment effect of palbociclib plus letrozole on PFS in the ITT population was also supported by a retrospective radiographic independent review [HR 0.621 (95% CI: 0.378, 1.019)]. However, the BICR results showed that the palbociclib treatment had a smaller improvement in PFS compared to the investigator assessed PFS analysis. As shown in Table 3, the BICR analysis of Part 1 did not support the corresponding investigator-assessed PFS results. To understand the differences between the investigator-assessment of PFS and the BICR-assessment of PFS, the FDA clinical review team thoroughly reviewed the case report forms, narratives, available radiology reports, BICR adjudication and datasets, from all patients in the trial.

The inconsistent BICR-assessed PFS results (Part 1) of the study are most likely due to the high BICR censoring. In most instances, the investigator determined progressive disease and took the patient off treatment, while the BICR did not confirm progressive disease by imaging. These differences appear to have been driven by bone progression. It is well known that bone lesion progression according to RECIST criteria is difficult to assess and could have accounted for the difficulty of the BICR to call disease progression in the bone. The clinical review team reviewed the narratives and case report forms from all the patients who had bone progression and believe that the investigator assessments were appropriate although it is not possible to rule out a certain level of bias. A sensitivity analysis was conducted in 96 patients where the investigator and BICR did not agree on the timing or censoring of the PFS events. Despite these concerns and

uncertainties, multiple sensitivity analyses supported the findings of clinical benefit (see clinical and statistical reviews for details).

Table 3 BICR-assessed PFS by Part (From Sponsor's CSR)

	Part 1		Part 2		Part 1 + Part2	
	P+L N=34	L N=32	P+L N=50	L N=49	P+L N=84	L N=81
Number of events (%)	11 (32.4%)	9 (28.1%)	20 (40%)	24 (49%)	31 (36.9%)	33 (40.7%)
Censored (%)	23 (67.6%)	23 (71.9%)	30 (60%)	25 (51%)	53 (63.1%)	48 (59.3%)
Median PFS (months)	31.6	38.6	20.3	14.6	25.7	14.8
95% CI	(11.2, NR)	(7.5, 38.6)	(12.2, NR)	(8.1, 20.0)	(17.7, NR)	(9.3, 20.4)
Hazard Ratio	0.731		0.576		0.621	
95% CI	(0.300 – 1.779)		(0.316 – 1.050)		(0.378 – 1.019)	
p-value*	0.242		0.0342		0.0286	

*1-sided p-value from the log-rank test

Objective Response Rate:

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%). The duration of response was longer in the palbociclib plus letrozole arm (20.3 months; 95% CI 13.4-25.8) compared to the letrozole alone arm (11.1 months; 95% CI: 9.3-31.6).

Overall Survival

At the data cut off in November 29, 2013, there were 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.

10.Safety

Safety data from 458 patients with malignant disease and 297 healthy subjects constitute the safety database for this application. The safety data is sufficient to detect uncommon adverse reactions occurring at an incidence of 2-3%. 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. Key safety findings are summarized as follows:

Deaths

As of November 29, 2013, 1 of 83 patients in the palbociclib plus letrozole arm and 0 of the 77 patients in the letrozole alone arm died on-study (within 28 days of the last dose). According to the investigator attributed this death to disease progression.

Serious Adverse Events

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%).

Dose Reductions and Discontinuations

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving palbociclib plus letrozole. Permanent discontinuation due to an adverse reaction occurred in 7 of 83 (8%) patients receiving palbociclib plus letrozole and in 2 of 77 (3%) patients receiving letrozole alone. Adverse reactions leading to discontinuation for those patients receiving palbociclib plus letrozole included neutropenia (6%), asthenia (1%), and fatigue (1%).

Neutropenia

Decreased neutrophil counts were observed in clinical trials with palbociclib. Grade 3 (57%) or 4 (5%) decreased neutrophil counts were reported in patients receiving palbociclib plus letrozole in the PALOMA-1 trial (A5481003). Median time to first episode of any grade neutropenia per laboratory data was 15 days (13-117 days). Median duration of Grade ≥ 3 neutropenia was 7 days. Febrile neutropenia events were reported in the palbociclib clinical program, although no cases of febrile neutropenia were observed in the PALOMA-1 trial (A5481003).

Infections

An increase incidence of infections events were observed in the palbociclib plus letrozole arm (55%) compared to the letrozole alone arm (34%). Febrile neutropenia events have been reported in the palbociclib clinical program, although no cases were observed in PALOMA-1 trial (A5481003). Grade ≥ 3 neutropenia was managed by dose reductions and/or dose delay or temporary discontinuation consistent with a permanent discontinuation rate of 6% due to neutropenia.

Pulmonary Embolism

Pulmonary embolism was reported at a higher rate in patients treated with palbociclib plus letrozole (5%) compared with no cases in patients treated with letrozole alone in the PALOMA-1 trial (A5481003).

Adverse drug reactions ($\geq 10\%$) reported in patients who received palbociclib plus letrozole or letrozole alone according to CTCAE Version 3.0, are listed in Table 4.

Table 4 Adverse Reactions (> 10%)

System Organ Class	IBRANCE + Letrozole (N=83)			Letrozole Alone (N=77)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Adverse Reaction	%	%	%	%	%	%
Infections and infestations						
URI ^a	31	1	0	18	0	0
Blood and lymphatic system disorders						
Neutropenia	75	48	6	5	1	0
Leukopenia	43	19	0	3	0	0
Anemia	35	5	1	7	1	0
Thrombocytopenia	17	2	0	1	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	7	0	0
Nervous system disorders						
Peripheral neuropathy ^b	13	0	0	5	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	11	0	0	1	0	0
Gastrointestinal disorders						
Stomatitis ^c	25	0	0	7	1	0
Nausea	25	2	0	13	1	0
Diarrhea	21	4	0	10	0	0
Vomiting	15	0	0	4	1	0
Skin and subcutaneous tissue disorders						
Alopecia	22 ^d	N/A	N/A	3 ^e	N/A	N/A
General disorders and administration site conditions						
Fatigue	41	2	2	23	1	0
Asthenia	13	2	0	4	0	0
URI=Upper respiratory infection. ^a URI includes: Influenza, Influenza like illness, Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Upper respiratory tract infection. ^b Peripheral neuropathy includes: Neuropathy peripheral, Peripheral sensory neuropathy. ^c Stomatitis includes: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis. ^d Grade 1 events - 21%; Grade 2 events - 1%. ^e Grade 1 events - 3%.						

11. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

12. Pediatrics

Palbociclib has not been studied in children.

The review for palbociclib will be conducted by the PeRC PREA Subcommittee on February 4, 2015. The Division presented a full waiver in pediatric patients because the disease/condition does not exist in the pediatric population, which is indicated 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.

13. Other Relevant Regulatory Issues

According to the Applicant, the study was conducted in full conformance with the principles of the Declaration of Helsinki or with the laws and regulations of the country where the research was conducted, whichever provided greater protection to the individual. The study adhered to the January 1997 ICH Guideline for Good Clinical Practice. Written informed consent was obtained from each participant in the study. The protocol and subsequent amendments were approved by local Independent Ethics Committees (IEC) or Institutional Review Boards (IRB).

The OSI inspected four of the highest accruing sites: Site 1033 (Professor John Paul Crown, Dublin, Ireland), Site 1011 (Dr. Istvan Lang, Budapest, Hungary), and Site 1008 (Dr. Katalin Boer, Budapest, Hungary) and Site 1001 (Dr. Richard Samuel Finn, Los Angeles, USA). The applicant and the CRO (b) (4) who performed the function of the Blinded Independent central Review (BICR)/Central Imaging Vendor were also inspected and found on interim classification to have no major issues

The inspectional findings revealed no significant deviations that would preclude the use of the clinical data provided in support of this NDA. Site (1001) was issued five inspectional observations for “failure to follow the investigational plan, failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation (AEs and concomitant medications), subjects not signing the most current informed consent document and inaccurate investigational drug disposition. A sensitivity analysis was performed removing all the patients from site 1001. This analysis does not change the conclusions of the study (see clinical review).

There were 381 investigators (58 principal investigators and 323 sub-investigators) in the PALOMA-1 trial (A5481003). All the investigators were screened for financial disclosures. Eight had financial information to disclose (see clinical review for additional information). A sensitivity analysis was performed removing the clinical sites of the conflicted investigators. The PFS effect remained in favor of the palbociclib plus letrozole arm providing reassurance there was no bias by leaving these clinical sites in the primary analysis.

14. Labeling

There were extensive internal labeling discussions with all review disciplines. Key clinical labeling recommendations included:

Changes to the proposed indication were added to avoid confusion by the breast cancer medical community.

From: “IBRANCE is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer **who have not received previous systemic treatment for their advanced disease**”

To: “IBRANCE is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer **as initial endocrine-based therapy for their metastatic disease.**”

Highlights Section and Indications and Usage Section 1, it was specified that the current approval is to be under accelerated approval provisions based on progression-free survival and that continued approval may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Dose modifications and management for neutropenia were included in Section 2.

The Warnings and Precautions Section included information on neutropenia, infections and pulmonary embolism.

In Clinical Studies Section, (b) (4) (see the statistical review for additional information regarding (b) (4)).

15.Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

We recommend that this NDA be approved under the accelerated approval regulations, 21 CFR 601.41, for the following indication:

“IBRANCE is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast as initial endocrine-based therapy for their metastatic disease”

- Risk Benefit Assessment

Metastatic breast cancer is incurable and therefore 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. It has been over 15 years since a drug was approved for this specific indication. There is a clear medical need to address 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.

The assessment of benefit in 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 and represents a large improvement over current therapy. 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%). However, there are limitations to the pivotal study. Many of the uncertainties in the clinical trial are due to the fact that the study was not planned or conducted with the expectation of supporting marketing approval. As a result there were data-driven changes to the statistical analysis plan, protocol deviations and issues with respect to compliance and conduct of the study. In addition, while Blinded Independent Central Review (BICR) analysis supported the primary endpoint of PFS (in the combined Part 1 and Part 2 population), the BICR analysis of Part 1 of the study alone did not support the corresponding investigator-assessed PFS results. This discrepancy likely resulted from disagreements of progression events and censoring which could indicate a level of investigator bias. Despite these concerns and uncertainties, multiple sensitivity analyses supported the finding of clinical benefit.

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. There is assurance given the data that the neutropenia can be appropriately managed as evidenced by a lower frequency of discontinuations in Part 2 of the study which took place after many of the dose modification issues were worked out in Part 1. There are no postmarketing safety requirements, however more information will be gained from multiple large planned or ongoing Phase 3 trials examining palbociclib in both the adjuvant and advanced breast cancer settings.

In conclusion, palbociclib in combination with letrozole for the first-line treatment of advanced breast cancer in postmenopausal patients with ^{(b) (4)}-positive HER2-negative disease demonstrates a favorable risk-benefit profile with enough evidence to recommend accelerated approval. Therefore, granting accelerated approval to palbociclib is justified due to the positive benefit risk and withholding this treatment from patients while awaiting results from the confirmatory trial will not be appropriate. Despite the concerns with the pivotal study, the benefit of introducing palbociclib for this patient population outweighs the potential risks. However, continued approval for this indication may be contingent upon verification and description of clinical benefit in the Phase 3 trial PALOMA-2 (A5481008).

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
The clinical review team believes that a REMS is not required for this product for the requested indication. When administered in accordance with product labeling, it is

anticipated that the risks of palbociclib will be tolerable and manageable. There are no unusual risks which required training to assure safe use, given that this therapy is generally prescribed and administered only by healthcare professionals with specific training and experience in medical oncology and use of agents with similar toxicities.

- Recommendation for other Postmarketing Requirements and Commitments

ACCELERATED APPROVAL REQUIREMENTS

Rationale for PMR:

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. If postmarketing studies/clinical trials fail to verify clinical benefit are not conducted with due diligence, FDA, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. The following is the description and milestones for this postmarketing requirement (PMR).

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

Trial Completion:	12/2016
Final PFS Report Submission:	06/2017
Final OS Report Submission:	11/2020

POSTMARKETING REQUIREMENTS UNDER 505(o)

Rationale for PMR:

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute. FDA have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of hepatic impairment and the effect of a moderate CYP3A inducer on the pharmacokinetics of palbociclib. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk. Therefore, based on appropriate scientific data, FDA has determined that Pfizer is required to conduct the following PMRs:

- 2860-2 Submit the final report for your clinical trial A5481013 entitled, “A phase 1, open-label, single dose, parallel-group study to evaluate the pharmacokinetics of palbociclib (PD-0332991) in subjects with impaired hepatic function”, to assess

the effect of moderate and severe hepatic impairment on the pharmacokinetics of palbociclib.

Trial Completion: 06/2017
Final Report Submission: 12/2017

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

Rationale for PMC:

Further biomarker exploration is needed given that the pivotal trial PALOMA-1 did not identify a biomarker for prediction or prognosis, but did indicate the potential that patients with *CDKN2A* loss might benefit less from palbociclib. These findings are preliminary in a small sample size and would require confirmation in a future study.

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

Trial Completion: 04/2015
Final Report Submission: 10/2015

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

Trial Completion: 12/2016
Final Report Submission: 06/2017

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

/s/

PATRICIA CORTAZAR
02/02/2015