CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207103Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

FDA	20-7103 (IND 69,324)
Submission Date:	8/13/14
Brand Name:	Ibrance™
Generic Name:	Palbociclib (PD-0332991 or PF-00080665)
Formulation:	75, 100, 125 mg capsules
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OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Pfizer Inc.
Submission Type; Code:	NDA 0000/01, 0012, 0014, 0017, 0056
Dosing regimen:	Once daily oral dose of 125 mg palbociclib for 3 weeks, and 1 week off. Once daily oral dose of 2.5 mg letrozole, continuously.
Indication:	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 who have not received previous systemic treatment for their advanced disease.

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1 Executive Summary

Palbociclib is a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). The proposed indication is 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 who have not received previous systemic treatment for their advanced disease. The proposed dosing regimen is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.

The registration trial (A5481003; 1003; PALOMA) was an open-label, randomized, Phase 1/2 trial in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease. In the phase 2 part, patients (N = 165) were randomized 1:1 to receive palbociclib (125 mg daily for 3 weeks, followed by 1 week off) in combination with letrozole (2.5 mg daily) or letrozole (2.5 mg daily) alone. In Part 1 of the Phase 2 portion (N=66), patients were not selected on the basis of cyclin D1 (CCND1) or CDKN2A status, whereas in Part 2 (N=99), only patients with CCND1 amplification and/or CDKN2A loss were included. The major efficacy outcome measure was investigator-assessed progression-free survival (PFS) in the overall Phase 2 portion of the trial. The final analysis showed that median PFS was statistically significantly prolonged at 20.2 months (95% confidence interval: 13.8-27.5) on the palbociclib plus letrozole arm compared to 10.2 months (95% confidence interval: 5.7-12.6) on the letrozole alone arm. Given the PFS benefit and preliminary clinical evidence that the composite biomarker (i.e., CCND1/CDKN2A) does not robustly differentiate responders beyond ER positivity, the proposed indication in ER-positive/HER2-negative breast cancer [redacted] (b) (4) appears acceptable pending further assessment of CDKN2A loss on palbociclib responses.

A definitive conclusion regarding an exposure-response relationship for PFS could not be made based on the limited data at a fixed dose of 125 mg from trial 1003. A greater reduction in absolute neutrophil count appears 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. A bioequivalence trial showed that the commercial freebase formulation was not bioequivalent to the isethionalte 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.

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.

In vitro, palbociclib is metabolized by CYP3A4 and SULT2A1. In vivo, palbociclib exposure was increased by 1.9-fold when it was coadministered with itraconazole (strong CYP3A4 inhibitor), and coadministration of strong CYP3A4 inhibitors should be avoided. If coadministration with a strong CYP3A inhibitor cannot be avoided, the daily palbociclib dose should be reduced to 75 mg. In vivo, palbociclib exposure was decreased by 85% when it was coadministered with rifampin (strong CYP3A inducer), and coadministration of strong CYP3A inducers should be avoided. The effect of moderate CYP3A inducers on palbociclib exposure is not known, and coadministration of moderate CYP3A4 inducers should be avoided. Coadministration of palbociclib with multiple doses of rabeprazole (proton pump inhibitor) under fed conditions did not have a clinically significant effect on palbociclib exposure. In vitro, palbociclib caused time-dependent inhibition of CYP3A. Palbociclib increased the midazolam (CYP3A substrate) AUC by 61% in healthy subjects, and coadministration of sensitive CYP3A substrates with a narrow therapeutic indices should be avoided.

Recommendations

The Office of Clinical Pharmacology (Divisions of Clinical Pharmacology V and Pharmacometrics) have reviewed the information contained in NDA 20-7103. This NDA is considered acceptable from a clinical pharmacology perspective. The adequacy or inadequacy of specific drug information is provided below:

Decision	Sufficiently Supported?	Recommendations and Comments
Evidence of Effectiveness	☒ Yes ☐ No ☐ NA	Pivotal and supportive trials
Proposed dose for general population	☒ Yes ☐ No ☐ NA	The proposed dose appears sufficiently efficacious and safe in the proposed patient population with the current capsule formulation. Please refer to the clinical reviews for safety and efficacy.
Dose adjustment in specific patients or patients with co-medications	☐ Yes ☒ No ☐ NA	PMR studies: 1. Submit the final study report for your ongoing clinical trial (A5481013) evaluating the effect of pre-existing moderate and severe hepatic impairment on palbociclib exposure. 2. Submit the final study report and datasets for your ongoing trial (A5481039) evaluating the effect of modafinil (a moderate CYP3A inducer) on palbociclib exposure in healthy volunteers.
Pivotal bioequivalence studies	☒ Yes ☐ No ☐ NA	The bioequivalence trial showed that the commercial freebase formulation was not bioequivalent to the isethionalte salt formulation used in the pivotal trial 1003, under fasting conditions. A comparative bioavailability trial showed that the exposure of the commercial freebase formulation administered with food (as proposed in the labeling) was comparable to the isethionate salt formulation used in the pivotal trial, administered under a fasted condition, (similar to the pivotal trial).
Labeling	☒ Yes ☐ No ☐ NA	

Labeling Recommendations
Please refer to Section 3 - Detailed Labeling Recommendations.

1.2 Post Marketing Requirements

1 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.

2 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.

Comments to the Applicant:

Submit the final study report and datasets for your ongoing clinical trial (A5481014) in patients with normal renal function and patients with pre-existing renal impairment to assess the effect of severe renal impairment on the pharmacokinetics of palbociclib.

Comment to the Clinical Review Team:

OCP concurs with the recommended post-marketing commitment to formally evaluate the effect of CDKN2A and other potential biomarkers of palbociclib response (e.g., RB1 status may be a critical determinant of response based on palbociclib's mechanism) in ongoing and planned trials (e.g., PALOMA-2 [A5481008]).

1.3 Summary of Clinical Pharmacology Findings

Palbociclib (IBRANCE^{TM}) is a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). Interaction with the D-type cyclins activates CDK4/CDK6, which in turn, phosphorylate the retinoblastoma protein (Rb), a critical checkpoint for G1/S cell cycle progression and commitment to cellular proliferation. The proposed indication is palbociclib in combination with letrozole, for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease. The proposed dosing regimen is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib should be taken with food in combination with letrozole 2.5 mg once daily given continuously.

The single and multiple dose pharmacokinetics of palbociclib were characterized in patients with solid tumors including advanced breast cancer and in healthy subjects. The maximum plasma palbociclib concentration (C_{max}) is generally observed between 6 to 12 hours (time to reach maximum concentration, T_{max}) following oral administration. The mean (± standard deviation) plasma elimination half-life was 29 hours (±5 hours), and the mean apparent oral clearance was 63.1 L/hr (29% CV). The mean absolute bioavailability of IBRANCE after an oral 125 mg dose is 46%. At steady state, the plasma mean C_{max} value for palbociclib is 116 ng/mL (28% CV) and the plasma mean predose trough value is 61 ng/mL (42% CV). In the dosing range of 25 mg to 225 mg, the AUC and C_{max} increased proportionally with dose. Steady state was achieved within 8 days following repeated once daily dosing, with a median accumulation ratio of 2.4 (range 1.5-4.2).

Palbociclib should be administered with food. A bioequivalence trial showed that the commercial freebase formulation was not bioequivalent to the isethionalte 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 the pivotal trial, administered under a modified fasted condition similar to the pivotal trial.

The palbociclib absorption/exposure of the commercial freebase formulation was very low in approximately 13% of the population under the fasted condition. Food intake can increase the palbociclib exposure in this small subset of the population, while not altering the palbociclib exposure in the rest of the population to a clinically relevant extent. As a result, food intake reduced the intersubject variability in palbociclib exposure for the commercial freebase formulation, compared to the overnight fasted condition, which supports the recommended administration of palbociclib with food.

The human mass balance trial showed that following a single oral dose of ^{14}C-palbociclib, palbociclib is primarily eliminated by hepatic metabolism, and renal elimination appears to play a minor role. Based on the population pharmacokinetic analysis, a dose reduction is not needed in patients with mild or moderate renal impairment, or mild hepatic impairment. Dedicated organ impairment trials are currently ongoing to assess the effect of severe renal impairment or moderate and severe hepatic impairment on the pharmacokinetics of palbociclib.

In vitro, palbociclib is metabolized by CYP3A4 and SULT2A1. Palbociclib exposure was increased by 1.9-fold when it was co-administered with itraconazole (strong CYP3A4 inhibitor), and coadministration of strong CYP3A4 inhibitors should be avoided. If coadministration with a strong CYP3A inhibitor cannot be avoided, the daily palbociclib dose should be reduced to 75 mg. In vivo, palbociclib exposure was decreased by 85% when it was coadministered with rifampin (strong CYP3A inducer), and coadministration of strong CYP3A inducers should be avoided. The effect of moderate CYP3A inducers on palbociclib exposure is not known, and coadministration of moderate CYP3A4 inducers should be avoided. A drug interaction trial to assess the effect of modafinil (moderate CYP3A inducer) on palbociclib exposure is currently ongoing. In vivo, coadministration of palbociclib with multiple doses of rabeprazole (proton pump inhibitor) under fed conditions did not have a clinically significant effect on the pharmacokinetics of palbociclib.

In vitro, palbociclib caused time-dependent inhibition of CYP3A. Palbociclib at steady state increased the midazolam (CYP3A substrate) AUC by 61% in healthy subjects, and coadministration of palbociclib with sensitive CYP3A substrates with a narrow therapeutic indices should be avoided. In vitro, palbociclib is a substrate for human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), however these transport mechanisms are unlikely to affect the extent to oral absorption of palbociclib at therapeutic doses. In vitro, palbociclib shows low potential to inhibit P-gp.

A definitive conclusion regarding an exposure-response relationship for the efficacy endpoint of PFS could not be made based on the limited data at a fixed dose of 125 mg from trial 1003. A greater reduction in absolute neutrophil count appears to be associated with increased palbociclib exposure. Palbociclib administered to steady state does not prolong the QT interval to any clinically relevant extent.

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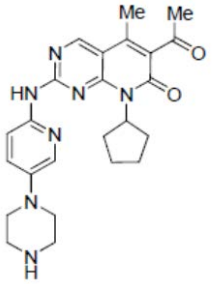
2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The immediate release capsules for oral administration each contains 75 mg, 100 mg, or 125 mg of palbociclib (PD-0332991; (b) (4) freebase).

Figure 1. Structural Formula of palbociclib



- **Established names:** Palbociclib (PD-0332991; (b) (4) freebase)
- **Molecular Weight:** 447.54 Daltons
- **Molecular Formula:** $C_{24}H_{29}N_7O_2$
- (b) (4) Palbociclib is an (b) (4) molecule.
- **Dissociation Constant (pKa):** There are two dissociation constants of palbociclib, pKa1 = 7.4 (the secondary piperazine nitrogen) and pKa2 = 3.9 (the pyridine nitrogen).
- **Chemical Name:** 6-Acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
- **Solubility:** At or below pH 4, palbociclib behaves as a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Interaction with the D-type cyclins activates CDK4/CDK6, which in turn, phosphorylate the retinoblastoma protein (Rb), a critical checkpoint for G1/S cell cycle progression and commitment to cellular proliferation. Palbociclib (PD 0332991) is a selective, reversible inhibitor of CDK4 and CDK6 that prevents cellular proliferation by prohibiting progression of the cell cycle from G1 into the S phase.

The proposed indication is 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 who have not received previous systemic treatment for their advanced disease.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed palbociclib dosing regimen is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib should be taken with food in combination with letrozole 2.5 mg once daily given continuously.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Three completed trials (trials 1001, 1002 and 1003) were conducted in patients with advanced malignant disease, and incorporated pharmacokinetic (PK) analyses.

Eleven phase 1 clinical pharmacology and biopharmaceutics trials of palbociclib were conducted in healthy subjects. Table 1 below summarizes the design features of the clinical trials that were used to support the Clinical Pharmacology and Biopharmaceutics Section of the NDA.

Table 1. Clinical trials that were used to support the Clinical Pharmacology and Biopharmaceutics.

Study No.	Study Type	Study Treatment	Palbociclib Formulation (Fasted/Fed Condition)	N	Full PK Sampling	Sparse Sampling	NCA	PopPK/ PK-PD[a]
Patients With Cancer: Palbociclib Administered Alone or in Combination With Other Drugs								
A5481001	Phase 1 dose escalation	All doses	Isethionate capsule (fasting for 2 hours before and 2 hours after dosing)	74	X	X	X	X
		Schedule 3/1:		41				
		25 mg QD		3				
		50 mg QD		3				
		75 mg QD		7				
		100 mg QD		3				
		125 mg QD		22				
		150 mg QD		3				
		Schedule 2/1:		33				
		100 mg QD		3				
		150 mg QD		4				
		200 mg QD		20				
		225 mg QD		6				
	Food effect (substudy)	Palbociclib 125 QD on Schedule 3/1 and 200 mg QD on Schedule 2/1	Isethionate capsule (either after an overnight fasting or a high-fat meal)	12	X	X	X	X
A5481002	Phase 1 PD and safety	Palbociclib 125 mg QD on Schedule 3/1	Isethionate capsule (fasting for 2 hours before and 2 hours after dosing)	17		X		X
A5481003	Phase 1/2 efficacy and safety (combination of palbociclib with letrozole)	All doses		172				
		Phase 1: palbociclib 125 mg QD on Schedule 3/1;[b] letrozole 2.5 mg QD	Phase 1: isethionate capsule (after an overnight fasting)	12	X	X	X	X
		Phase 2: palbociclib 125 mg QD on Schedule 3/1; letrozole 2.5 mg QD	Phase 2: isethionate capsule (fasting for 1 hour before and 2 hours after dosing)	160		X		X
A5481010[c]	Phase 1/2 single-agent dose escalation; safety and efficacy (combination of palbociclib with letrozole)	Part 1: palbociclib 100 and 125 mg QD on Schedule 3/1	Isethionate capsule (fasting for 2 hours before and 2 hours after dosing)	12	X		X	
		Part 2: palbociclib 125 mg QD on Schedule 3/1; letrozole 2.5 mg QD	Isethionate capsule (fasting for 2 hours before and 2 hours after dosing)	6		X		

Table 1 Continued: Clinical trials to support the Clinical Pharmacology and Biopharmaceutics.

Study No.	Study Type	Study Treatment	Palbociclib Formulation (Fasted/Fed Condition)	N	Full PK Sampling	Sparse Sampling	NCA	PopPK/ PK-PD[a]
Healthy Subjects: ADME and DDI Studies								
A5481011	Phase 1 ADME	[14C]Palbociclib 125 mg	Oral suspension (after an overnight fasting)	6	X		X	
A5481012	Phase 1 DDI (midazolam)	Palbociclib 125 mg QD; midazolam 2 mg	Free base capsule[e] (after an overnight fasting)	26	X[g]	X[g]	X	
A5481017	Phase 1 DDI (rifampin)	Palbociclib 125 mg; rifampin 600 mg QD	Free base capsule[f] (after an overnight fasting)	15	X		X	
A5481018	Phase 1 DDI (rabeprazole)	Palbociclib 125 mg; rabeprazole 40 mg QD	Free base capsule[f] (after an overnight fasting)	26	X		X	
A5481026	Phase 1 DDI (tamoxifen)	Palbociclib 125 mg; tamoxifen 60 mg QD (loading dose) followed by 20 mg QD	Free base capsule[d] (after an overnight fasting)	25	X[g]	X[g]	X	
Healthy Subjects: Biopharmaceutic Studies								
A5481009	Phase 1 relative BA	Palbociclib 50 mg (oral solution) and 125 mg (capsule)	Any formulation A: isethionate capsule; B: free base capsule[b] (particle size (b) (4) D C: free base capsule[b] (particle size (b) (4) D D: oral solution (all after an overnight fasting)	24	X		X	
A5481015	Phase 1 absolute oral BA	Palbociclib 50 mg (IV solution) and 125 mg (capsule)	Any formulation A: free base capsule[d] (after an overnight fasting); B: IV solution (after an overnight fasting)	14	X		X	
A5481020	Phase 1 BE	Palbociclib 125 mg	Any formulation A: isethionate capsule; B: free base capsule[d] C: free base capsule[f] (all after an overnight fasting)	73	X		X	
A5481021	Phase 1 food effect	Palbociclib 125 mg	Free base capsule[f] A: an overnight fasting; B: a high-fat meal; C: a low-fat meal; D: in between 2 separate moderate-fat meals	28	X		X	

Study No.	Study Type	Study Treatment	Palbociclib Formulation (Fasted/Fed Condition)	N	Full PK Sampling	Sparse Sampling	NCA	PopPK/ PK-PD[a]
Healthy Subjects: Biopharmaceutic Studies (continued)								
A5481022	Phase 1 relative BA	Palbociclib 125 mg	Free base capsule[f] after an overnight fasting A: particle size (b) (4) dissolution Level 1; B: particle size (b) (4) dissolution Level 1; C: particle size (b) (4)) and dissolution Level 2; D: particle size (b) (4) and dissolution Level 3	24	X		X	
A5481036	Phase 1 relative BA	Palbociclib 125 mg	Any formulation A: isethionate capsule (after an overnight fasting) B: isethionate capsule (1 hour after and 2 hours before 2 separate meals); C: free base capsule[f] (after a moderate-fat meal)	36	X		X	

Data source: A5481001, A5481002, A5481003, A5481009, A5481011, A5481012, A5481015, A5481017, A5481018, A5481020, A5481021, A5481022, A5481026, and A5481036 CSRs; A5481010 Interim PK Report.

ADME=absorption, distribution, metabolism, and excretion; BA=bioavailability; BE=bioequivalence; CSRs=Clinical Study Reports; DDI=drug-drug interaction; ECG=electrocardiogram; IV=intravenous; N=total number of patients/subjects in the treatment arm; NCA=noncompartmental analysis; No.=number; PD=pharmacodynamics; PK=pharmacokinetic(s); PopPK=population PK; QD=once daily.

a. The PopPK analyses were performed using data from A5481001, A5481002, and A5481003. The PK-PD analyses to assess the relationship between palbociclib exposure and ECG data as well as safety endpoints (thrombocytopenia and neutropenia) were performed using data from A5481001, A5481002, and A5481003; while a PK-PD analysis to assess the relationship between palbociclib exposure and efficacy endpoints was performed using data from A5481003.

b. Palbociclib 125 mg QD was administered on Schedule 2/1 during Cycle 1.

c. Study is ongoing, and data cutoff date was 29 November 2013.

d. Initial Phase 3 free base capsule (Module 3, Section 3.2.P.2.2-1).

e. Full PK sampling for midazolam and sparse PK sampling for palbociclib.

f. Final Phase 3/commercial free base capsule (b) (4) . Final Phase 3 free base capsules and commercial free base capsules are identical except for white preprinting on the commercial free base capsules (Module 3, Section 3.2.P.2.2-1).

g. Full PK sampling for palbociclib and sparse PK sampling for tamoxifen and its metabolites.

h. (b) (4) initial Phase 3 free base capsule (Module 3, Section 3.2.P.2.2-1).

Note: Schedule 3/1=3 weeks on treatment/1 week off treatment; Schedule 2/1=2 weeks on treatment/1 week off treatment.

Reports for two additional trials were submitted during the review cycle (Table 2).

Table 2. Additional Clinical trials to support the Clinical Pharmacology submitted on 9/12/14 and 12/.8/14.

Study	Design
A5481038	A Phase 1, Open-Label, 3-Period Study of the Effect of an Antacid, a Proton Pump Inhibitor and an H2-Receptor Antagonist on Palbociclib (PD-332,991) Bioavailability Under Fed Conditions in Healthy Volunteers
A5481016	A Phase 1, Open-Label, Fixed-Sequence 2-Period Study to Investigate the Effect of Multiple Doses of Itraconazole on the Single Dose Pharmacokinetics of Palbociclib (PD-0332991) in Healthy Volunteers

Applicant's Population PK and Population Pharmacokinetic-Pharmacodynamic (PK-PD) Reports:

Population PK Analysis (PMA-EQDD-A548b-DP4-269):
Data from Studies A5481001, A5481002 and A5481003 which included 184 patients with advanced cancer, previously treated mantle cell lymphoma and ER-positive, HER2-negative advanced breast cancer, respectively were used to develop a population PK model of palbociclib pharmacokinetics. In these 3 studies, palbociclib was formulated as isethionate salt capsules. The objective of the population PK analysis was to assess cofactors that contribute to inter-individual variability in palbociclib PK and the need for dose adjustment based on age, body weight, gender, baseline creatinine clearance (BCCL), baseline serum creatinine (BSCR), baseline alkaline phosphatase (BALK), baseline alanine aminotransferase (BALT), baseline aspartate aminotransferase (BAST), baseline total bilirubin (BBIL), baseline albumin (BALB), baseline neutrophils (BNEU) and baseline lymphocytes (BLYM) to support labeling claims.

Exposure-response analysis (PMAR-387-Efficacy):
Data from study 1003 were used to perform an exposure-response analyses for efficacy (progression-free survival (PFS)) in patients with advanced breast cancer. Exposure variables were the average palbociclib concentration (Cavg) value over the entire treatment duration for each patient.

Exposure-response analysis (PMAR-271-Neutropenia):
Data pooled from Studies 1001, 1002, and 1003 were used to establish a population PK-PD model that describes the longitudinal observations of absolute neutrophil count (ANC) in patients with advanced cancer on treatment with palbociclib.

Exposure-response analysis (PMAR-286-Thrombocytes):
Data pooled from Studies 1001, 1002, and 1003 were used to establish a population PK-PD model that describes the longitudinal observations of absolute thrombocyte count (ATC) in patients with advanced cancer on treatment with palbociclib.

Exposure-response Analysis (PMAR-287 PK ECG):
Data pooled from Studies 1001, 1002, and 1003 were used to establish a population PK-PD model that describes the effects of palbociclib exposure on the QT interval (QTc or heart rate-corrected QT) in cancer patients.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The major efficacy outcome measure of trial A5481003 (referred to as 1003) was to assess the effect of palbociclib plus letrozole compared with that of letrozole alone on investigator-assessed PFS per RECIST v1.0. A statistically-significant and clinically-meaningful improvement in PFS or time to progression has been the basis for approval of several drugs for treatment of breast cancer.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

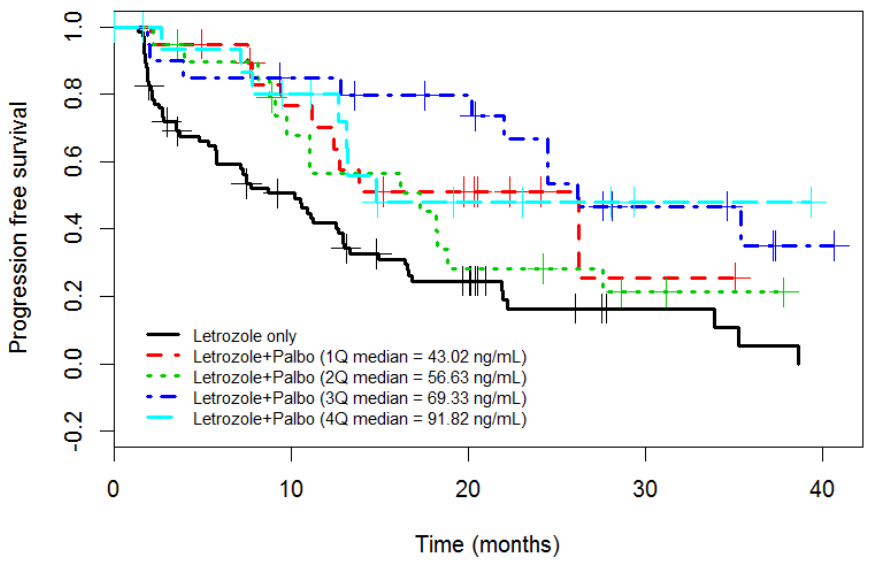
Yes, the clinical pharmacology related studies appropriately analyzed plasma and urine samples for the active parent compound (palbociclib) to assess PK parameters and exposure response relationships. Palbociclib accounts for 23% of the total radioactivity in plasma in the ADME trial (1011).

The plasma and urine concentrations of the active lactam metabolite (PF-05089326; MW 461.22) were also measured in some clinical trials. The active lactam metabolite has comparable potency with that of palbociclib for inhibiting CDK 4/6 in vitro. It represents < 10% of the circulating radioactivity in plasma (Trial 1009 and 1011), and full in vivo characterization of this metabolite was not conducted (See Section 2.2.12).

2.2.4 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The E-R relationship for efficacy is inconclusive due to the limited data (n=81) with a fixed dose of 125 mg in study 1003. There is no clear trend for better PFS with increasing exposure (Figure 2). Similarly, a consistent E-R relationship for efficacy was not established by the sponsor's analyses using a multivariate cox proportional hazard model and a parametric time-to-event model. Therefore, due to the limited data in the E-R analysis, a reliable estimate of the effect of palbociclib exposure on efficacy cannot be achieved, and a definitive conclusion on the E-R relationship for efficacy cannot be made at this time. (see Pharmacometrics Review).

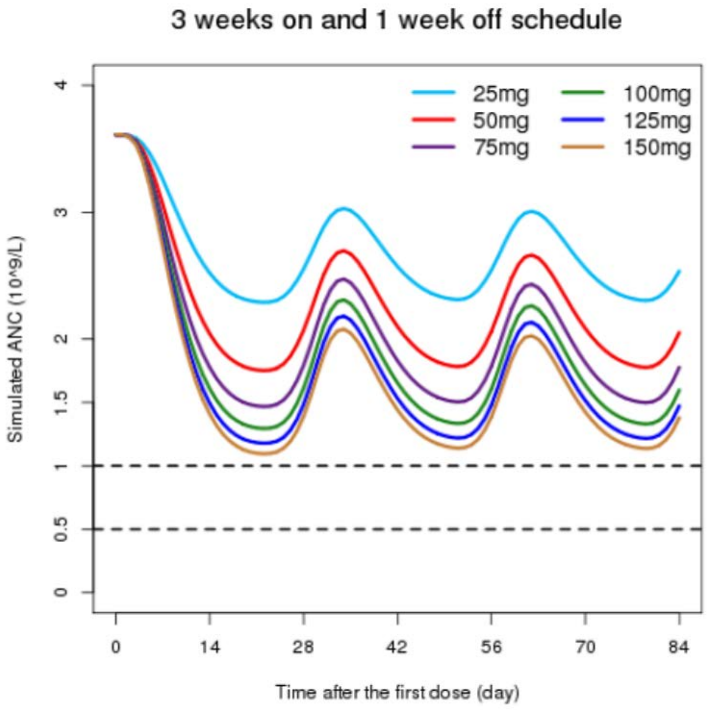
Figure 2. Inconclusive E-R relationship for PFS based on Study 1003.



2.2.5 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

A greater reduction in absolute neutrophil count (ANC) appears to be associated with increased palbociclib exposure. The relationship between palbociclib exposure and neutrophil count change over the time is adequately described by a semi-mechanistic population PK/PD modeling by sponsor. Longitudinal neutrophil changes at different doses with 3 weeks on and 1 week off schedule were simulated using sponsor's model (Figure 3) suggesting lower dose/exposure will lead to less neutrophil reduction. This supports the proposed dose modification in the label in order to manage the neutropenia (see Pharmacometrics Review).

Figure 3. Simulated longitudinal ANC profiles at different doses (3 weeks on and 1 week off schedule).



2.2.6 Does this drug prolong the QT or QTc interval?

Data from 184 patients enrolled in trials 1001, 1002, and 1003 were analyzed, and palbociclib did not prolong the QT interval to any clinically relevant extent. No large change (i.e., > 20 ms) in the QTc interval was detected when administrated of therapeutic dosing regimen of palbociclib. The studies did not have a positive control (moxifloxacin) arm (See the QT/IRT review).

2.2.7 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

There are no unresolved dosing or administration issues. Trial 1001 was a phase 1 dose escalation trial in patients with advanced solid tumors to determine the dosing schedule and recommended phase 2 dose (RP2D) of palbociclib. Two dosing schedules were evaluated. The first dose schedule comprised a 4-week treatment cycle consisting of a 21-day course followed by a 7-day interval without treatment (the 21/28 day schedule). The second dose schedule comprised a shorter 3-week schedule comprising 14 days of treatment followed by a 7 day interval (the 14/21 day schedule). Doses of 225 mg QD on Schedule 14/21 and 150 mg QD on Schedule 21/28 were identified as the maximum administered doses. The 200-mg QD dose on the 14/21 schedule and the 125-mg QD dose on the 21/28 schedule were identified as the RP2Ds and maximum tolerated doses (MTDs). Compared to the 14/21 schedule, the long-term antitumor activity and smaller proportion of patients with treatment-emergent adverse events in the 21/28 schedule led to the selection of 125 mg QD within the 21/28 schedule for further development in patients with ER-positive, HER2-negative advanced breast cancer. The daily dosing regimen is justified based on the elimination half-life of palbociclib.

Palbociclib is recommended to be administered in combination with letrozole at its current approved formulation/dose/regimen. Letrozole can be administered without regard to food intake.

Palbociclib (b) (4) isethionate salt; 25 mg and 100 mg capsule) was administered in a modified fasted condition in pivotal trial 1003. The sponsor's proposed administration of palbociclib (commercial freebase capsule) with food in the current package insert is justified based on the comparative bioavailability trial 1036 (see Section 2.5.5).

Pharmacokinetic characteristics of the drug and its major metabolites

2.2.8 What are the single dose and multiple dose pharmacokinetic (PK) parameters?

Trial describing the single dose and multiple dose PK of palbociclib in patients with advanced cancer (trial 1001):
Trial 1001 was an open-label, dose-finding study conducted in patients with advanced cancer. Patients were administered palbociclib (125 mg daily dose; (b) (4) isethionate capsule formulation) by repeated cycles either in accordance with dosing Schedule 21/28 or 14/21. Blood samples for characterizing the single dose palbociclib PK were obtained prior to dosing (0 hour) and at approximately 1, 2, 4, 7 and 10 hours after dosing on Days 1 and 8 of Cycle 1. As the PK sample collections for the majority of patients on Day 1 and Day 8 (steady-state) were limited to only 10 hours, the data for Day 1 and Day 8 were insufficient for estimation of meaningful secondary PK parameters due to the inability to characterize the terminal elimination phase. Therefore, for Days 1 and 8, only the Cmax, Tmax, and $AUC_{0\text{-}10h}$ were estimated.

Trial describing the multiple dose PK of palbociclib patients with breast cancer (trial 1003):
In trial 1003 the (b) (4) isethionate 25 mg and 100 mg capsule formulation was administered to patients. The study was comprised of Phase 1 and Phase 2 portions. The Phase 1 portion was conducted to assess the safety and tolerability of palbociclib administered in combination with letrozole and to evaluate the PK of palbociclib and letrozole when given in combination. The Phase 2 portion determined the steady state PK of palbociclib, with plasma samples collected before dosing and between 1 to 8 hours after dosing on Day 14 of Cycles 1 and 2 and on Day 1 of Cycles 3, 4, and 5.

Trials describing the single dose PK of palbociclib in healthy volunteers:
The single-dose PK of palbociclib have been evaluated in a total of 10 clinical studies in healthy subjects (Studies 1009, **1011**, **1015**, **1017**, **1018**, **1020**, **1021**, 1022, 1026, and **1036**) following administration of a single oral dose (125 mg) of palbociclib (See Table 1 above).

Trial describing the single dose PK of palbociclib and PF-05089326 in healthy subjects (1011):
The mass-balance trial 1011 also initially characterized the PK parameters of the palbociclib metabolite (PF-05089326) following administration of [^{14}C]palbociclib (125 mg, oral suspension) in healthy subjects.

Single dose

Table 3 summarizes the single dose plasma PK parameters of palbociclib ((b) (4) isethionate salt formulation (also referred to as isethionate salt) and final phase 3/commercial freebase formulation) following administration of a 125 mg oral dose in patients with advanced cancer and healthy volunteers.

The single dose palbociclib (isethionate salt formulation) PK parameters were not obtained in trial 1003. The single dose palbociclib (isethionate salt formulation) PK parameters were obtained in trial 1001

following an overnight fast. Trial 1036 showed that the PK for the isethionate salt formulation under minimal fasted condition (1 hour after and 2 hours before 2 separate moderate-fat meals) were comparable to those obtained for the isethionate salt formulation under the overnight fasted condition (See Section 2.5.5).

Trial 1036 showed comparative palbociclib exposure when the final phase 3/commercial freebase formulation was administered with a moderate-fat meal, vs. the isethionate salt capsule formulation administered in a modified fasted condition (fast from 1 hour before dosing until 2 hours after dosing), as implemented in the pivotal trial 1003 (See Section 2.5.5). *Therefore, the PK of the palbociclib commercial freebase formulation administered with a moderate-fat meal as recommended in the proposed package insert are comparable to the PK of the palbociclib isethionate salt formulation obtained in trial 1001 and 1003.*

The palbociclib PK profiles were generally comparable across studies conducted in healthy volunteers and patients (Table 3). Following a single oral dose of palbociclib (commercial freebase capsule; administered after a moderate-fat meal; See Section 2.5.5 for details), the median Tmax value was 8 hours (range: 6 hours to 12 hours). The geometric mean apparent oral clearance (CL/F) was 77 L/hr (%CV geometric mean: 26), and the arithmetic mean (± SD) plasma elimination half-life was approximately 22 (±4) hours.

Table 3. Summary of Palbociclib PK Parameters in Patients With Advanced Cancer (1001) and Healthy Subjects (1009, 1021 and 1036) by Study and Treatment Arm Following Administration of a Single Oral Dose (125-mg) of Palbociclib.

Study No./Data Set	Palbociclib formulation; Fasted/Fed Condition	n	AUCinf (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
Patients with Cancer								
1001	Isethionate capsule; fasting overnight	11[b]	290(30)[c]	42 7 (32)	7 0 (4 0-10 0)	NC	NC	NC
Healthy Subjects								
1009	Isethionate capsule; fasting overnight	24	1388 (24)	43 3 (24)	6 0 (6 0-12 0)	22 4 (±3 3)	90 1 (24)	2880 (19)
1021[a]	Commercial Free base capsule; fasting overnight	25	1525 (25)	48 3 (23)	8 0 (6 0-8 0)	23 7 (±5 2)	82 0 (25)	2741 (21)
	Commercial Free base capsule; after high-fat meal	28	1672 (23)	53 7 (21)	8 0 (6 0-12 1)	22 1 (±4 4)	74 7 (23)	2342 (17)
	Commercial Free base capsule; after low-fat meal	27	1573 (23)	50 2 (24)	8 0 (6 0-12 0)	22 0 (±4 6)	79 5 (22)	2475 (20)
	Commercial Free base capsule; in between moderate-fat meals	28	1580 (27)	48 6 (21)	8 0 (4 0-12 0)	22 9 (±4 5)	79 1 (26)	2573 (18)
1036	Isethionate capsule; fasting overnight	36	1468 (28)	50 5 (33)	6 0 (4 0-12 0)	22 7 (±4 1)	85 2 (28)	2748 (28)
	Isethionate capsule; fasting in between moderate-fat meals[i]	36	1596 (23)	54 3 (25)	6 0 (4 0-8 0)	22 6 (±4 4)	78 3 (23)	2510 (22)
	Commercial Free base capsule after moderate-fat meal	35	1624 (26)	52 3 (32)	8 0 (6 0-12 0)	22 4 (±3 6)	76 9 (26)	2453 (26)

AUC(0-10)=area under the plasma concentration-time curve from time 0 to 10 hours after dosing; AUCinf=area under the plasma concentration-time curve from time 0 to infinity; CL/F=apparent oral clearance; Cmax=maximum observed plasma concentration; CSR=Clinical Study Report; %CV=percent coefficient of variation; IV=intravenous; n=number of subjects for whom AUCinf, t½, CL/F, and Vz/F parameters were estimable; NC=not calculated;PK=pharmacokinetic; RP2D= recommended Phase 2 dose; Std Dev=standard deviation; t½=terminal plasma half-life; Tmax=time to first occurrence of Cmax; Vz/F=apparent volume of distribution

Geometric mean (geometric %CV) is shown for all PK parameters except median (range) for Tmax and arithmetic mean (±Std Dev) for t½ For trial 1001, geometric mean (arithmetic %CV) is shown for AUC(0-10) and Cmax, because geometric %CV was not estimated

a Dataset excluding "low-liers"

b Six of the 11 patients received 200 mg palbociclib, and their PK data was dose-normalized to a 125-mg palbociclib dose level AUC(0-10) could not be estimated for 1 patient on Day 1 of Cycle 2

c As the pharmacokinetic sample collections on Day 1 in trial 1001 in cancer patients were limited to only 10 hours, the data for Day 1 were considered to be insufficient for estimation of meaningful secondary PK parameters due to the inability to characterize the terminal elimination phase In trial 1001, AUCinf could not be calculated; instead AUC(0-10) was calculated

i Administration 1 hour after completion of a moderate-fat breakfast, followed by a second moderate-fat meal 2 hours after administration

Summary statistics of the single dose plasma palbociclib ((b) (4) isethionate capsule formulation) pharmacokinetic parameters with all dose groups combined are shown in Table 4. The interpatient variability (arithmetic %CVs) after a single dose of palbociclib (Day 1), across all dose levels, for AUC0-10h and Cmax ranged from 5% to 55% and from 3% to 63%, respectively.

Food decreased inter-subject variability for the palbociclib commercial freebase formulation PK parameters, compared to the overnight fasted condition. This appears to be due to the elimination of "low-liers" (as defined by the sponsor) when the palbociclib commercial freebase is administered with food (See Section 2.2.10 and 2.5.5). In trial 1021, inter-subject variability for palbociclib commercial freebase exposures under fed conditions were similar irrespective of fat and calorie content of the meal, with %CV values ranging between 23% to 27% for AUCinf and 21% to 24% for Cmax values (Table 34). The observed inter-subject variability under the overnight fasted condition (PK analysis that includes the "low-liers") were higher than under the fed conditions, with %CV values of 39% for AUCinf and 73% for Cmax values (See Section 2.5.5, Table 34 and Table 36).

Table 4. Summary of Plasma Palbociclib (isethionate capsule) Pharmacokinetic Parameters Following Oral Administration of Escalating Single doses and Multiple doses of Palbociclib (1001). In this trial, oral palbociclib was administered QD on an empty stomach. No food or liquids other than water were to be consumed for 2 hours before and 2 hours following each dose. On PK sampling days, palbociclib was administered following an overnight fast.

Palabociclib PK Parameter Summary Statistics by Dose (Study 1001)[a]				
Dose QD (mg)	**Study Day**	**Cmax (ng/mL)**	**Tmax (hr)**	**AUC0-10h (ng.hr/mL)[b]**
25	1(n=3) 8 (n=3)	8 3 (63) 15 4 (32)	4 0 (4 0-4 0) 4 0 (2 0-7 0)	53 0 (51) 115 (32)
50	1(n=3) 8 (n=3)	20 7 (3) 35 4 (16)	4 0 (4 0-4 3) 4 1 (2 0-7 0)	134 (5) 272 (15)
75	1(n=7) 8 (n=6)	28 0 (24) 57 2 (24)	4 0 (4 0-10 0) 4 0 (4 0-9 0)	196 (20) 478 (27)
100	1(n=6) 8 (n=6)	42 0 (45) 67 3 (31)	4 0 (2 0-10 0) 5 5 (4 0-10 0)	315 (34) 468 (45)
125	1(n=22) 8 (n=13)	47 2 (43) 81 7 (34)	7 0 (2 0-24 4) 4 0 (1 0-10 0)	266 (44) 678 (38)
150	1(n=7) 8 (n=6)	82 6 (17) 147 (44)	4 0 (4 0-9 8) 7 0 (7 0-10 0)	631 (9) 1222 (42)
200	1(n=20) 8 (n=8)	75 7 (35) 171 (17)	5 7 (1 0-10 2) 4 0 (2 0-7 0)	491 (36) 1363 (23)
225	1(n=6) 8 (n=6)	89 3 (58) 151 (64)	4 0 (4 0-7 0) 4 5 (1 0-7 0)	618 (55) 1196 (64)

AUC(0-10)=area under the plasma concentration-time curve from time 0 to 10 hours after dosing; Cmax=maximum observed plasma concentration; CSR=Clinical Study Report; n=number of patients; %CV=percent coefficient of variation; PK=pharmacokinetic; QD=once daily; Tmax=time to first occurrence of Cmax a Geometric mean (arithmetic %CV [geometric %CV was not estimated]) is shown for Cmax and AUC(0-10); median (range) is shown for Tmax b For AUC(0-10), the number of patients on Day 1 for the 100-mg, 125-mg, 150-mg and 200-mg groups were 5, 21, 5 and 19, respectively; and on Day 8 for the 75-mg, 100-mg, and 125-mg groups were 5, 4, and 12, respectively

Multiple doses

The multiple-dose (125 mg once daily) PK of palbociclib (isethionate capsule formulation) was evaluated in patients with advanced solid malignant tumors (trial 1001 and 1003). The PK parameters computed are summarized in Table 5. Following repeated 125-mg daily dosing to steady state, palbociclib was absorbed with a median Tmax ranging from approximately 4 hours to 8 hours. The geometric mean apparent oral clearance (CL/F) of palbociclib was 63.1 L/h (%CV geometric mean: 29%) The palbociclib mean elimination t½ ranged from 26.5 hours to 28.8 hours. Palbociclib accumulated after repeated dosing (median Rac=2.4; range 1.5 to 4.2). Variability (%CV) of palbociclib was approximately 29% for AUC0-24h and 28% for Cmax (Table 5).

Table 5. Summary of Palbociclib Pharmacokinetic Parameters at Steady State Following Administration of Palbociclib (isethionate salt capsule) Multiple Oral Doses (125-mg QD) to Patients With Advanced Cancer in A5481001 and A5481003.

Study Number	Visit	N,n	Palbociclib PK Parameter Summary Statistics[a] AUC_{τ}[b] (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{½}$ (hr)	CL/F (L/hr)	V_z/F (L)	R_{ac}
1001c	Cycle 1 D14/D21	13,13	1633 (59)	94.9 (48)	4.2 (2.0-9.8)	26.5 (±7.0)	76.5 (50)	2825 (40)	2.4 (1.5-4.2)
1003d	Cycle 1, D14	12,12	1982 (29)	116 (28)	7.9 (2.2-8.2)	28.8 (±5.0)	63.1 (29)	2583 (26)	NC

AUC_{τ}=area under the plasma concentration-time curve over dosing interval τ; CL/F=apparent oral clearance; C_{max}=maximum observed plasma concentration; CSR=Clinical Study Report; %CV=percent coefficient of variation; D=day; N=total number of patients in the treatment arm; n=number of patients for whom $t_{½}$, CL/F, and V_z/F parameters were estimable; NC=not calculated; PK=pharmacokinetic; QD=once daily; R_{ac}=accumulation ratio (AUC_{τ} after multiple dosing)/AUC_{τ} after single dose); Std Dev=standard deviation; $t_{½}$=terminal plasma half-life; T_{max}=time to first occurrence of C_{max}; V_z/F=apparent volume of distribution.
a. Geometric mean (geometric %CV) is shown for all PK parameters except median (range) for T_{max} and R_{ac} and arithmetic mean (±Std Dev) for $t_{½}$. For 1001, arithmetic %CV is shown as geometric %CV was not estimated.
b. $AUC_{\tau}=AUC_{(0-24)}$.
c. In A5481001, combined PK parameter data from Day 14 (200 mg QD) and Day 21 (125 mg QD) were normalized to the 125-mg dose level.
d. Phase 1 portion.

The palbociclib geometric mean and median C_{trough} values following administration of multiple palbociclib 125-mg once daily doses to patients with advanced malignant disease in trials 1001, and 1003 are shown in Table 6. The mean (%CV) C_{trough} palbociclib concentration was 61 ng/mL (42%).

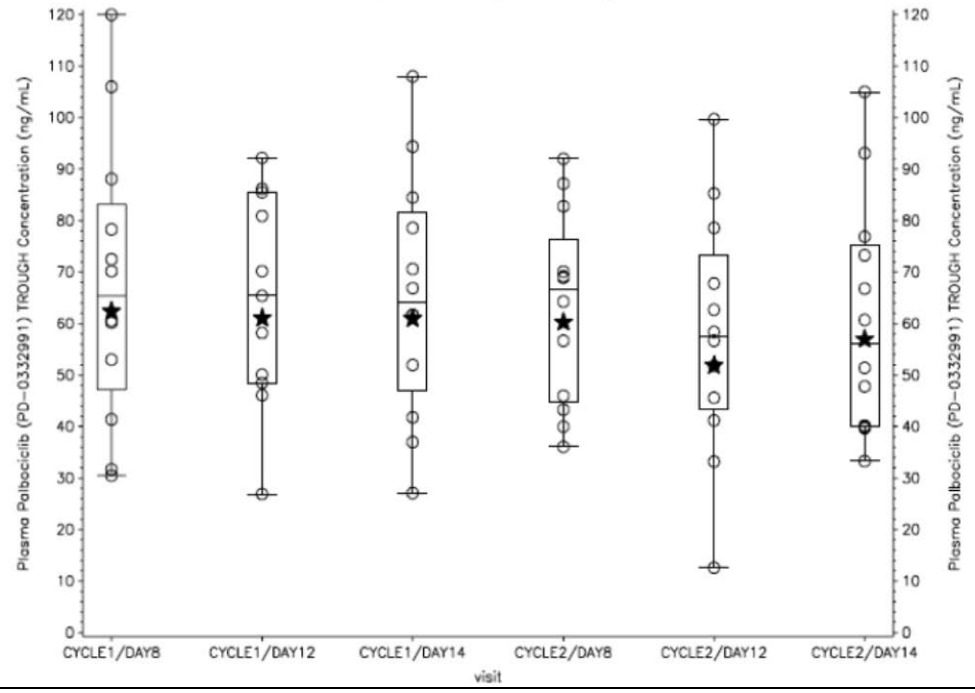
Table 6. Summary of Palbociclib plasma trough concentrations (C_{trough}) (ng/mL) at steady state following administration of multiple oral dose of palbociclib (125-mg QD; isethionate salt formulation) to patients with advanced cancer (1001 and 1003).

Study Number	N	Geometric Mean (Geometric % CV)	Median (Range)
1001	20	47.0 (48.9)	46.2 (17.5-119)
1003	71	60.8 (42.4)	62.7 (8.0-225)

%CV=percent coefficient of variation; N=total number of patients providing trough concentration values in each study; QD=once daily.

As shown in Figure 4, similar C_{trough} (predose) palbociclib concentrations were obtained on Day 8, Day12 and Day 14 for Cycle 1 (when palbociclib was given alone) and Cycle 2 (when palbociclib was given in combination with letrozole). This indicates that palbociclib steady-state exposures are achieved on or before Day 8 after repeated oral daily administration of palbociclib within the proposed dosing regimen.

Figure 4. C_{trough} (predose) palbociclib concentrations on Day 8, Day12 and Day 14 for Cycle 1 (when palbociclib was given alone) and Cycle 2 (when palbociclib was given in combination with letrozole) (Study 1003).



Stars represent the geometric mean and open circles represent individual patient values. Box plot provides median and 25%/75% quartiles with whiskers to the last data point within 1.5 times the interquartile range (trial 1003).

2.2.9 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The PK of palbociclib is comparable for patients and healthy volunteers. For the current submission, PK data with the commercial freebase palbociclib formulation were only available from healthy volunteers, and not from patients.

The palbociclib geometric mean CL/F value at steady state (125-mg; once daily) in patients with cancer participating in trial 1003 was 63.1 L/hr. (Table 7). This CL/F value from patients was generally in a comparable range to that observed in healthy subjects following single-dose (125 mg) administration of palbociclib (e.g.,76.9 L/hr (Table 3, Table 7)).

Table 7. Summary of Palbociclib Pharmacokinetic Parameters following a single dose (125 mg) of palbociclib (commercial free base formulation) in healthy volunteers in trial 1036, and palbociclib pharmacokinetic parameters at Steady State Following Administration of Palbociclib (isethionate capsule) Multiple Oral Doses (125-mg QD) to Patients With Advanced Cancer in trial 1003.

				Palbociclib PK parameters[a]		
Study No./Data Set	**Palbociclib formulation; Fasted/Fed Condition for PK sampling**	**n**	**Visit**	**T1/2 (hr)**	**CL/F (L/hr)**	**Vz/F (L)**
1036 Healthy Volunteers	Commercial Free base capsule. PK collected after moderate-fat meal	35	Single Dose, Day 1	22.4 (±3.6)	76.9 (26)	2453 (26)
1003 Cancer Patients[b]	Isethionate salt formulation administered following an overnight fast on serial PK collection days.	12	Steady state, Cycle 1, Day 14	28.8 (±5)	63.1 (29)	2583 (26)

CL/F=apparent oral clearance; CSR=Clinical Study Report; %CV=percent coefficient of variation; D=day; n=number of patients for whom t½, CL/F, and Vz/F parameters were estimable; NC= not calculated; PK= pharmacokinetic; QD=once daily; Std Dev=standard deviation; t½=terminal plasma half-life; Vz/F=apparent volume of distribution.

a. Geometric mean (geometric %CV) is shown for all PK parameters except median (range) for Tmax and arithmetic mean (±Std Dev) for t½.
b. Phase 1 portion.

2.2.10 What are the characteristics of drug absorption?

Following a single oral dose of palbociclib (commercial freebase capsule; administered after a moderate-fat meal; trial 1036), the median Tmax value was 8 hours (range 6 hours and 12 hours).

The absolute oral bioavailability study (1015) showed that the mean absolute oral bioavailability of a single 125 mg oral palbociclib dose (initial phase 3 immediate release freebase capsule formulation), administered in the fasted state, was 45.7% (90% CI: 39.3%, 53.2%). In this trial, an IV solution palbociclib formulation was used that comprised of (b) (4) free base drug substance, (b) (4) . The final phase 3 freebase capsule contains the (b) (4) of drug substance as the initial phase 3 drug product used in the absolute bioavailability trial 1015. With the exception of capsule shell printing, the final phase 3 freebase drug product is equivalent to the commercial free base capsule formulation.

In the mass-balance trial (1011), a single oral 125 mg dose of palbociclib as an oral suspension containing 100 µCi of [^{14}C]-palbociclib was administered to 6 healthy volunteers. The oral suspension formulation was comprised of 125-mg palbociclib freebase and a (b) (4) Palbociclib was shown to be extensively absorbed, metabolized and excreted in feces (74.1%) and urine (17.5%). The urinary excretion of unchanged palbociclib was approximately 6.9% of the administered parent drug over the 192-hours collection period. Recovery of unchanged palbociclib in the feces was minimal, at 2.3% of the dose.

The palbociclib absorption/exposure of the commercial freebase formulation was very low in approximately 13% of the population (defined as "low-liers" below) under the fasted condition. Food intake can increase the palbociclib exposure in this small subset of the population, while not altering the palbociclib exposure in the rest of the population to a clinically relevant extent (trial 1021). As a result,

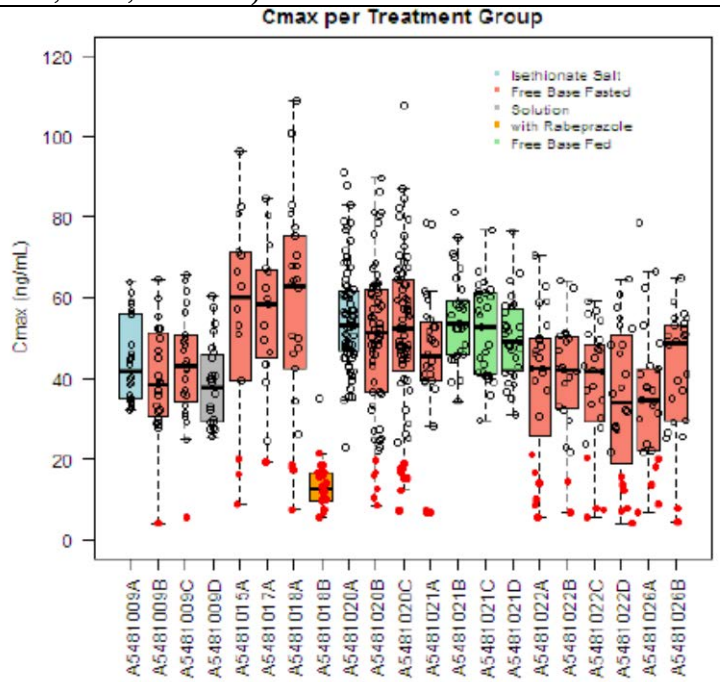
food intake reduced the intersubject variability in palbociclib exposure for the commercial freebase formulation, compared to the overnight fasted condition, which supports the recommended administration of Ibrance with food (see Section 2.5.3).

Trial 1038 assessed the effect of multiple doses of the proton pump inhibitor (PPI) rabeprazole on the single dose pharmacokinetics of palbociclib (commercial freebase formulation) administered with food in healthy volunteers. When palbociclib is administered with food, rabeprazole did not have a clinically significant impact on palbociclib exposure (Section 2.4.3).

Rationale to support removal of "low-liers" in statistical PK analyses in clinical trials where the palbociclib freebase formulation is administered in the overnight fasted condition:
The applicant conducted an analysis of the available data in healthy volunteers showed that significant lower exposure (Cmax and AUC) occurred in approximately 13% (53/415 patients) of the profiles across palbociclib treatments when a freebase formulation was used under the fasted condition. Since "low-liers" only represent a subpopulation with low exposure when palbociclib freebase was given under the overnight fasted condition (different from the current labeling recommendation), final PK statistical analyses using data excluding "low-liers" were conducted in trials 1017, 1018, 1021, 1036, 1018 and 1038 to evaluate the drug-drug interaction potential, the effect of food, relative exposure and the effect of PPIs on palbociclib exposure.

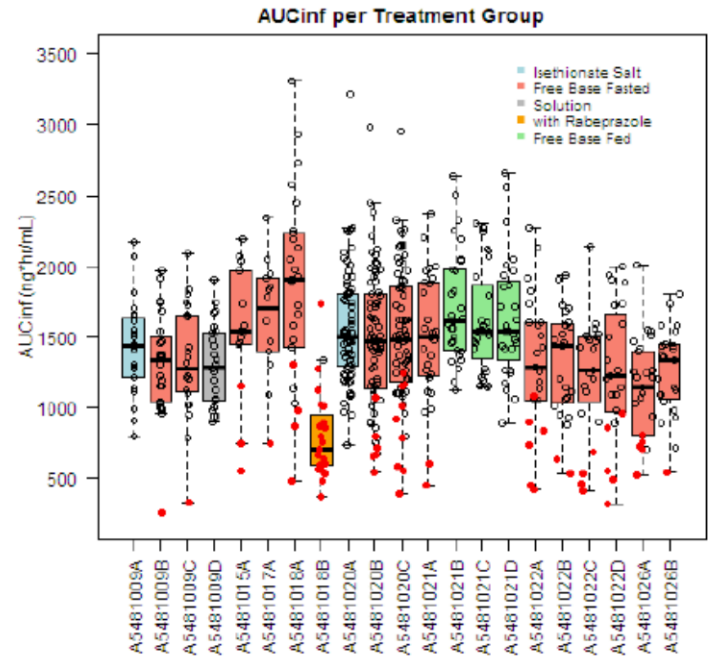
Figure 5 and Figure 6 show the distribution of palbociclib exposure PK parameters, Cmax and AUCinf, respectively, across all studies conducted in healthy subjects, in which serial palbociclib PK samples were collected. These figures include all treatments when palbociclib was given alone. In addition, the results for the palbociclib (administered under overnight fasted condition) plus rabeprazole treatment arm (Study 1018) are included to illustrate the effect of a PPI on palbociclib exposure. As shown in these figures "low-liers" (shown as red dots) were observed in all studies or treatment arms that used palbociclib freebase capsules under an overnight fasted condition.

Figure 5. Cmax Values Across Studies in Healthy Subjects by Treatment (1009, 1015, 1017, 1018, 1020, 1021, 1022, and 1026).



Note: Cmax values are not shown for palbociclib intravenous solution administered in A5481015 nor for palbociclib final Phase 3/commercial free base capsules plus rifampin administered after an overnight fasting in A5481017. Note: The Cmax values shown as red dots represent "low-liers" based on Cmax ≤21.4 ng/mL or Cmax that has a marginal studentized residual <–2.

Figure 6. AUCinf Values Across Studies in Healthy Subjects by Treatment (1009, 1015, 1017, 1018, 1020, 1021, 1022, and 1026).



AUCinf=area under the plasma concentration-time curve time 0 to infinity. Note: AUCinf values not shown for palbociclib i.v. solution administered in 1015 nor for palbociclib final commercial free base capsules + rifampin administered after an overnight fasting in 1017. Note: The AUCinf values shown as red dots = "low-liers" identified based on Cmax ≤ 21.4 ng/mL or Cmax with a marginal studentized residual <–2.

The palbociclib concentration-time profiles for "low-liers" were similar to those observed in trial 1018 in the rabeprazole + palbociclib (administered under overnight fasted condition) arm (Figure 11). The sponsor used the C*max in trial 1018 (rabeprazole + palbociclib arm) as a parameter to identify "low-liers". Specifically the upper 95% percentile of Cmax, 21.4 ng/mL, in the palbociclib + rabeprazole treatment arm of trial 1018 was selected as one of the criteria for the cutoff point of "low-liers" in all clinical trials with the palbociclib commercial freebase formulation administered following an overnight fast. A "low-lier" was defined as any PK profile with a Cmax ≤ 21.4 ng/mL or with a Cmax that has a marginal studentized residual lower than -2.*

"Low-liers" were not identified in any trials conducted with palbociclib isethionate capsules or oral solution nor were they observed with the commercial freebase capsule formulation administered with a meal or in between meals (moderate-fat meal 1 hour before and 2 hours after dosing) in the food effect trial (Study 1021). *The absence of "low-liers" when the commercial freebase is administered with food supports the recommended administration of the palbociclib commercial freebase formulation with food.*

In vitro experiments (Study PD-332991/25Mar09/142925) with transfected MDCK cells showed that palbociclib was a substrate of the efflux transporter, p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) at low concentrations, but not at clinically relevant higher concentrations. Palbociclib concentrations evaluated ranged from 0.05 to 25 μM. For P-gp and BCRP, palbociclib was a substrate up to a nominal concentration of 0.25 μM based on BA/AB efflux ratios. For P-gp and BCRP, efflux was concentration dependent, and increased up to a measured concentration of 0.038 μM, and declined at higher concentrations. Therefore, efflux mechanisms are unlikely to affect the extent of oral absorption of palbociclib administered at therapeutic doses in humans.

2.2.11 What are the characteristics of drug distribution?

The geometric mean (%CV) apparent volume of distribution (V/F) of palbociclib in patients was 2583 L (26%) (trial 1003) (Table 8).

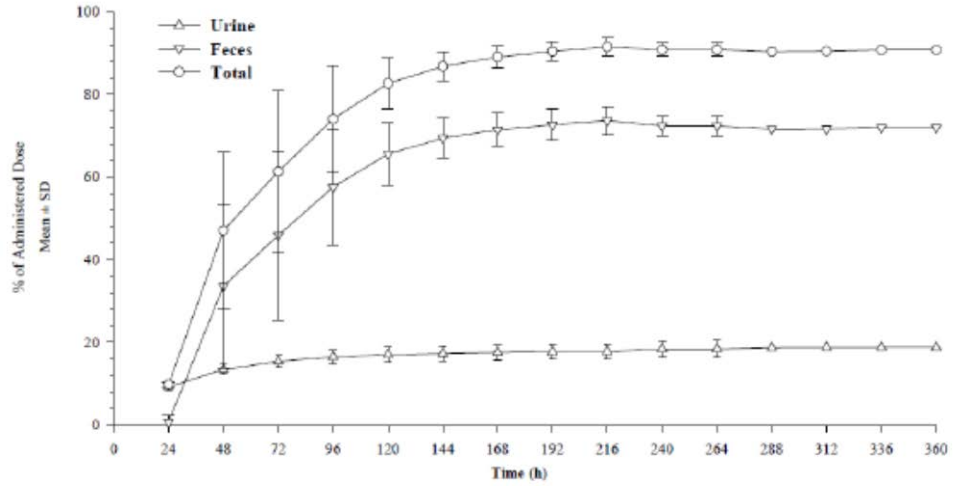
In vitro Plasma Protein Binding Assays:
The in vitro plasma protein binding of palbociclib (trial RR 764-04174) was determined in human plasma by equilibrium dialysis. The concentration range of palbociclib used was 0.5 to 5 μg/mL (1.12 to 11.2 μM), and appears appropriate (mean steady state palbociclib Cmax for the 125 mg/day dosing regimen is 116 ng/mL (0.26 μM) (trial 1003)). The average binding of palbociclib to proteins in human plasma was 85.3% (ie, the average fraction unbound in plasma was 0.147) over a concentration range of 0.5 to 5 μg/mL. Palbociclib protein binding in human plasma was independent of drug concentration over the dose range studied. Binding of palbociclib (0.5 to 5 μg/mL) to human serum albumin and α1-acid glycoprotein was low, with a mean value of 37.8% and 35.4%, respectively.

Blood to Plasma Ratio:
The blood-to-plasma partitioning of palbociclib in humans was evaluated in vitro at a nominal concentration of 2.5 μg/mL (study RR 764-0430204302). The human blood-to-plasma concentration ratio (Cb/Cp) for palbociclib was 1.63, suggesting a modest preferential distribution into blood cells relative to the plasma compartments. Based on the mass-balance trial (1011), the radioactivity in red blood cells was low, compared to those in plasma and whole blood, indicating that the amount of radioactive moieties partitioning into red blood cells was relatively small.

2.2.12 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Palbociclib is primarily eliminated by hepatic metabolism. Palbociclib is not substantially eliminated renally (See Section 2.2.13 and 2.2.14 below). In the mass balance trial (1011), a single 125 mg palbociclib dose (combined with a tracer dose 100 μCi of [^{14}C]-palbociclib) was administered orally to 6 healthy male volunteers as an oral suspension following an overnight fast. The oral suspension formulation was comprised of 125-mg palbociclib freebase (b) (4) Greater than 90% of the administered radioactivity was recovered from each of the 6 subjects, with a median recovery of the radioactive dose in urine and feces of 17.5%, and 74.1%, respectively over the 192-hour collection period (Figure 7). Recovery of drug-derived entities in urine and feces was comprised mainly of primary and secondary oxidative metabolites, primary conjugative metabolites, acylated products and unchanged parent in urine (see Section 2.2.13 for details).

Figure 7. Mean cumulative ^{14}C-radioactivity recovery-time profile in urine and feces following administration of a single oral dose of ^{14}C-palbociclib (125 mg; 100 μCi) to healthy male volunteers (trial 1011) (N=6).



Plasma:

Plasma PK parameters obtained in the mass-balance trial 1011 for palbociclib and its metabolite PF-05089326, are summarized in Table 8. PK parameters (AUCinf and Cmax) for the oral suspension palbociclib formulation (Table 8) were comparable to PK parameters obtained following administration of the palbociclib freebase tablet formulation (Table 3).

The PK of the active metabolite PF-05089326 was initially characterized in trial 1011 and accounts for less than 10% of plasma radioactivity. The metabolite to parent drug ratios for Cmax, corrected for molecular weight (MRCmax), and AUCinf, corrected for molecular weight (MRAUCinf), were 0.18 and 0.10, respectively. The geometric mean Cmax was approximately 2.7-fold higher and total exposure (AUCinf) was almost 5-fold higher for total radioactivity than those for palbociclib in plasma. The geometric mean AUCinf for PF-05089326 (150 ng•hr/mL) accounted for less than 3% of the difference between the geometric mean AUCinf values for total radioactivity in plasma (7162 ng-eq•hr/mL) and plasma palbociclib (1424 ng•hr/mL), indicating that the higher exposure for radioactivity may be due to the presence of additional circulating metabolic product(s) of palbociclib in plasma.

Table 8. Summary of Plasma Palbociclib, and PF-05089326 PK Following Administration of [^{14}C]Palbociclib (125 mg) to Healthy Subjects (1011)

	Palbociclib PK Parameter Summary Statistics[a]		
PK Parameter	Plasma Total Radioactivity	Plasma Palbociclib	Plasma PF-05089326
N,n	6,4	6,6	6,5
C_{max} (ng/mL)[b]	151 (15)	56.1 (23)	10.4 (37)
T_{max} (hr)	4.0 (4.0-6.0)	6.0 (4.0-12.0)	4.0 (4.0-6.0)
AUC_{last} (ng•hr/mL)[b]	6163 (14)	1383 (27)	144 (28)
AUC_{inf} (ng•hr/mL)[b]	7162 (17)	1424 (25)	150 (30)
$t_{½}$ (hr)	77.0 (±8.2)	20.9 (±2.8)	20.6 (±2.5)
CL/F (L/hr)	17.4 (17)	87.8 (25)	NC
V_z/F (L)	1928 (21)	2618 (22)	NC
$MRAUC_{inf}$	NC	NC	0.10 (18)
$MRAUC_{last}$	NC	NC	0.10 (18)
MRC_{max}	NC	NC	0.18 (32)

AUC_{inf}=area under the plasma concentration-time curve from time 0 to infinity; AUC_{last}=area under the plasma concentration-time curve from time 0 to time of last measurable concentration; CL/F=apparent oral clearance; C_{max}=maximum observed plasma concentration; CSR=Clinical Study Report; %CV=percent coefficient of variation; eq=equivalent; $MRAUC_{inf}$=metabolite to parent drug ratio for AUC_{inf}, corrected for molecular weight; $MRAUC_{last}$=metabolite to parent drug ratio for AUC_{last}, corrected for molecular weight; MRC_{max}=metabolite to parent drug ratio for C_{max}, corrected for molecular weight; N=total number of subjects in the treatment arm; n=number of subjects for whom AUC_{inf}, $t_{½}$, CL/F, and V_z/F parameters were estimable; NC=not calculated (not applicable for the analyte); PK=pharmacokinetic; Std Dev=standard deviation; $t_{½}$=terminal plasma half-life; T_{max}=time to first occurrence of C_{max}; V_z/F=apparent volume of distribution.

a. Geometric mean (geometric %CV) is shown for all PK parameters except median (range) for T_{max} and arithmetic mean (±Std Dev) for $t_{½}$.

b. Parameter units for radioactivity are ng-eq/mL (C_{max}) and ng-eq•hr/mL (AUC).

2.2.13 What are the characteristics of drug metabolism?

In vitro screens with human hepatocytes, liver cytosolic and S9 fractions and recombinant sulfotransferase (SULT) enzymes indicated that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

Metabolic Profile from the Mass-Balance trial (1011):
Following oral administration of a single dose of [^{14}C]palbociclib to healthy subjects, recovery of drug-derived entities in urine and feces was comprised mainly of primary and secondary oxidative metabolites (>50% of dose), primary conjugative metabolites (27.3%), acylated products (2.6%), and unchanged parent in urine (6.9%).

The most abundant circulating metabolite was a glucuronide conjugate of palbociclib (14.8% of circulating radioactivity), with the remainder of the metabolites, individually, accounting for less than 10% of plasma radioactivity.

Profiling of a plasma sample pooled across all 6 subjects and over the time interval of 0 hours to 120 hours after dosing showed that unchanged palbociclib was the primary drug-related material, accounting for 23.3% of the total plasma radioactivity. The palbociclib glucuronide (M22, was the most abundant circulating metabolite, at 14.8% of circulating radioactivity (pharmacological activity not assessed). Other minor metabolites (<10% of circulating radioactivity each) included sulfamic acid conjugate (M11), acetyl derivative of palbociclib (M12), a carboxylic acid metabolite (M16), a lactam of palbociclib (M17, PF-05089326), a dilactam of palbociclib (M24), a metabolite with the pyrido-piperazine substructure cleaved (M25), and a formyl derivative of palbociclib (M26).

Three metabolites contributed, on average, 45% of the dose excreted in human feces: the sulfamic acid (sulfonated metabolite) of palbociclib (M11; PF-06754233 [25.8% of dose]), a carboxylic acid metabolite (M16 [14.2% of dose]), and a cyclopentyl ring-hydroxylated metabolite of palbociclib lactam (M20 [5.0% of dose]).

In urine specimens collected 0-96 hours after dosing, the unchanged palbociclib and 2 isomeric mono-hydroxylated metabolites of palbociclib (M23a and M23b) were the major urinary components accounting for 3.7% and 3.5% of the dose, respectively. Bioanalytical quantitation of urine specimen collected over a longer duration (192-hours) indicated that unchanged palbociclib accounted for 6.9% of the administered dose. *This would account for approximately 15% of the orally absorbed palbociclib dose based on results from the absolute oral bioavailability study (1015) (See section 2.2.10).*

2.2.14 What are the characteristics of drug excretion?

Elimination
Following administration of a single oral dose of 125 mg [^{14}C]palbociclib to six healthy subjects, within the 192 hours post-dose collection period, a median of 74.1% and 17.5% of the drug-related radioactivity was recovered in the feces and urine, respectively (trial 1011). Metabolism is the major route of elimination of palbociclib, with excretion of unchanged palbociclib in the feces and urine at 2.3% and 6.9% of the dose, respectively (trial 1011).

Clearance
The geometric mean (%CV) CL/F of palbociclib was 63.1 L/h (29%) (trial 1003) Table 8.

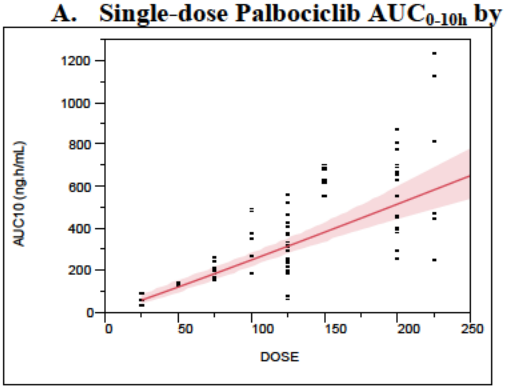
Half-life
The palbociclib mean (±SD) terminal elimination half-fife ($T_{1/2}$) is 28.8 hours (±5) in patients with advanced breast cancer (trial 1003).

2.2.15 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Single Dose:
The Day 1 single dose noncompartmental analysis estimated AUC0-10h and Cmax obtained from trial 1001 were used to assess the dose proportionality of palbociclib in plasma at 25, 50, 75, 100, 125, 150, 200 and 225 mg/day. Over the dose range of 25 to 225 mg, the slope of the line of the log AUC0-10h vs. log dose plot was 1.05. Over the dose range of 25 to 225 mg, the slope of the line of the log Cmax vs. log dose plot was 1.05. These results from the analyses with AUC0-10h and Cmax suggest dose-proportional pharmacokinetics of the daily dose range of 25 to 225 mg palbociclib (Figure 8).

Figure 8. A: Log $AUC_{0\text{-}10\ hours}$ vs. Log of Dose and B: Log Cmax vs. Log of Dose over the 25 to 225 mg single oral dose range (Cycle 1, Day 1) in patients with advanced cancer. The shaded area is the 90% CI of the slope (Trial 1001).

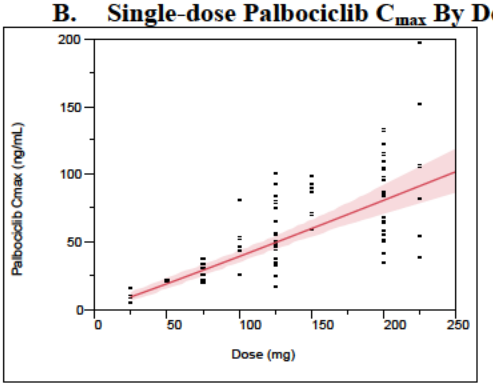
A. Single-dose Palbociclib $AUC_{0\text{-}10h}$ by Dose



Transformed Fit Log to Log

Log(y) = 0.6981258 + 1.0468563*Log(x); R^2 = 0.59

B. Single-dose Palbociclib C_{max} By Dose



Transformed Fit Log to Log

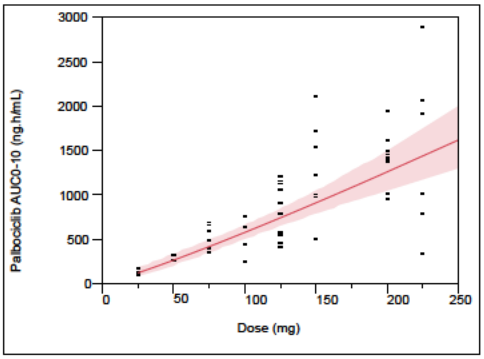
Log(y) = -1.149044 + 1.0456937*Log(x); r^2 = 0.63

Multiple-dose:

The multiple-dose (Cycle 1, Day 8) noncompartmental analysis estimated individual AUC0-10h and Cmax obtained from trial 1001 were used to assess the dose proportionality of palbociclib in plasma following daily dosing at 25, 50, 75, 100, 125, 150, 200 and 225 mg/day. Over the dose range of 25 to 225 mg, the slope of the line of the log AUC0-10h vs. log dose plot was 1.13. Over the dose range of 25 to 225 mg, the slope of the log Cmax vs. log dose plot was 1.10. These results from the analyses with multiple-dose AUC0-10h and Cmax indicate approximately dose-proportional pharmacokinetics of the daily dose range of 25 to 225 mg palbociclib (Figure 9).

Figure 9. A: Log AUC0-10h vs. Log of Dose and B: Log Cmax vs. Log of Dose over the 25 to 225 mg multiple oral dose range (Cycle 1, Day 8) in patients with advanced cancer. The shaded area is the 90% CI of the slope (Trial 1001).

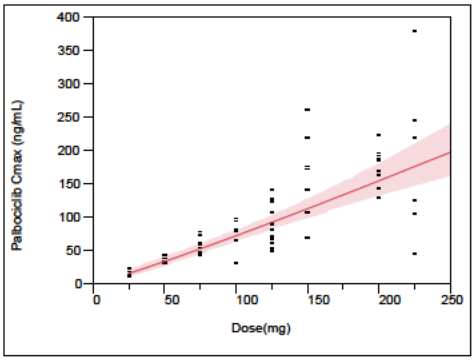
A. Multiple-dose Palbociclib AUC_{0-10h} By Dose



Transformed Fit Log to Log

Log(y) = 1.1754954 + 1.1252745*Log(x); r^2 = 0.69

B. Multiple Dose Palbociclib C_{max} By Dose



Transformed Fit Log to Log

Log(y) = -0.764703 + 1.0957239*Log(x); r^2 = 0.71

2.2.16 How do the PK parameters change with time following chronic dosing?

Based on results from trial 1001, palbociclib exposure increases with repeated dosing in patients with advanced cancer (median accumulation ratio (Rac) = 2.4; range 1.5 to 4.2) (Table 5).

The single-dose and multiple-dose (125 mg QD) pharmacokinetics of palbociclib (isethionate capsule formulation) were evaluated in trial 1001 and 1003. In patients, the interindividual variability (% CV) values for palbociclib Cmax and AUC were higher following a single dose versus multiple doses to steady state. The %CV was approximately 44% for AUC0-10h and 43% for Cmax (Table 4). Following repeated 125-mg daily dosing to steady state (Cycle 1 Day 14, 125 mg once daily; trial 1003), the %CV was approximately 29% for AUC0-24h and 28% for C_{max} (Table 5).

2.2.17 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The inter-subject variability of palbociclib PK parameters appear comparable between patients with cancer and healthy subjects. The geometric mean (%CV) for the palbociclib CL/F value at steady state (125 mg, once daily) in patients with cancer in trial 1003 was 63.1 L/h (29%). The geometric mean (%CV) for palbociclib CL/F following a single-dose (125 mg) of palbocilcib in healthy volunteers was 76.9 L/h (26%) Table 7.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, weight, height, genetic polymorphisms and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The applicant population PK analysis (PMAR-EQDD-A548b-DP4-269) included data from trial 1001, 1002 and 1003, and assessed the influence of covariates age, sex, body weight, renal impairment (CrCL values ≥ 30 mL/min) and hepatic impairment (mild) on the between-patient differences in palbociclib PK parameters. In all of the studies, plasma concentrations of palbociclib were measured using the same validated analysis method with the lower limit of qualification (LLOQ) of 2.50 ng/mL. The population PK model characterized the concentrations of palbociclib (isethionate salt formulation) from 184 patients. Overall, the FDA pharmacometrics reviewer concluded that the labeling related to the intrinsic factors below is adequate and supported by the population PK analysis.

The FDA pharmacometrics reviewer made the following conclusions based on the population PK analysis for the effects of the covariates age, sex, body weight, mild to moderate renal impairment and mild hepatic impairment on palbociclib exposure:

Relationship between Gender and Exposure
The results of the population PK analysis in 50 male and 133 female patients with cancer indicated that there was no effect of gender on the PK of palbociclib.

Relationship between Race and Exposure
It was not possible to assess the effect of race due to the limited enrollment of races other than Caucasians (167 White, 4 Black, 8 Asian, 4 Other) in the submitted clinical trials. PK data were available for the population PK analysis from 183 patients with advanced cancer, and 91% of these were White.

Relationship between Weight and Exposure and between Age and Exposure
No dose adjustment is recommended with respect to body weight and age. Body weight (range: 37.9-123 kg) and age (range: 22-89 years) were significant covariates on clearance. In comparison with a typical subject at a median age of 61 years and a median body weight of 73.7 kg, clearance was increased by 14.7% at an age of 45 years and decreased by 8.33% at an age of 74 years. For body weight, clearance was decreased by 13.2% and increased by 14.2% at a weight of 55 kg and 97 kg, respectively. Therefore, body weight and age have no clinically significant effect on exposure of palbociclib (see Pharmacometrics Review).

Relationship between Renal Impairment and Exposure:
Based on the pharmacometrics reviewer's analysis of the applicant population PK dataset described above, no dose adjustments are needed for patients with calculated CrCL values ≥ 30 mL/min. The CrCL was calculated by the Cockcroft and Gault equation, and the CL/F was estimated for each individual in the PK data set, i.e. normal renal function (CrCL ≥ 90 mL/min, N=81), mild renal impairment (CrCL 60 to < 90 mL/min, N=74) and moderate renal impairment (CrCL 30 to < 60 mL/min, N=29). Mild and moderate renal impairment was not a significant covariate on palbociclib clearance, and there is no need for dose adjustment in patients with CrCL ≥ 30 mL/min (see Pharmacometrics Review). This is consistent with renal elimination being a minor clearance pathway of palbociclib. The potential effect of severe renal impairment or end stage renal disease on palbociclib pharmacokinetics cannot be determined as clinical and PK data are not available.

The sponsor is currently conducting a dedicated renal impairment trial (1014) in which the effect of renal impairment on the plasma PK (total and unbound) of palbociclib after a single oral 125 mg dose administered as the commercial free base capsule formulation in the fed state is being assessed. This trial aims to enroll patients with normal renal function (CrCL ≥ 90 mL/min; N=(b)(4) and mild (CrCL 60 – (b)(4) mL/min; N = 7), moderate (CrCL (b)(4); N=(b)(4) and severe (CrCL < 30 mL/min; N=(b)(4) renal impairment. Based on the results from the mass balance trial (1011), renal elimination is not a major clearance pathway with 18% of a single oral palbociclib dose eliminated in urine (6.9% as unchanged palbociclib). *A comment to the applicant will be to submit the final study report and datasets from this ongoing trial to FDA for review.*

Relationship between Hepatic Impairment and Exposure:
Mild hepatic impairment does not have a significant effect on the palbociclib exposure. PK data to assess the effect of moderate hepatic impairment were only available from one patient. There were no available PK data to assess the effect of severe hepatic impairment on palbociclib PK.

The population PK analysis assessed the effect of mild hepatic impairment (based on National Cancer Institute - Organ Dysfunction Working Group (NCI-ODWG) criteria) on palbociclib plasma PK. No significant relationship between palbociclib clearance and liver function was identified based on population PK analysis (142 patients with normal liver function, 40 patients with mild hepatic impairment, 1 patient with moderate hepatic impairment and no patients with severe hepatic impairment). Therefore, No dose adjustment is recommended for patients with mild hepatic impairment (See Pharmacometrics review).

The sponsor is currently designing a dedicated hepatic impairment trial (1013) in which the effect of hepatic impairment on the plasma PK (total and unbound) of palbociclib after a single oral 75 mg dose administered as the commercial free base capsule formulation in the fed state will be assessed. The final protocol is planned to be submitted to FDA for review in November, 2014. This trial aims to enroll patients with normal hepatic function (N=(b)(4) and mild (Child-Pugh Class A, score (b)(4); N = (b)(4) moderate (Child-Pugh Class B, score (b)(4); N=(b)(4) and severe (Child-Pugh Class C, score (b)(4); N=(b)(4) hepatic impairment. *A PMR for the current submission will be to submit the final protocol, final study report and datasets from this proposed trial to FDA for review.*

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Renal Impairment:
No dose adjustments are necessary for patients with calculated CrCL values ≥ 30 mL/min (Section 2.3.1).

There were no pharmacokinetic data available to assess the effect of severe renal impairment (CrCL < 30 mL/min) or end-stage renal disease on palbociclib pharmacokinetics. Based on results from the mass-balance trial (1011), the urinary excretion of palbociclib appears to be a minor route of elimination with approximately 6.9% of the administered parent drug, palbociclib, excreted unchanged in the urine over the 192-hour collection period (See Section 2.2.10 and 2.2.12).

Hepatic Impairment:
No dose adjustments are needed for use in patients with mild hepatic impairment (Section 2.3.1). The effect of moderate hepatic impairment on the PK of palbociclib could not be determined as data were only

available from one patient. The effect of severe hepatic impairment on the PK of palbociclib has not been studied.

Pediatric patients
Palbociclib has not been studied in pediatric patients.

2.3.3 What pregnancy and lactation use information is there in the application?

None.

2.3.4 Is palbociclib appropriate for all patients with ER-positive, HER2-negative breast cancer based on a clinical trial primarily conducted in patients with CCND1 amplification and/or CDKN2A loss?

In contrast to how Part 2 of the pivotal trial was conducted, the proposed indication for palbociclib is not limited to patients who test positive for CCND1 amplification and/or CDKN2A loss. Given the PFS benefit and preliminary clinical evidence that the composite biomarker (i.e., CCND1/CDKN2A) does not robustly differentiate responders beyond ER positivity, the proposed indication in ER-positive/HER2-negative breast cancer (b) (4) appears acceptable pending further assessment of CDKN2A loss on palbociclib responses. As a post-marketing commitment, the applicant should formally evaluate the effect of CDKN2A and other potential biomarkers of palbociclib response (e.g., RB1 status may be a critical determinant of response based on palbociclib's mechanism) in ongoing and planned trials (e.g., PALOMA-2 [A5481008]).

Nonclinical studies analyzing differentially expressed genes between palbociclib-sensitive and -resistant breast cancer cell lines suggested that increased retinoblastoma (RB1) and cyclin-D1 (CCND1) and decreased cyclin dependent kinase inhibitor 2A (CDKN2A) were associated with sensitivity to palbociclib [PMID: 19874578]. Also, sensitive cell lines mostly represented the luminal/ER-positive subtype. These nonclinical results and the mechanism of palbociclib informed the final design of the Phase 2 portion of the pivotal Phase 1/2 trial, A5481003, which evaluated investigator-assessed progression-free survival (PFS) in 165 ER-positive, HER2-negative advanced breast cancer patients that were randomly assigned in a 1:1 ratio to receive palbociclib plus letrozole or letrozole alone. The trial was conducted in two parts: Part 1 enrolled 66 patients regardless of tumor CCND1 and/or CDKN2A status (i.e., biomarker positive, negative or unknown) and Part 2 enrolled 99 patients whose tumors tested positive for CCND1 gene amplification, loss of CDKN2A, or both, as measured by fluorescence in situ hybridization (FISH). An interim, retrospective analysis of investigator-assessed PFS by composite CCND1/CDKN2A biomarker status conducted on Part 1 data did not find a correlation between biomarker status and outcomes. For the biomarker positive subgroup, the median PFS was 26.1 months in the palbociclib plus letrozole arm vs. 7.5 months in letrozole arm [HR 0.2 (95% CI: 0.07-0.71)] and for the biomarker negative subgroup, the median PFS was 35.3 months in the palbociclib plus letrozole arm vs. 5.7 months in the letrozole arm [HR 0.2 (95% CI: 0.07-0.71)]. As such, enrollment in Part 2 was terminated after accrual of 99 patients and the protocol was then amended to evaluate clinical benefit in all patients randomized in both Parts 1 and 2. For the two parts combined, the median PFS by investigator assessment was 20.2 months vs. 10.2 months, favoring the palbociclib plus letrozole arm [HR 0.488 (95% CI: 0.319-0.748); 1-sided p=0.0004].

Approximately 87% of biomarker positive patients had CCND1-amplified tumors, while 28% had tumors with CDKN2A loss (with or without concomitant CCND1 amplification) in Parts 1 and 2 combined. In

Part 1, CCND1 and CDKN2A status was retrospectively determined in 46 out of 66 randomized patients who had available tumor samples for analysis (22 in the palbociclib plus letrozole arm and the 24 in the letrozole arm). All patients classified as biomarker positive (N=21) had CCND1-amplified tumors and only 2 patients also had tumors positive for CDKN2A loss. In the biomarker-selected Part 2, most patients similarly had CCND1-amplified tumors, although 19 patients in the combination arm and 12 patients in the letrozole arm had tumors with CDKN2A loss (with or without CCND1 amplification) (Table 9).

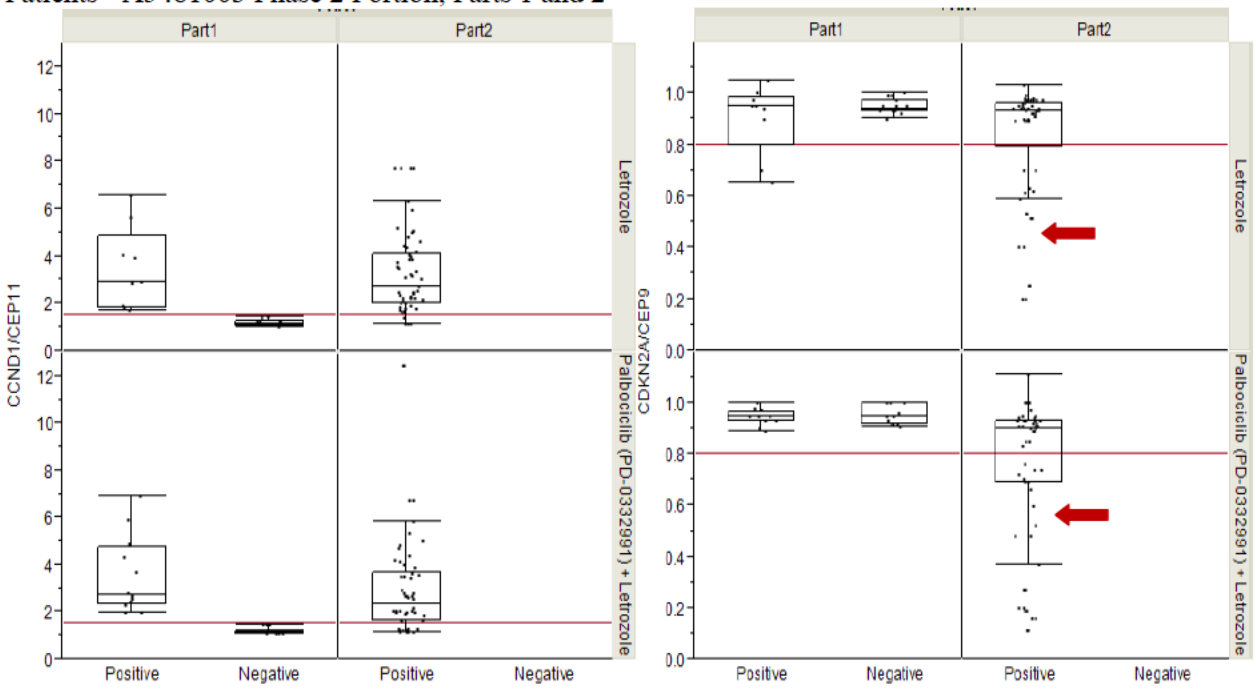
Table 9. CCND1 and CDKN2A Status - A5481003 Phase 2 Portion, Parts 1 and 2

	Biomarker Status	CCND1 amplification only		CDKN2A loss only		Both CCND1amplification and CDKN2A loss		Total Biomarker CCND1amplification and/or CDKN2A loss	
		Palbociclib + letrozole	Letrozole	Palbociclib + letrozole	Letrozole	Palbociclib + letrozole	Letrozole	Palbociclib + letrozole	Letrozole
Part 1	Positive	12	7	0	0	0	2	12	9
	Negative							10	15
	Unknown							12	8
Part 2	Positive	31	37*****	11	4	8	8	50	49*****

***1 patient in the letrozole arm was not treated; Biomarker Positive: CCND1/CEP11≥1.5 and/or CDKN2A/CEP9 <0.8, Biomarker Negative: CCND1/CEP11<1.5 and CDKN2A/CEP9 ≥0.8. CCND1=Cyclin D1; CDKN2A= Cyclin-dependent kinase inhibitor 2A.*

As shown in the figure below, the distribution and range of FISH ratios especially for CDKN2A loss was different in Parts 1 and 2 (Figure 10).

Figure 10. Distribution of CCND1 and CDKN2A FISH ratios in Biomarker Positive and Negative Patients - A5481003 Phase 2 Portion, Parts 1 and 2

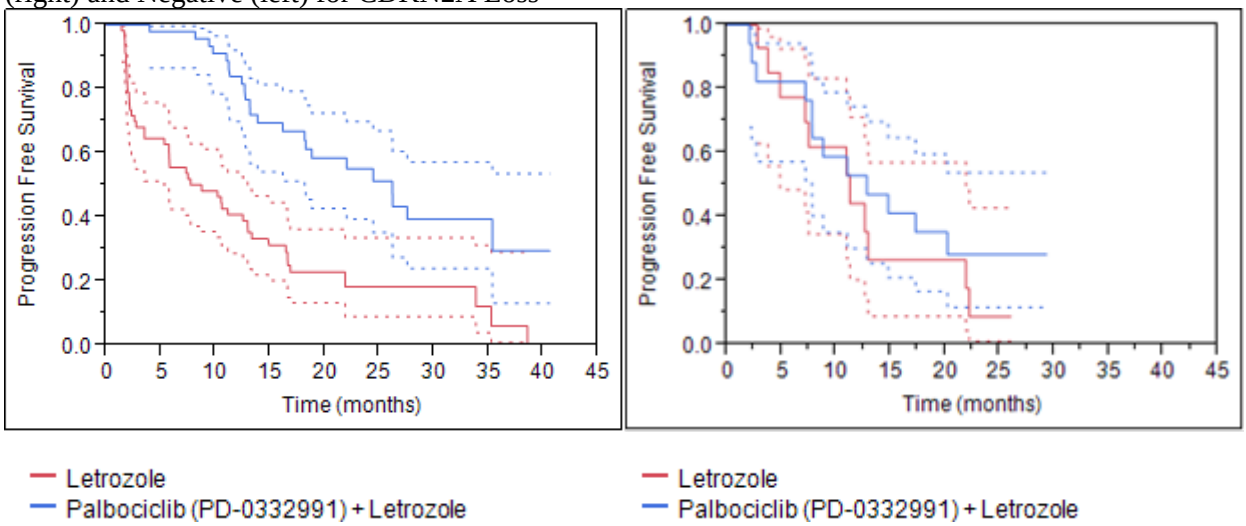


Source: Reviewer analyses; Biomarker Positive: CCND1/CEP11 ≥1.5 and/or CDKN2A/CEP9 <0.8, Biomarker Negative: CCND1/CEP11 <1.5 and CDKN2A/CEP9 ≥0.8; cutoffs for genetic amplification (1.5) and loss (0.8) indicated as a horizontal red line. FISH: fluorescence in situ hybridization; CCND1=Cyclin D1; CDKN2A= Cyclin-dependent kinase inhibitor 2A; CEP=chromosome enumeration probe. 20 patients had "biomarker unknown" status in Part 1 and were not represented.

The Phase 2 trial was mostly confined to biomarker positive patients whose tumors were CCND1-amplified. Except for two patients in the letrozole arm in Part 1, biomarker-positive patients with tumors positive for CDKN2A loss were only observed in Part 2. This subset of patients was therefore underrepresented in Part 1 interim analysis that suggested a lack of correlation between CCND1/CDKN2A status and outcomes. It is not clear whether both genetic events (i.e., CCND1 amplification and CDKN2A loss) would equally affect prognosis or sensitivity to therapy.

The review team conducted exploratory analysis of investigator-assessed PFS by CDKN2A loss (as defined by the applicant). The results suggest that patients with tumors positive for CDKN2A loss may derive less benefit from adding palbociclib to letrozole (as shown below in the Figure 11).

Figure 11. Kaplan-Meier Plot of Investigator-Assessed PFS: Subset of Patients with Tumors Positive (right) and Negative (left) for CDKN2A Loss



Source: Reviewer analyses (exploratory); *Positive for CDKN2A loss: CDKN2A/CEP9 ratio <0.8, Negative for CDKN2A loss: CDKN2A/CEP9 ratio ≥0.8; CDKN2A= Cyclin-dependent kinase inhibitor 2A*; *A5481003 Phase 2 portion, Parts 1 and 2; Dotted lines represent 95% confidence intervals.*

The unexpected findings for patients with tumors positive for CDKN2A loss may be related to the presence of unknown tumor genetic events and/or compensatory signaling mechanisms that modify the molecular phenotype and influence response to therapy. Alternatively these findings may be related to the small sample sizes, imbalances and exploratory nature of the analyses. As a post-marketing commitment, the applicant should formally evaluate the effect of CDKN2A, RB1, and other potential biomarkers of palbociclib response in ongoing and planned trials (e.g., PALOMA-2 [A5481008]).

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effects of extrinsic factors such as herbal products, smoking and alcohol use on the dose-exposure and/or dose-response for palbociclib were not assessed in a formal study.

Drug-drug interactions

2.4.2 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

As a substrate (*in vitro*)

In vitro screens with human hepatocytes, liver cytosolic and S9 fractions and recombinant sulfotransferase (SULT) enzymes indicate that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

Study PD-0332991_05Mar13_095443 characterized the in vitro metabolic profile of palbociclib using human hepatocytes and chemical inhibitors for the specific CYP isozymes. Positive control probe

substrates were appropriate based on the current FDA drug interaction Guidance (Feb 2012), and included tizanidine, efavirenz, rosiglitazone, tolbutamide, s-mephenytoin, timolol and disopyramide for CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A, respectively. *Results showed that CYP3A was the major cytochrome P450 isozyme responsible for the oxidative metabolism of palbociclib (34%). Results also showed that human CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6 are not likely to contribute significantly to the metabolism of palbociclib.*

The oral administration of palbociclib to healthy volunteers resulted in the recovery of a major sulfonated metabolite (PF-06754233) excreted in feces, and represents a major clearance mechanism (mass-balance trial 1011). Study PD-0332991_18Sep13_170350 was an in vitro screen to identify the major human SULT isozymes involved in the sulfonation of palbociclib. Following incubations with palbociclib (250 μM), recombinantly expressed human SULT2A1 formed the sulfamic acid metabolite (PF-06754233) in greatest abundance. The remaining eight recombinant SULTs (SULT1A1, 1A2, 1A3, 1E1, 1B1, 1C2, 1C4 and 2B1) were also able to catalyze the formation of the sulfamic acid metabolite, at apparent formation rates ≥ 97% lower than those observed for SULT2A1. *These data suggest that SULT2A1 is the predominate enzyme involved in the sulfonation of palbociclib.*

As an inhibitor (*in vitro*)

In vitro studies with human liver microsomes (study PD-0332991_27MAY10_181141 and PD-332991/05SEP09/130322) show that palbociclib and its circulating lactam metabolite (PF-05089326), cause time-dependent inhibition of CYP3A. These studies also show that palbociclib and PF-05089326 do not cause reversible inhibition of human CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A (midazolam 1'-hydroxylase, testosterone 6β-hydroxylase marker substrates) at tested concentrations comparable to plasma concentrations that would be achieved with therapeutic doses of palbociclib.

In study PD-0332991_27MAY10_181141, the potential for palbociclib to cause reversible inhibition of seven major CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) and CYP2A6 was investigated by incubating pooled human liver microsomes with isoform-selective marker substrates (near Km values). Reversible inhibition was measured in the presence of palbociclib (0.0952 to 30.0 μM). The concentration range evaluated in this study appears appropriate, as the mean steady state Cmax for the 125 mg/day dosing regimen is 116 ng/mL (0.26 μM) (trial 1003). The IC_{50} values reported for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5 and CYP2A6 were reported as > 30 μM (Table 9). Based on the FDA Drug Interaction Guidance (Feb 2012), the K_i values were calculated to be 15 μM ($IC_{50}/2$) for all isoforms listed in Table 10. The calculated R values ($1 + I/K_i$) for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5 and CYP2A6 at the clinically relevant palbociclib Cmax concentration (125 mg/day dose) at steady state (0.26 μM) were all < 1.1. *This indicates the potential for in vivo drug-drug interactions based on competitive inhibition by palbociclib is not likely for substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5 and CYP2A6.*

Table 10. Summary of IC50 Data for palbociclib in Human Liver Microsomes

Marker Substrate Activity	Enzyme	% of control at [I] = 30 μM	IC_{50} (μM) Mean	±	SE
Phenacetin O-Deethylase	CYP1A2	120	>30		
Bupropion Hydroxylase	CYP2B6	100	>30		
Coumarin 7-Hydroxylase	CYP2A6	99	>30		
Amodiaquine *N*-Deethylase	CYP2C8	93	>30		
Diclofenac 4'-Hydroxylase	CYP2C9	75	>30		
S-Mephenytoin 4'-Hydroxylase	CYP2C19	87	>30		
Dextromethorphan O-Demethylase	CYP2D6	90	>30		
Felodipine Oxidase	CYP3A	70	>30		
Midazolam 1'-Hydroxylase	CYP3A	87	>30		
Testosterone 6β-Hydroxylase	CYP3A	72	>30		

In study PD-0332991_27MAY10_181141, the potential for palbociclib to cause time dependent inhibition of seven major CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) was investigated by incubating pooled human liver microsomes with isoform-selective marker substrates (concentrations near Km values). The concentration of palbociclib used was 10-fold that which was predicted to cause 25% inhibition under reversible inhibition conditions or 100 µM, whichever was lower. A summary of the percent change in inhibitory potency for each enzyme evaluated is listed in Table 11. *Palbociclib demonstrated little or no change in time dependent inhibitory potency for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 activities. Palbociclib demonstrated a relevant change in time dependent inhibitory potency for CYP3A (midazolam 1'-hydroxylase, testosterone 6β-hydroxylase) activities of 91% and 67% respectively.*

Table 11. Summary of Single Concentration-Time Dependent Inhibition Data for palbociclib in Pooled Human Liver Microsomes (Percent Decrease in Activity with 30 minute Pre-incubation).

Marker Substrate Activity	Enzyme	Preincubation Conc. (µM)	Result (Percent Decrease)
Phenacetin O-Deethylase	CYP1A2	100	-0.34
Bupropion Hydroxylase	CYP2B6	100	-0.17
Paclitaxel 6α-Hydroxylase	CYP2C8	100	-12
Diclofenac 4'-Hydroxylase	CYP2C9	100	5.8
S-Mephenytoin 4'-Hydroxylase	CYP2C19	100	-1.2
Dextromethorphan O-Demethylase	CYP2D6	100	-20
Midazolam 1'-Hydroxylase	CYP3A	100	91
Testosterone 6β-Hydroxylase	CYP3A	100	67

The time dependent inhibitory potency of palbociclib for CYP3A demonstrated above was further investigated in study PD-0332991_27MAY10_181141 to determine the K_I (concentration at 50% kinact) and k_{inact} (maximal inactivation) values. Palbociclib demonstrated time dependent inhibition of CYP3A midazolam 1'-hydroxylase and testosterone 6β-hydroxylase activities. A summary of the K_I and k_{inact} and k_{inact}/K_I values are listed in Table 12.

Based on the current FDA Guidance for drug interactions (Feb 2012), an R value > 1.1 is considered positive and may warrant further in vivo investigations. The R value is calculated as follows, $R = (K_{obs} + K_{deg})/K_{deg}$ and $K_{obs} = k_{inact} \times [I]/(K_I + [I])$. Here [I] represents the maximal total systemic palbociclib concentration in plasma, and k_{deg} is the degradation constant of the enzyme. The mean steady state C_{max} for the 125 mg/day dosing regimen is 116 ng/mL (0.26 µM) (trial 1003) and the $K_{deg} = 0.18$. The estimated R values for palbociclib time dependent inhibition of CYP3A midazolam 1'-hydroxylase and testosterone 6β-hydroxylase activities were < 1.1 at 1.05 and 1.06, respectively.

Based on the current FDA guidance (Feb 2012), for CYP3A inhibitors that are dosed orally, [I] should also be estimated by $[I]=I_{gut}$=Molar Dose/250 mL and the cutoff for this alternate R is 11. When$[I] = I_{gut}$ = molar dose/250 mL, the calculated R values for palbociclib time dependent inhibition of CYP3A midazolam 1'-hydroxylase and testosterone 6β-hydroxylase activities were < 11.

The applicant conducted a drug-drug interaction trial (1012) to assess the effect of palbociclib on the pharmacokinetics of midazolam (sensitive CYP3A4 substrate) (See Section 2.4.3).

Table 12. A summary of the K_I and k_{inact} values for palbociclib in pooled human liver microsomes.

		K_I (µM)			k_{inact} (min^{-1})			k_{inact}/K_I
Marker Substrate Activity	Enzyme	Mean	±	SE	Mean	±	SE	(mL/min/µmol)
Midazolam 1'-Hydroxylase	CYP3A	10	±	2	0.036	±	0.002	3.6
Testosterone 6β-Hydroxylase	CYP3A	19	±	4	0.087	±	0.007	4.6

In study PD-332991/05SEP09/130322, the potential for PF-05089326 to cause reversible inhibition of seven major CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) was investigated by incubating pooled human liver microsomes with isoform-selective

marker substrates. The study design was similar study PD-0332991_27MAY10_181141 described above. PF05089326 was tested at 0 (control), 0.0793, 0.251, 0.792, 2.50, 7.91, and 25 µM. The tested concentration range of PF05089326 appears appropriate based on the mean single dose PF05089326 Cmax (22.5 nM) in plasma following a single 125 mg oral dose of palbociclib (Trial 1011) (Table 13).

Based on these in vitro data (Table 13), PF-05089326 does not cause reversible inhibition of human CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6 at therapeutically relevant concentrations. Based on the FDA Drug Interaction Guidance (Feb 2012), the K_i values were calculated ($Ki = IC_{50}/2$) to be 8 µM for CYP3A and 12.5 µM for CYP1A2, 2B6, 2C8, 2C19 and 2D6. The calculated R values ($1 + I/K_i$) for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 at the clinically relevant PF-05089326 C_{max} concentration (single 125 mg plabociclib dose) (22.5 nM) were all < 1.1. *The potential for in vivo drug-drug interactions based on competitive inhibition by PF-05089326 is not likely for substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5.*

Table 13. Summary of IC50 Data for PF-05089326 in Human Liver Microsomes.

Marker Substrate Activity	Enzyme	% of control at [I] = 30 µM	IC_{50} (µM) Mean	±	SE
Phenacetin *O*-Deethylase	CYP1A2	76	>25		
Bupropion Hydroxylase	CYP2B6	64	>25		
Paclitaxel 6α-Hydroxylase	CYP2C8	58	>25		
Diclofenac 4'-Hydroxylase	CYP2C9	58	>25		
S-Mephenytoin 4'-Hydroxylase	CYP2C19	91	>25		
Dextromethorphan *O*-Demethylase	CYP2D6	60	>25		
Felodipine Oxidase	CYP3A	42	16	±	3
Midazolam 1'-Hydroxylase	CYP3A	104	>25		
Testosterone 6β-Hydroxylase	CYP3A	56	>25		

In study PD-332991/05SEP09/130322, PF- 05089326 demonstrated little or no change in time dependent inhibitory potency for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. PF-05089326 demonstrated a relevant change in time dependent inhibitory potency for CYP3A (midazolam 1'-hydroxylase and testosterone 6β-hydroxylase) activities of 77% and 41% respectively (Table 14).

Table 14. Summary of Single Concentration-Time Dependent Inhibition (SC-TDI) Data for PF-05089326 in Pooled Human Liver Microsomes (Percent Decrease in Activity with 30 minute Pre-incubation)

Marker Substrate Activity	Enzyme	Result (Percent Decrease)
Phenacetin *O*-Deethylase	CYP1A2	-4.9
Bupropion Hydroxylase	CYP2B6	10
Paclitaxel 6α-Hydroxylase	CYP2C8	-7.7
Diclofenac 4'-Hydroxylase	CYP2C9	6.3
S-Mephenytoin 4'-Hydroxylase	CYP2C19	1.7
Dextromethorphan *O*-Demethylase	CYP2D6	-6.6
Midazolam 1'-Hydroxylase	CYP3A	77
Testosterone 6β-Hydroxylase	CYP3A	41

Based on the above results, the effects of PF-05089326 on CYP3A (midazolam 1'- hydroxylase and testosterone 6β-hydroxylase) activities were examined in greater detail in order to determine K_I and k_{inact} values (Table 15). The mean single dose PF05089326 Cmax in plasma following a single 125 mg oral dose of palbociclib is 22.5 nM (Trial 1011), and the $K_{deg} = 0.18$. The estimated R values for PF05089326 time dependent inhibition of CYP3A midazolam 1'-hydroxylase and testosterone 6β-hydroxylase activities were < 1.1 at 1.01 and 1.03, respectively.

Table 15. Summary of KI/kinact Data for PF-05089326 in Pooled Human Liver Microsomes

		K_I (μM)			k_{inact} (min^{-1})			k_{inact}/K_I
Marker Substrate Activity	**Enzyme**	**Mean**	**±**	**SE**	**Mean**	**±**	**SE**	**(mL/min/μmol)**
Midazolam 1'-Hydroxylase	CYP3A	7.0	±	1.2	0.094	±	0.004	13
Testosterone 6β-Hydroxylase	CYP3A	6.4	±	1.9	0.15	±	0.01	23

As an inducer (*in vitro*)
Study (b) (4)123065 evaluated the potential of palbociclib to induce enzymatic activity and mRNA of CYP1A2, CYP2B6, CYP2C8, or CYP3A4 in cryopreserved human hepatocytes. Palbociclib did not cause induction of CYP1A2, CYP2B6, CYP2C8 and CYP3A4 activity or mRNA in all three lots of human hepatocytes up to 3 μM, which was the highest concentration at which there was >80% cell viability. The 3 μM concentration significantly exceeds the palbociclib steady-state Cmax determined for the therapeutic dosing regimen of 125 mg palbociclib once daily. *Thus, the potential for palbociclib to induce these enzymes is considered to be low at clinically relevant concentrations.*

2.4.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

In vivo evaluation of palbociclib dosed to apparent steady state on the single-dose pharmacokinetics of a sensitive CYP3A4/5 substrate in healthy women (1012):
Results from trial 1012, combined with the in vitro data above showed that palbociclib is a weak time-dependent inhibitor of CYP3A. *A dose reduction of the concomitant CYP3A4 substrate drug should be considered when dosing palbociclib concurrently with sensitive CYP3A4 substrates that have a narrow therapeutic index.*

Trial 2012 was a phase 1, open-label, randomized, 2-sequence, 2-period, 2-way crossover study to evaluate the effect of multiple doses of palbociclib (freebase formulation, 125 hard capsule), to apparent steady state, on the single dose midazolam PK in healthy women.

Subjects were to abstain from ingesting any food or beverages other than water from 1 hour before until 2 hours after each palbociclib dose (except on Day 7 of Treatment B). During Treatment A, subjects received a single dose of midazolam 2 mg oral syrup on Day 1 following a 10-hour overnight fast. During Treatment B, subjects received a single oral dose of palbociclib 125 mg every day for a total of 8 days. After a 10-hour overnight fast, on the morning of Day 7 palbociclib was administered first and was immediately followed by the administration of midazolam 2 mg oral syrup. There was at least a 14-day washout between Day 8 of Treatment B and Day 1 of Treatment A.

Midazolam plasma PK samples were collected prior to dosing, and up to 36 hours post dose. Palbociclib PK samples were to be drawn prior to palbociclib dosing on Days 2, 6, 7, and 8 during Treatment B.

Coadministration of palbociclib and midazolam increased midazolam AUCinf and Cmax by 61% and 37%, respectively, relative to midazolam given alone (Table 16). *These results indicate that palbociclib is a weak time-dependent inhibitor of CYP3A (≥ 1.25 but < 2-fold increase in AUC).*

Table 16. Summary of Plasma Midazolam Pharmacokinetic Parameters Following Single Oral 2 mg Dose of Midazolam Alone and With Multiple Oral 125 mg Doses of Palbociclib

Plasma Midazolam Parameter (Unit)	Parameter Summary Statistics[a] by Treatment: Midazolam 2 mg (Reference)	Palbociclib 125 mg QD + Midazolam 2 mg (Test)
N, n	26, 24	26, 26
AUC_{inf} (ng•hr/mL)	39.56 (40)	62.46 (40)
AUC_{last} (ng•hr/mL)	36.37 (44)	59.96 (41)
C_{max} (ng/mL)	14.49 (38)	19.93 (42)
T_{max} (hr)	0.500 (0.500–1.00)	0.500 (0.500–1.07)
$t_{½}$ (hr)	7.243 ± 1.796	8.159 ± 1.470

Abbreviations: %CV=percent coefficient of variation, hr=hour, N=number of subjects in the treatment group, n=number of subjects where $t_{½}$ and AUC_{inf} were determined, QD=once daily, SD=standard deviation
a. Geometric mean (Geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ±SD for $t_{½}$.

Statistical Summary of Treatment Comparisons

Plasma Midazolam Parameter (Unit)	Adjusted Geometric Means: Test	Adjusted Geometric Means: Reference	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng•hr/mL)	62.46	38.77	161.10	(146.26, 177.45)
AUC_{last} (ng•hr/mL)	59.96	36.37	164.88	(150.73, 180.35)
C_{max} (ng/mL)	19.93	14.49	137.49	(124.47, 151.87)

Test=palbociclib 125 mg QD + midazolam 2 mg; Reference=midazolam 2 mg alone
Pharmacokinetic parameters are defined in Table 7.
Abbreviations: CI=confidence interval, QD=once daily
a. The ratios (and 90% CIs) are expressed as percentages.

In vivo evaluation of the effect of a potent CYP3A inhibitor, itraconazole, on the single dose palbociclib pharmacokinetics in healthy volunteers (1016):

Results from trial 1016 showed that multiple oral doses of itraconazole 200 mg (strong CYP3A inhibitor) increased the single dose geometric mean palbociclib AUCinf and Cmax by 87% and 34%, relative to a single 125 mg plabociclib dose given alone. Palbociclib demonstrates linear PK. As the mean AUC increases about 1.87-fold with the use of the strong CYP3A inhibitors, a dose of 67 mg once daily would be predicted to result in exposures in the range of 125 mg once daily. Therefore, we recommend a dose of 75 mg once daily.

Trial 1016 was a Phase 1, open-label, 2-period, fixed-sequence crossover study to investigate the effect of multiple doses of itraconazole on palbociclib (commercial freebase formulation) PK in the fed condition. A total of 12 subjects were enrolled. Each enrolled subject was to receive Treatment A in Period 1 and then Treatment B in Period 2 with a washout period of at least 10 days between the 2 single doses of palbociclib. PK sampling to measure plasma palbociclib concentrations was performed pre-dose and for 120 hours post-dose for each treatment.

Treatments:

Period 1, Treatment A [Reference]: Following an overnight fast of at least 10 hours, subjects started the recommended high-fat (approximately 50% of total caloric content of the meal), high-calorie breakfast (approximately 800-1000 calories with 150, 250, and 500-600 calories from protein, carbohydrate and fat, respectively) at 30 minutes prior to administration of palbociclib. This meal was consumed within a 20-minute period with study drug administered within approximately 10 minutes after completion of the meal. At least 80% of the provided breakfast must have been consumed prior to administration of palbociclib (125 mg). No additional food was allowed for at least 4 hours post-dose.

Period 2, Treatment B [Test]: Subjects took two 100 mg itraconazole capsules (200 mg dose) once daily on Days 1, 2, 3, and 4 with a high-fat, high-calorie breakfast (same content as for Period 1). Subjects were given a full meal at approximately 30 minutes prior to itraconazole dosing.

On Day 5, following an overnight fast of at least 10 hours, subjects were provided a high-fat, high-calorie breakfast (same content as for Period 1) at 30 minutes prior to the concomitant administration of itraconazole and palbociclib. This meal was consumed within a 20 minute period with study drugs administered within approximately 10 minutes after completion of the meal. At least 80% of the provided breakfast must have been consumed prior to administration of itraconazole (two 100 mg capsules) and palbociclib (a single 125 mg dose). Administration of palbociclib in each period occurred at approximately the same time followed by at least 4 hours fast post-dosing. Administration of 200 mg itraconazole was continued once daily with a high fat, high-calorie breakfast from Day 6 to Day 11.

Median palbociclib plasma concentrations were higher in the presence of multiple oral doses of itraconazole (200 mg QD) than those observed when palbociclib (125 mg) was administered alone (Figure 12, Table 17). The ratios of the adjusted geometric means for palbociclib AUCinf and Cmax (90% CI) were 186.84% (172.90%, 201.90%) and 134.30% (126.18%, 142.94%), respectively, when palbociclib was coadministered with multiple doses of itraconazole (Test) as compared to its administration alone (Reference) (Table 18).

Figure 12. Median Plasma Palbociclib Concentration-Time Profiles Following a Single Oral Dose of Palbociclib 125 mg Alone and in Combination With Multiple Oral Doses of Itraconazole 200 mg.

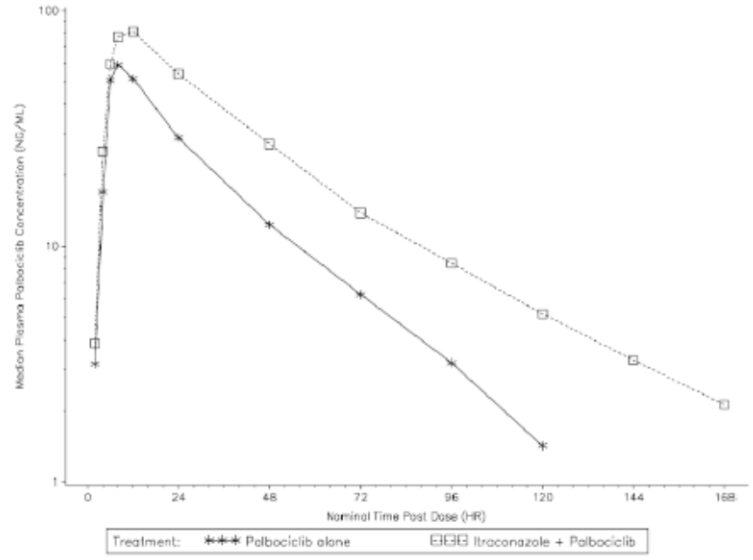


Table 17. Summary of Plasma Palbociclib PK Parameters Following a Single Oral Dose of Palbociclib 125 mg Alone and in Combination With Multiple Oral Doses of Itraconazole 200 mg

	Summary Statistics[a] by Treatment	
Plasma Palbociclib Parameter (units)	**Palbociclib 125 mg Alone**	**Itraconazole 200 mg QD + Palbociclib 125 mg**
N, n	12, 12	11, 11
AUC_{inf} (ng•hr/mL)	1864 (19)	3456 (18)
AUC_{last} (ng•hr/mL)	1804 (18)	3341 (17)
C_{max} (ng/mL)	59.58 (16)	80.29 (26)
T_{max} (hr)	8.08 (4.00-12.1)	7.35 (5.35-11.4)
$t_{½}$ (hr)	22.05 ± 3.10	33.87 ± 3.85
CL/F (L/hr)	67.09 (19)	36.18 (18)
Vz/F (L)	2114 (17)	1758 (19)

Table 18. Statistical Summary of Treatment Comparisons for Palbociclib PK Parameters

Plasma Palbociclib Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Itraconazole 200 mg QD + Palbociclib 125 mg (Test)	Palbociclib 125 mg Alone (Reference)		
AUC_{inf} (ng•hr/mL)	3482	1864	186.84	(172.90, 201.90)
AUC_{last} (ng•hr/mL)	3363	1804	186.42	(172.48, 201.49)
C_{max} (ng/mL)	80.02	59.58	134.30	(126.18, 142.94)

a. The ratios (and 90% CIs) are expressed as percentages.

In vivo evaluation of the effect of a potent CYP3A inducer, rifampin, on the single dose palbociclib pharmacokinetics in healthy volunteers (1017):

Results from trial 1017 showed that multiple oral doses of rifampin (strong CYP3A inducer) decreased the geometric mean palbociclib AUC0inf and Cmax by 85% and 70%, respectively, relative to a single 125 mg palbociclib dose given alone. *The concomitant use of strong CYP3A inducers including carbamazepine, phenytoin, rifampin and St. John's wort, and moderate CYP3A inducers including bosentan, efavirenz, etravirine, modafinil and nafcillin should be avoided.*

Based on the results from trial 1017, the sponsor is currently conducting 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". In this trial, the effect of a moderate CYP3A inducer (modafinil) and a mild CYP3A inducer (pioglitazone) on the single dose palbociclib commercial freebase formulation PK will be assessed. In this trial, palbociclib is administered with a moderate fat, standard calorie breakfast (approximately 15% protein, 50% carbohydrate, 35% fat diet of 500-700 calorie). A PMR will be issued for the sponsor to submit the final study report and datasets (for the moderate inducer) from trial A5481039 to FDA for review.

Trial 1017 was a phase 1, open-label fixed-sequence study performed in 14 healthy volunteers. Subjects received Reference treatment in Period 1 and then Test treatment in Period 2 with a washout period of at least 12 days between the two single 125 mg doses of palbociclib (125 mg commercial freebase hard capsule formulation). The Reference treatment (Period 1) was palbociclib 125 mg orally on Day 1. The Test treatment (Period 2) was rifampin 600 mg (two 300 mg capsules) orally once daily for 12 days and palbocilcib 125 mg orally on Period 2 Day 8. Subjects were instructed to fast from 2 hours prior to 2 hours after administration of rifampin. Subjects received plabocilib 125 mg after a 10-hour overnight fast. PK sampling to measure plasma palbociclib concentrations was performed pre-dose and for 120 hours post-dose.

Based on the sponsor's analysis described in Section 2.2.10, a "low-lier" was defined as a palbociclib PK profile with a Cmax less than or equal to 21.4 ng/mL or with a Cmax that had a marginal studentized residual lower than -2. Based on this definition, one "low-lier" was removed from the statistical PK analysis in the current trial. In this study, the identification of "low-lier(s)" was conducted in only the palbociclib alone treatment as the "low-lier" effect could have been confounded by the induction effect of rifampin. The subject ID for the "low-lier" was 10011011, with the AUCinf, AUClast and Cmax values of 744 ng.hr/mL, 698 ng.hr/mL and 19.2 ng/mL, respectively. The Studentized marginal residual for the identified "low-lier" was -1.84.

Table 19 summarizes the plasma palbociclib PK parameters following a single oral dose of palbociclib

alone and co-administration of palbociclib with rifampin. Results of the statistical comparisons of palbociclib exposure parameters for the "low-lier" exclusion population are summarized in Table 20.

Table 19. Summary of Plasma Palbociclib Pharmacokinetic Parameters Following Single Oral Dose of Palbociclib Alone and Co-Administration of Palbociclib with Rifampin ("Low-Lier" Excluded)

Plasma Palbociclib Parameters [Units]	Summary Statistics[a] by Treatment	
	Palbociclib Alone	Palbociclib + Rifampin
N, n	14, 13	14, 10
AUC_{inf} [ng•hr/mL]	1657 (22)	246.6 (47)
AUC_{last} [ng•hr/mL]	1605 (22)	176.6 (53)
C_{max} [ng/mL]	55.17 (34)	15.58 (76)
T_{max} [hr]	8.00 (6.00-8.02)	3.01 (1.03-6.02)
$t_{½}$ [hr]	22.62 ± 3.456	7.78 ± 0.631
CL/F [L/hr]	75.44 (22)	506.7 (47)
V_z/F [L]	2436 (29)	5666 (49)

Abbreviations: %CV = percent coefficients of variation; hr = hour(s); N = number of subjects in the treatment; n = number of subjects with reportable AUC_{inf}, CL/F, V_z/F and $t_{½}$ parameters; SD = standard deviation.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}, arithmetic mean (±SD) for $t_{½}$.

Table 20. Statistical Summary of Treatment Comparisons for Palbociclib Pharmacokinetic Parameters ("Low-Lier" Excluded)

Plasma Palbociclib Parameters [Units]	Adjusted Geometric Means		Ratios (Test/Reference) of Adjusted Means[a]	90% CIs for Ratios
	Palbociclib + Rifampin (Test)	Palbociclib Alone (Reference)		
AUC_{inf} [ng•hr/mL]	245.3	1660	14.78	(11.75, 18.60)
AUC_{last} [ng•hr/mL]	176.0	1586	11.10	(8.78, 14.04)
C_{max} [ng/mL]	15.52	51.95	29.87	(22.30, 40.00)

Abbreviations: CI = confidence interval; hr = hour(s).
a. The ratios (and 90% CIs) are expressed as percentages.

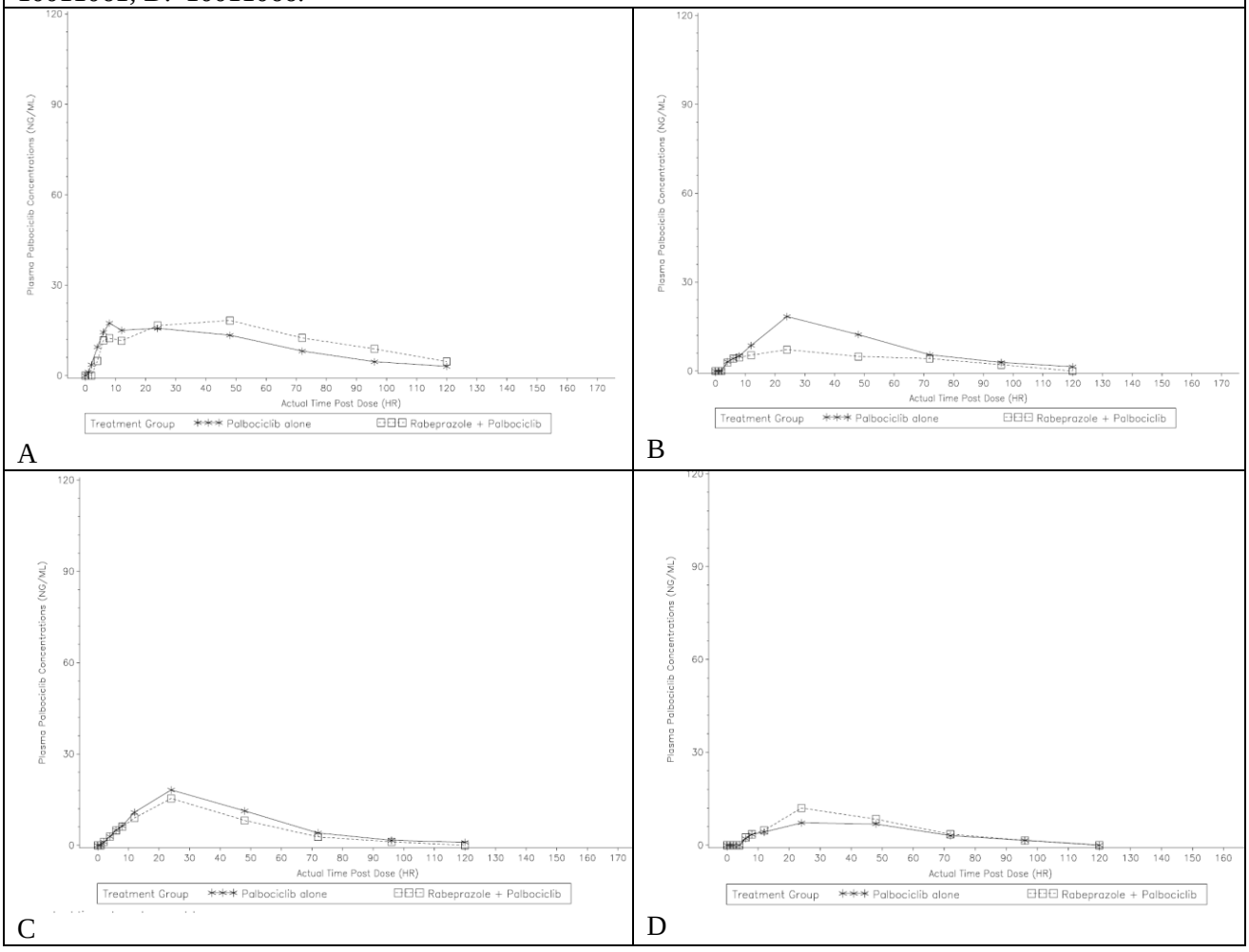
*In vivo evaluation of the effect of an acid reducing agent, rabeprazole, treatment on the single dose palbociclib PK in healthy volunteers under **fasted** conditions (1018):*
Results from trial 1018 showed that rabeprazole once daily significantly decreased palbociclib (commercial freebase formulation) exposure when palbociclib was administered following an overnight fast. Coadministration of palbociclib plus once daily rabeprazole decreased palbociclib AUCinf and Cmax by 62% and 80%, respectively. It is recommended that palbociclib commercial freebase be administered with food. *Trial 1038 evaluated the effect of rabeprazole on palbociclib PK when the palbociclib commercial freebase formulation was administered with food. The results from trial 1038 (described below) are more clinically relevant compared to those from trial 1018.*

Trial 1018 was s a phase 1, open-label, 2-period, fixed-sequence crossover study to investigate the effect of multiple doses of the proton pump inhibitor (PPI) rabeprazole on palbociclib (125 mg commercial freebase formulation) PK in healthy subjects (N= 25) in the fasted state. The study consisted of two treatments. (Treatment A [reference] = single oral dose of palbociclib 125 mg alone after a 10-hour overnight fast which continued for at least 4 hours post dose. Treatment B [test] = multiple doses of rabeprazole (40 mg once daily; two 20 mg tablets), plus a single oral dose of palbociclib 125 mg at least 4 hours after the seventh dose of rabeprazole. Each enrolled subject was to receive Treatment A first and then Treatment B with a washout period of at least 10 days between 2 single 125 mg doses of palbociclib. During Treatment B, subjects were instructed to take rabeprazole at approximately 30 minutes before food intake on Day -5 to Day 0. The seventh dose of rabeprazole (Treatment B, Day 1) was taken and at

6:00 AM following a fast from approximately midnight on Day 1, then at least 4 hours later on Day 1, the single dose of palbociclib 125 mg was administered. During Treatment B, no food was to be allowed for at least 4 hours post dosing of palbociclib on Day 1. PK sampling to measure plasma palbociclib concentrations was performed pre-dose and at 120 hours post-dose. The seven days of rabeprazole dosing is appropriate, as published reports indicate that once daily dosing of rabeprazole 40 mg for 5 or 7 days results in intragastric pH >4 for 65% to 80% of the 24-hour dosing period.

The final PK analysis was conducted using subjects with evaluable PK after exclusion of profiles identified as "low-liers" from the palbociclib alone treatment (See Section 2.2.10). Four "low-liers" (Subject ID: 10011002, 10011047, 10011061 and 10011066) were excluded from the final PK analysis as the Cmax values for these subjects were ≤ 21.4 ng/mL in Treatment A, where palbociclib was administered alone following an overnight fast (Figure 13). The Cmax values for the four identified "low-liers" were 17.4 ng/mL, 18.4 ng/mL, 18.2 ng/mL and 7.2 ng/mL. The Studentized Marginal residuals for the four identified "low-liers" were -1.94, -1.83, -1.85 and -3.58, respectively.

Figure 13. Plasma palbociclib concentration-time profiles for "low-liers". A: 10011002; B: 10011047; C: 10011061; D: 10011066.



In trial 1018, for the population excluding the "low-liers", co-administration of palbociclib plus once daily rabeprazole decreased palbociclib exposures as measured by AUCinf and Cmax by approximately 62% and 80%, respectively (Table 21, Table 22).

Table 21. Summary of Plasma Palbociclib Pharmacokinetic Parameter Values Following Single Oral Doses Alone and After Rabeprazole Treatment ("Low-liers" Excluded).

Parameter Summary Statistics[a] by Treatment		
Parameter (units)	**Palbociclib Alone**	**Palbociclib + Rabeprazole**
N, n	22[b], 22	25, 23
AUC_{inf} (ng•hr/mL)	1949 (29)	754.4 (38)
AUC_{last} (ng•hr/mL)	1895 (30)	672.8 (40)
T_{last} (hr)	120 (72.0-120)	96.0 (72.0-120)
C_{max} (ng/mL)	61.74 (36)	12.25 (44)
T_{max} (hr)	6.00 (6.00-24.0)	24.0 (6.00-48.0)
$t_{½}$ (hr)	21.35 ±1.8598	22.45 ± 4.2139
CL/F (L/hr)	64.15 (29)	165.7 (38)
V_z/F (L)	1968 (29)	5289 (31)

Abbreviations: %CV = percent coefficient of variation, hr = hour(s), n = number of subjects ("low-liers" excluded) for whom t½, AUCinf, CL/F and Vz/F were estimable, N = number of subjects in the treatment group excluding "low-liers", SD = standard deviation. a. Geometric mean (geometric %CV) for all except: median (range) for Tmax and Tlast; arithmetic mean (±SD) for t½. b. The subjects who were identified as "low-liers" within palbociclib alone treatment are listed above.

Table 22. Statistical Summary of Palbociclib Treatment Comparison ("Low-liers" Excluded)

	Adjusted Geometric Means			
Parameter (units)	**Palbociclib + Rabeprazole (Test)**	**Palbociclib Alone (Reference)**	**Ratio (Test/Reference) of Adjusted Means[a]**	**90% CI for Ratio**
AUC_{inf} (ng•hr/mL)	745.4	1975	37.74	(33.53, 42.47)
AUC_{last} (ng•hr/mL)	666.7	1902	35.05	(31.09, 39.52)
C_{max} (ng/mL)	12.19	61.84	19.71	(16.76, 23.17)

Abbreviation: CI=confidence interval.
a. The ratios (and 90% CIs) are expressed as percentages.

*In vivo evaluation of the effect of a H2-receptor antagonist (famotidine), an acid reducing agent (rabeprazole), and an antacid (Mi-Acid Maximum Strength Liquid®), on the single dose palbociclib pharmacokinetics in healthy volunteers under **fed** conditions (1038):*

Famotidine (an H2-receptor antagonist) given 10 hours before and 2 hours after palbociclib had no clinically significant impact on the exposure of palbociclib (administered with food), compared to palbociclib alone (Table 24, Table 25). Rabeprazole given daily for 6 days before and 4 hours prior to palbociclib (administered with food) did not significantly affect palbociclib exposure, compared to palbociclib alone. Co-administration of palbociclib plus once daily rabeprazole decreased the geometric mean palbociclib AUCinf and Cmax by 13% and 41%, respectively (Table 24, Table 25). Mi-Acid Maximum Strength Liquid (antacid) given 2 hours before or 2 hours after palbociclib had no clinically significant impact on the exposure of palbociclib (administered with food) compared to palbociclib given alone (Table 26, Table 27). *Results from trial 1038 indicate that PPIs, H2-receptor antagonists and antacids may be coadministered with the palbociclib commercial freebase formulation when the freebase formulation is administered with food, as proposed in the current submission.*

Trial 1038 investigated the effect of a PPI on palbociclib exposure when palbociclib (commercial freebase 125 mg capsule) is administered with food. Additionally, this trial evaluated the effects of the timing of alternative acid-reducing agents (an antacid and a H2-receptor antagonist) administration on palbociclib bioavailability in the presence of food. Trial 1038 was a phase 1, open-label, 3-period, fixed-sequence study in 2 parallel cohorts of healthy volunteers with a design as shown in Table 23. Palbociclib was administered under a fed condition: Following an overnight fast of at least 10 hours and after the collection of the pre-dose palbociclib PK sample, subjects were to start the recommended moderate-fat standard calorie breakfast (approximately 15% protein, 50% carbohydrate, 35% fat diet of 500-700 calories) approximately 25 minutes prior to administration of palbociclib. Breakfast was to be consumed

within a 20-minute period with study drug administered approximately 5 minutes after completion of the meal. PK sampling to measure plasma palbociclib concentrations was performed pre-dose and at 120 hours post-dose.

Table 23. Study Design

	Period 1	Washout:	Period 2	Washout:	Period 3
Cohort 1; n=14	A	≥10 days between palbociclib doses	B	≥10 days between palbociclib doses	C
Cohort 2; n=14	A		D		E

Treatment A (reference treatment): Single dose of palbociclib 125 mg in the fed state.
Treatment B: Single dose of palbociclib 125 mg in the fed state, plus single dose of famotidine (H2 antagonist) 20 mg oral tablet 10 hours prior to and 2 hours after palbociclib administration.
Treatment C: Single dose of palbociclib 125 mg in the fed state, plus single dose of rabeprazole (PPI) 2 × 20 mg oral tablets daily from Day -5 to Day 0 and 4 hours before palbociclib administration.
Treatment D: Single dose of palbociclib 125 mg in the fed state, plus Mi-Acid Maximum Strength Liquid (antacid) 30 mL 2 hours before palbociclib administration.
Treatment E: Single dose of palbociclib 125 mg in the fed state, plus Mi-Acid Maximum Strength Liquid (antacid) 30 mL 2 hours after palbociclib administration.

Table 24. Summary of Plasma Palbociclib PK Parameter Values Following Single Oral Doses (Cohort 1)

	Parameter Summary Statistics[a] by Treatment		
Parameter (unit)	Palbociclib Alone	Famotidine + Palbociclib	Rabeprazole + Palbociclib
N, n	14, 14	14, 14	14, 14
AUC_{inf} (ng•hr/mL)	1574 (20)	1512 (28)	1367 (29)
AUC_{last} (ng•hr/mL)	1524 (20)	1455 (28)	1302 (28)
T_{last} (hr)	120 (96.0-120)	120 (96.0-120)	120 (96.0-120)
C_{max} (ng/mL)	51.21 (15)	48.65 (38)	30.30 (44)
T_{max} (hr)	6.01 (6.00-8.00)	6.05 (6.00-12.0)	8.04 (6.00-24.1)
$t_{½}$ (hr)	22.64 ± 3.3475	23.44 ± 3.6441	24.99 ± 4.2411
CL/F (L/hr)	79.31 (20)	82.69 (28)	91.37 (29)
V_z/F (L)	2567 (15)	2768 (28)	3260 (23)

Abbreviations: %CV=percent coefficient of variation; hr=hour; N=number of subjects in the treatment group; n=number of subjects; a. Geometric mean (geometric %CV) for all except: median (range) for Tmax and Tlast; arithmetic mean (±SD) for t½.

Table 25. Statistical Summary of Treatment Comparison for Palbociclib (Cohort 1)

	Adjusted Geometric Means			
Parameter (unit)	Test	Reference	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Famotidine + Palbociclib (Test) Versus Palbociclib Alone (Reference)			
AUC_{inf} (ng•hr/mL)	1512	1574	96.02	(87.90, 104.89)
AUC_{last} (ng•hr/mL)	1455	1524	95.50	(87.25, 104.54)
C_{max} (ng/mL)	48.65	51.21	95.00	(79.23, 113.90)
	Rabeprazole + Palbociclib (Test) Versus Palbociclib Alone (Reference)			
AUC_{inf} (ng•hr/mL)	1367	1574	86.85	(79.50, 94.87)
AUC_{last} (ng•hr/mL)	1302	1524	85.43	(78.05, 93.52)
C_{max} (ng/mL)	30.30	51.21	59.18	(49.36, 70.95)

Abbreviation: CI=confidence interval; hr=hour
a. The ratios (and 90% CIs) are expressed as percentages.

Table 26. Summary of Plasma Palbociclib PK Parameter Values Following Single Oral Doses (Cohort 2)

Parameter Summary Statistics[a] by Treatment			
Parameter (unit)	**Palbociclib Alone**	**Antacid 2 hours Before Palbociclib**	**Antacid 2 hours After Palbociclib**
N, n	13, 13	13, 13	13, 13
AUC_{inf} (ng•hr/mL)	1787 (21)	1892 (16)	1879 (21)
AUC_{last} (ng•hr/mL)	1738 (21)	1841 (15)	1823 (21)
T_{last} (hr)	120 (96.0-120)	120 (96.0-120)	120 (96.1-120)
C_{max} (ng/mL)	62.48 (21)	60.02 (16)	59.84 (26)
T_{max} (hr)	6.03 (6.00-12.0)	8.00 (6.00-8.00)	8.00 (6.00-12.0)
$t_{½}$ (hr)	22.11 ± 2.3479	21.88 ± 2.3102	22.64 ± 2.5247
CL/F (L/hr)	69.93 (21)	66.07 (16)	66.52 (21)
V_z/F (L)	2218 (22)	2073 (15)	2160 (21)

%CV=percent coefficient of variation; N=number of subjects in the treatment group; n=number of subjects; SD=standard deviation; a. Geometric mean (geometric %CV) for all except: median (range) for Tmax and Tlast; arithmetic mean (±SD) for t½.

Table 27. Statistical Summary of Treatment Comparison for Palbociclib (Cohort 2)

	Adjusted Geometric Means			
Parameter (unit)	**Test**	**Reference**	**Ratio (Test/Reference) of Adjusted Means[a]**	**90% CI for Ratio**
Antacid 2 hours Before Palbociclib (Test) Versus Palbociclib Alone (Reference)				
AUC_{inf} (ng•hr/mL)	1892	1787	105.86	(100.53, 111.47)
AUC_{last} (ng•hr/mL)	1841	1738	105.96	(100.58, 111.63)
C_{max} (ng/mL)	60.02	62.48	96.07	(89.93, 102.62)
Antacid 2 hours After Palbociclib (Test) Versus Palbociclib Alone (Reference)				
AUC_{inf} (ng•hr/mL)	1879	1787	105.15	(99.86, 110.72)
AUC_{last} (ng•hr/mL)	1823	1738	104.90	(99.57, 110.52)
C_{max} (ng/mL)	59.84	62.48	95.79	(89.67, 102.32)

Abbreviations: CI=confidence interval
a. The ratios (and 90% CIs) are expressed as percentages.

2.4.4 Are other metabolic/transporter pathways important?

No. In vitro experiments (Study PD-332991/25Mar09/142925) with transfected MDCK cells showed that palbociclib was a substrate of P-gp and breast cancer resistance protein (BCRP) at low concentrations, but not at clinically relevant higher concentrations. Therefore, these efflux mechanisms are unlikely to affect the extent of oral absorption of palbociclib administered at therapeutic doses in humans (See Section 2.2.10).

Based on the in vitro results, and consistent with the draft FDA draft guidance (2012), palbociclib showed a low potential to inhibit the activities of drug transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, OATP1B3 at clinically relevant concentrations (studies PF-00080665_06_Dec12_163603, (b) (4) 128431, (b) (4) 128430. (b) (4) 128429).

2.4.5 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

The label specifies co-administration of letrozole with palbociclib. An in vivo trial evaluated the drug interaction potential between letrozole and palbociclib when the two drugs are coadministered (See Section 2.4.6).

2.4.6 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Letrozole: Based on results from phase 1 in trial 1003, letrozole does not cause a change in the steady-state palbociclib exposure (Table 28), and palbociclib does not cause a change in letrozole exposure (Table 29). In vivo, there is no drug interaction between letrozole and palbociclib when the two drugs are coadministered according to the regimen recommended for approval. In vitro, letrozole is a substrate for CYP3A4 and CYP2A6, a strong inhibitor of CYP2A6, and a moderate inhibitor of CYP2C19 (current package insert FEMARA).

Table 28. Statistical Summary of Treatment Comparison for Palbociclib PK Parameters (Phase 1), N=12

	Adjusted Geometric Means			
Parameter [Units]	Palbociclib + Letrozole (Test)	Palbociclib Alone (Reference)	Ratio (Test/Reference)of Adjusted Means[a]	90% CI for Ratio
AUC_{24} [ng·hr/mL]	1933	1982	97.54	(90.16, 105.52)
C_{max} [ng/mL]	108.4	115.8	93.60	(84.24, 104.00)

[a] The ratios (and 90% CIs) are expressed as percentages.
Abbreviations: AUC24=Area under the plasma concentration-time curve from time zero to 24 hours; CI=confidence interval; Cmax=Maximum observed plasma concentration.

Table 29. Statistical Summary of Treatment Comparison for Letrozole PK Parameters (Phase 1), N=12

	Adjusted Geometric Means			
Parameter [Units]	Palbociclib + Letrozole (Test)	Letrozole Alone (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{24} [ng·hr/mL]	1739	1936	89.84	(84.54, 95.47)
C_{max} [ng/mL]	94.95	104.0	91.30	(85.21, 97.83)

[a] The ratios (and 90% CIs) are expressed as percentages.
Abbreviations: AUC24=Area under the plasma concentration-time curve from time zero to 24 hours; CI=confidence interval; Cmax=Maximum observed plasma concentration.

Tamoxifen: A phase 1 drug interaction trial (1026) was conducted to investigate the effect of steady-state concentrations of tamoxifen and its active metabolites (4-hydroxy-tamoxifen, N-desmethyl-tamoxifen, and 4-hydroxy-N-desmethyl-tamoxifen) on the PK of a single oral 125-mg dose of palbociclib (commercial freebase formulation) in healthy male volunteers (N=25)) under an overnight fasted condition. This trial was done to inform the starting dose selection for palbociclib in a Phase 3 study where palbociclib would be co-administered with tamoxifen (trial not submitted in current submission). When a single 125-mg dose of palbociclib was coadministered with multiple doses of tamoxifen in healthy subjects, the exposure of palbociclib was comparable with that when palbociclib was given alone.

This was a phase 1, open-label, 2-period, fixed-sequence study of the effect of multiple doses of tamoxifen on palbociclib PK in healthy males. Subjects received a single oral dose of palbociclib 125 mg on Day 1 of Period 1 following a 10-hour overnight fast which was to continue for at least 4 hours post dose. Palbociclib PK was assessed over the next 144 hours. The morning of Day 1 Period 2, subjects began the tamoxifen loading dose regimen consisting of 4 daily 60-mg oral doses of tamoxifen (Days 1 to 4) followed by 23 daily 20-mg oral doses of tamoxifen (Day 5 through Day 27 of Period 2). After a 10-hour overnight fast (which was to continue for at least 4 hours post dose), on the morning of Day 22 of Period 2, palbociclib was to be administered immediately following the administration of the Day 22 tamoxifen dose. Palbociclib PK was then assessed over the next 144 hours.

In this trial, 7 of the 49 palbociclib concentration-time profiles collected across both treatments were identified as "low-liers" (defined in Section 2.2.10); 5 "low-lier" profiles were identified in the palbociclib alone treatment period, and 2 "low-lier" profiles were identified in the treatment period where palbociclib was co-administered with steady-state tamoxifen. PK parameters by treatment are summarized in (Table 30). For the population excluding "low-liers", the geometric mean Cmax and AUCinf values were 1.16- and 1.08-fold, respectively, when palbociclib was co-administered with steady-state tamoxifen as compared to its administration alone (Table 31).

Table 30. Summary of Plasma Palbociclib Pharmacokinetic Parameters Following Single Oral 125-mg Doses of Palbociclib Alone and with Steady-State Tamoxifen, "Low-Liers" Excluded.

Plasma Palbociclib PK Parameters (Unit)	Summary Statistics[a] by Treatment	
	Palbociclib 125 mg Alone (Reference)	Palbociclib 125 mg + Steady-State Tamoxifen (Test)
N, n	20, 20	22, 22
AUC_{inf} (ng•hr/mL)	1216 (25)	1253 (24)
AUC_{last} (ng•hr/mL)	1166 (25)	1205 (24)
C_{max} (ng/mL)	38.74 (36)	43.08 (31)
T_{max} (hr)	6.03 (4.00-12.0)	7.07 (5.98-12.0)
$t_{½}$ (hr)	23.52 ± 3.49	22.46 ± 3.82
CL/F (L/hr)	102.8 (25)	97.77 (24)
Vz/F (L)	3454 (26)	3194 (30)

Abbreviations: hr=hour; N=number of subjects in the treatment group; n=number of subjects where t½, AUCinf, CL/F and Vz/F were determined

a. Geometric mean (geometric %CV) for all except: median (range) for Tmax; arithmetic mean (±SD) for t½.

Table 31. Statistical Summary of Treatment Comparisons for Palbociclib, "Low-Liers" Excluded.

Plasma Palbociclib PK Parameters (Unit)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Palbociclib 125 mg Alone (Reference)	Palbociclib 125 mg + Steady-State Tamoxifen (Test)		
Low-Liers Excluded				
AUC_{inf} (ng•hr/mL)	1278	1186	107.77	(104.17, 111.49)
AUC_{last} (ng•hr/mL)	1228	1136	108.12	(104.42, 111.95)
C_{max} (ng/mL)	43.59	37.56	116.08	(104.73, 128.65)
CYP2D6 PMs Excluded				
AUC_{inf} (ng•hr/mL)	1281	1185	108.06	(104.42, 111.83)
AUC_{last} (ng•hr/mL)	1232	1136	108.42	(104.77, 112.18)
C_{max} (ng/mL)	43.36	38.63	112.26	(102.17, 123.34)

Abbreviations: CI=confidence interval; CYP2D6=cytochrome P450 2D6; PK=pharmacokinetic; PM = [poor metabolizer

a. The ratios (and 90% CIs) are expressed as percentages.

2.5 General Biopharmaceutics

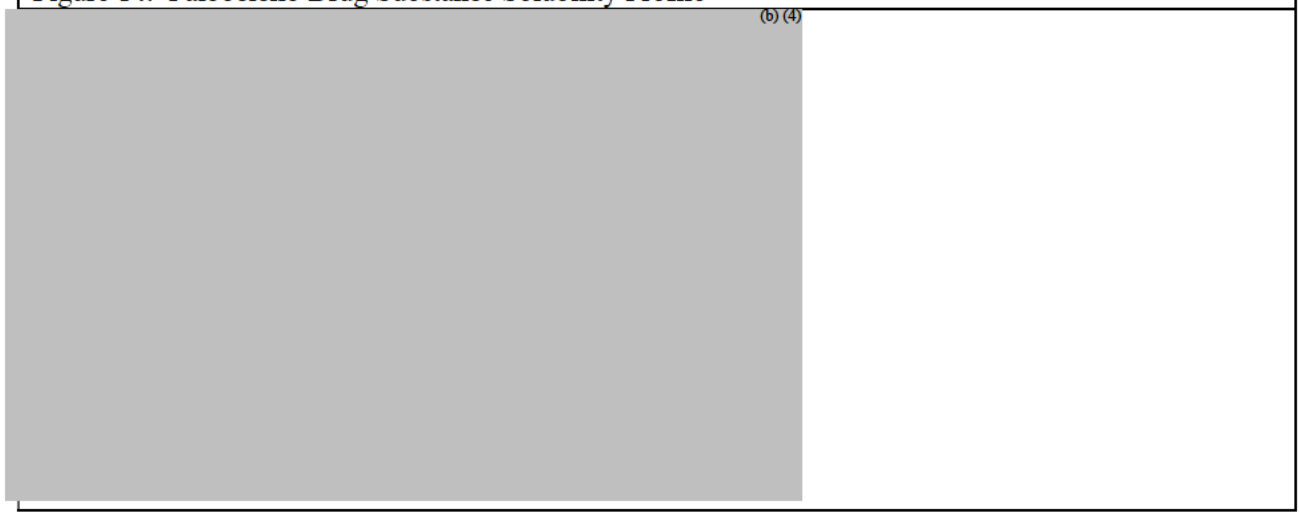
2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The commercial palbociclib drug product is formulated as an immediate release oral capsule (75, 100 and 125 mg) containing the freebase drug substance. Palbociclib is categorized by the applicant as a (b) (4) (b) (4) drug substance (Biopharmaceutics Classification System (BCS) Class (b) (4) The applicant's rationale for classifying palbociclib as a (b) (4) drug substance is based on the applicant's statement that (b) (4)

Palbociclib has not received official BCS classification from the BCS Classification Committee within the FDA.

Solubility:
Plabociclib exhibits (b) (4). The solubility of palbociclib is pH dependent. The (b) (4) (b) (4) For palbociclib, the maximum dose can be completely dissolved in (b) (4) (b) (4) but as shown in Figure 14. (b) (4) and therefore palbociclib is a (b) (4) drug substance.

Figure 14. Palbociclib Drug Substance Solubility Profile



Permeability:
The FDA Guidance for industry entitled " Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2000)" defines a (b) (4) (b) (4)

The applicant classifies palbociclib as a (b) (4) drug substance based on their conclusion that (b) (4)

[redacted]

2.5.2 What is the composition of the to-be-marketed formulation?

The palbociclib commercial freebase formulation has been formulated as immediate-release 75 mg, 100 mg and 125 mg oral capsules. The inactive ingredients are: Microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and hard gelatin capsule shells.

2.5.3 What moieties should be assessed in bioequivalence studies?

Palbociclib should be assessed in bioequivalence trials. Based on the mass-balance trial (1011), palbociclib was the main circulating moiety (23.3%), with palbociclib glucuronide accounting for 14.8% (pharmacological activity not assessed) and other minor metabolites accounting for < 10% of circulating radioactivity each.

2.5.4 Is the to-be-marketed formulation the same as the clinical trial formulation and if not, is there bioequivalence data to support the to-be marketed formulation?

Palbociclib has been formulated as an immediate-release oral capsule. The 25-mg and 100-mg strength isethionate capsules (also referred to as [redacted] isethionate capsule or isethionate salt capsule) were used in the pivotal phase 1/2 efficacy trial 1003. The isethionate salt drug product was not designed to be commercialized. Subsequently, the *initial phase 3* [redacted] *freebase capsule* form of the drug substance was developed, and was initially used in the ongoing phase 3 trial 1008. The *final phase 3 freebase capsule formulation* (125 mg capsule) is currently used in the ongoing phase 3 trial 1008 and replaced the initial phase 3 [redacted] freebase capsule formulation. [redacted]

With the exception of capsule shell printing, the *final phase 3 freebase formulation* is [redacted] equivalent to the *commercial freebase capsule formulation*. The commercial freebase capsule formulation was used in bioequivalence trial 1020, food effect trial 1021 and comparative bioavailability trial 1036, as well as other biopharmaceutics studies and clinical pharmacology studies.

Bioequivalence trial with isethionate salt formulation and the final commercial freebase formulation (1020):

In the pivotal trial (1003), subjects fasted from 1 hour before and until 2 hours after palbociclib (isethionate formulation) administration. Trial 1020 showed that under an overnight fasted condition, the final commercial freebase formulation was not bioequivalent to the isethionate salt formulation used in the pivotal trial (1003). The lower bound of 90% CI for Cmax fell outside of the pre-defined bioequivalence limits (80% to 125%) at 76.36% (Table 33). *Note that the proposed 125 mg/day dose of palbociclib was defined as the maximum tolerated dose, based on the initial phase 1 dose finding trial, and there is no exposure response relationship for efficacy identified in the FDA pharmacometrics review. In addition, at steady state, the difference in Cmax between the two formulations may be even smaller, given the accumulation of palbociclib. Therefore, for the proposed dosing regimen, at steady state, a less than 15 % decrease in Cmax for the commercial freebase formulation vs. the isethionate formulation is not likely to affect the efficacy of palbociclib. A 15% or less decrease in Cmax should also not adversely affect the safety profile of palbociclib.* Results from trial 1020 also show that the palbociclib final commercial formulation demonstrated bioequivalence with the palbociclib final phase 3 freebase formulation under an overnight fasted condition (Table 33).

Trial 1020 was an open-label, randomized, 6-sequence, 3-period crossover study with healthy subjects. Each subject was to receive 3 treatments (A, B, and C) Following an overnight fast of least 10 hours, with a washout period of at least 10 days between each treatment. Following treatment administration, subjects underwent PK sampling to determine palbociclib concentrations for 144 hours.

The 3 treatments were as follows:

- Treatment A (Reference 1): single dose of palbociclib 125 mg (as a 25-mg capsule and a 100-mg hard capsules) with the isethionate salt form as used in the Phase 1/2 Studies 1001, 1002 and 1003.
- Treatment B (Reference 2): single dose of palbociclib 125 mg (as a 125-mg single capsule) final phase 3 formulation used in the ongoing phase 3 trial A5481008.
- Treatment C (Test): single dose of palbociclib 125 mg (as a 125-mg single capsule) final commercial formulation.

PK parameters by treatment are summarized descriptively for the PK evaluable population in Table 32. Nine “low-liers” (Subject ID: 10011002, 10011004, 10011009 and 10011010, 10011052, 10011060, 10011071, 1001115, 10011130 and 10011135) were identified for Treatment C, (Cmax $\leq$ 21.4 ng/mL), and six “low-liers” (Subject ID: 10011002, 10011004, 10011015, 10011019, 10011086 and 10011130) were identified for Treatment B, (Cmax $\leq$ 21.4 ng/mL).

Table 32. Summary of Plasma Palbociclib PK Parameter Values Following Single Oral Doses			
Parameter (units)	**Treatment A Palbociclib 125 mg Isethionate**	**Treatment B Palbociclib 125 mg Final Phase 3 Freebase formulation**	**Treatment C Palbociclib 125 mg Final Commercial Formulation**
N, n	71, 71	71, 70	71, 70
AUC_{inf} (ng•hr/mL)	1521 (25)	1398 (36)	1427 (36)
AUC_{last} (ng•hr/mL)	1472 (26)	1330 (39)	1355 (40)
T_{last} (hr)	119 (71.5-145)	119 (71.6-145)	119 (48.0-145)
C_{max} (ng/mL)	53.63 (25)	44.82 (54)	45.24 (61)
T_{max} (hr)	6.00 (4.00-8.02)	6.00 (4.00-48.0)	6.00 (4.00-48.0)
$t_{½}$ (hr)	22.36 ± 4.76	22.66 ± 4.84	22.23 ± 4.67
CL/F (L/hr)	82.17 (25)	89.41 (36)	87.58 (36)
V_z/F (L)	2596 (23)	2866 (37)	2751 (38)

Abbreviations: %CV = percent coefficient of variation, API = active pharmaceutical ingredients, hr = hour(s), N = number of subjects in the treatment group, n = number of subjects where t½, AUCinf, CL/F and Vz/F were determined, SD = standard deviation a Geometric mean (geometric %CV) for all except: median (range) for Tmax and Tlast; arithmetic mean (±SD) for t½

Table 33. Statistical Summary of Treatment Comparison for Palbociclib Adjusted Geometric Means				
Parameter (units)	**Test**	**Reference**	**Ratio (Test/Reference) of Adjusted Means[a]**	**90% CI for Ratio**
Palbociclib 125 mg final commercial formulation (Test, Treatment C) vs Palbociclib 125 mg final phase 3 Freebase (Reference 2, Treatment B)				
AUC_{inf} (ng•hr/mL)	1437	1389	103.44	(98.14, 109.03)
AUC_{last} (ng•hr/mL)	1363	1329	102.54	(96.57, 108.87)
C_{max} (ng/mL)	45.39	44.83	101.24	(91.19, 112.39)
Palbociclib 125 mg final commercial formulation (Test, Treatment C) vs Palbociclib 125 mg Isethionate (Reference 1, Treatment A)				
AUC_{inf} (ng•hr/mL)	1437	1516	94.80	(89.97, 99.90)
AUC_{last} (ng•hr/mL)	1363	1466	92.94	(87.53, 98.69)
C_{max} (ng/mL)	45.39	53.54	84.78	(76.36, 94.12)

Abbreviations: CI=confidence interval.
a. The ratios (and 90% CIs) are expressed as percentages.

2.5.5 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Effect of Food on the bioavailability of the freebase commercial formulation of palbociclib (trial 1021):
The effect of a high-fat meal, a low-fat meal or administration in between two moderate-fat meals on palbociclib (freebase commercial formulation) exposure was evaluated. Food intake increased palbociclib exposure in "low-liers", but did not change the palbociclib exposure in the rest of the population to a clinically relevant extent (Table 37). Compared to palbociclib given under overnight fasted conditions, the AUCinf and Cmax of palbociclib increased by 21% and 38% when given with a high-fat meal, by 12% and 27% when given with low-fat meal, and by 13% and 24% when moderate fat food was given 1 hour before and 2 hours after palbociclib dosing (Table 37). Administration of the palbociclib freebase formulation with food increased palbociclib exposure in the "low-liers" observed under overnight fasted conditions, and decreased the intersubject variability compared to administration

of the freebase formulation in the overnight fasted state (Table 34 and Table 36). The results support administration of the palbociclib freebase commercial formulation with food to avoid low exposure in a subset of patients ("low-liers") and to decrease intersubject variability compared to the overnight fasted condition.

Trial 1021 was a randomized, single-dose, open-label, 4-sequence, 4-period cross-over study in healthy volunteers. Twenty-eight subjects received a single dose of palbociclib (freebase commercial formulation) 125 mg under 4 different conditions or treatments as shown below. There was a washout period of at least 10 days between study periods. Following treatment administration, subjects underwent PK sampling over 144 hours to determine palbociclib concentrations.

Treatments were as follows:
Fasted Treatment (A): Following an overnight fast of at least 10 hours, subjects were administered a single dose of palbociclib 125 mg with 240 mL (8 ounces) of ambient temperature water. No food was allowed for at least 4 hours post dose.
Fed Treatment (B): Following an overnight fast of at least 10 hours, subjects started the recommended high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate and fat, respectively) breakfast 30 minutes prior to administration of palbociclib. No food was allowed for at least 4 hours post dose.
Fed Treatment (C): Following an overnight fast of at least 10 hours, subjects started the recommended low fat (approximately 7% of total caloric content of the meal), low-calorie (approximately 400 to 500 calories with 120, 250, and 28 to 35 calories from protein, carbohydrate and fat, respectively) breakfast 30 minutes prior to administration of palbociclib. No food was allowed for at least 4 hours post dose.
Fed Treatment (D): Following an overnight fast of at least 10 hours, subjects were given the first of two moderate-fat standard calorie meals (approximately 15% protein, 50% carbohydrate, 35% fat diet of 500 to 700 calories) 1 hour and 20 minutes before palbociclib administration, the meal was consumed within a 20-minute period with study drug administered approximately 1 hour after completion of the meal. Two hours after palbociclib administration, the second moderate-fat standard calorie meal was consumed. Both meals were consumed within a 20-minute period. Water could be consumed without restriction 3 hours following dosing.

The palbociclib PK parameters for the different treatments are summarized in Table 34, and the individual and Geometric Mean Plasma Palbociclib AUCinf (Upper Panel) and Cmax (Lower Panel) Values by Treatment are shown in Figure 15 ("low-liers" included). Three subjects (10011006, 10011018 and 10011028) in the palbociclib overnight fasted treatment (A) met the defined criteria for "low-liers" described in Section 2.2.10. Food increased the AUCinf and Cmax values of these three "low-liers (Table 35) to fall closer to the respective population median values within 1.5 times the interquartile range (Table 34). The palbociclib PK parameters for the different treatments, with the "low-liers" removed from the overnight fasted treatment (Treatment A) are summarized in Table 36.

Table 34. Summary of Plasma Palbociclib PK Parameter Values Following Single Oral Doses (with "low-liers")

Parameter[a] (units)	Palbociclib 125 mg			
	A: Fasted	B: Fed High Fat	C: Fed Low Fat	D: Fed Moderate Fat
N, n	28, 28	28, 28	27, 27	28, 28
AUC_{inf} (ng•hr/mL)	1408 (39)	1672 (23)	1573 (23)	1580 (27)
AUC_{last} (ng•hr/mL)	1284 (50)	1627 (23)	1524 (23)	1533 (26)
T_{last} (hr)	119 (72.0-144)	119 (94.5-145)	118 (72.0-145)	119 (94.0-145)
C_{max} (ng/mL)	39.22 (73)	53.67 (21)	50.20 (24)	48.64 (21)
T_{max} (hr)	8.00 (6.00-48.0)	8.00 (6.00-12.1)	8.00 (6.00-12.0)	8.00 (4.00-12.0)
$t_{½}$ (hr)	23.90 ± 5.2784	22.14 ± 4.3877	22.03 ± 4.5747	22.91 ± 4.4890
CL/F (L/hr)	88.77 (39)	74.74 (23)	79.45 (22)	79.10 (26)
V_z/F (L)	2993 (39)	2342 (17)	2475 (20)	2573 (18)

Abbreviations: %CV=percent coefficient of variation; hr=hour(s); N=number of subjects in the treatment arm; n=number of subjects where t½, AUCinf, CL/F and Vz/F were determined; SD=standard deviation.
a. Geometric mean (geometric %CV) for all except: median (range) for Tmax and Tlast; arithmetic mean ± SD for t½.

Table 35. Listing of "Low-Lier" Plasma Palbociclib PK Parameters Following Single Oral doses under fasted and fed conditions (1021).

	Palbociclib Fasted	
"Low-Lier" Subject ID	AUCinf (ng.hr/mL)	Cmax (ng/mL)
10011006	-	6.7
10011018	599	7.4
10011028	450	6.7
	Palbociclib Fed High Fat	
	AUCinf (ng.hr/mL)	Cmax (ng/mL)
10011006	1400	59.0
10011018	2030	44.8
10011028	1320	52.6
	Palbociclib Fed Low Fat	
	AUCinf (ng.hr/mL)	Cmax (ng/mL)
10011006	1150	45.0
10011018	1190	29.6
10011028	1270	41.4
	Palbociclib Fed Moderate Fat	
	AUCinf (ng.hr/mL)	Cmax (ng/mL)
10011006	1260	58.2
10011018	1930	38.2
10011028	1120	36.5

Table 36. Summary of Plasma Palbociclib PK Parameter Values Following Single Oral Doses ("Low-Liers" Excluded)

Parameter[a] (units)	Palbociclib 125 mg			
	A: Fasted	B: Fed High Fat	C: Fed Low Fat	D: Fed Moderate Fat
N, n	25, 25	28, 28	27, 27	28, 28
AUC_{inf} (ng•hr/mL)	1525 (25)	1672 (23)	1573 (23)	1580 (27)
AUC_{last} (ng•hr/mL)	1472 (26)	1627 (23)	1524 (23)	1533 (26)
T_{last} (hr)	119 (72.1-144)	119 (94.5-145)	118 (72.0-145)	119 (94.0-145)
C_{max} (ng/mL)	48.31 (23)	53.67 (21)	50.20 (24)	48.64 (21)
T_{max} (hr)	8.00 (6.00-8.03)	8.00 (6.00-12.1)	8.00 (6.00-12.0)	8.00 (4.00-12.0)
$t_{½}$ (hr)	23.70 ± 5.2315	22.14 ± 4.3877	22.03 ± 4.5747	22.91 ± 4.4890
CL/F (L/hr)	81.96 (25)	74.74 (23)	79.45 (22)	79.10 (26)
V_z/F (L)	2741 (21)	2342 (17)	2475 (20)	2573 (18)

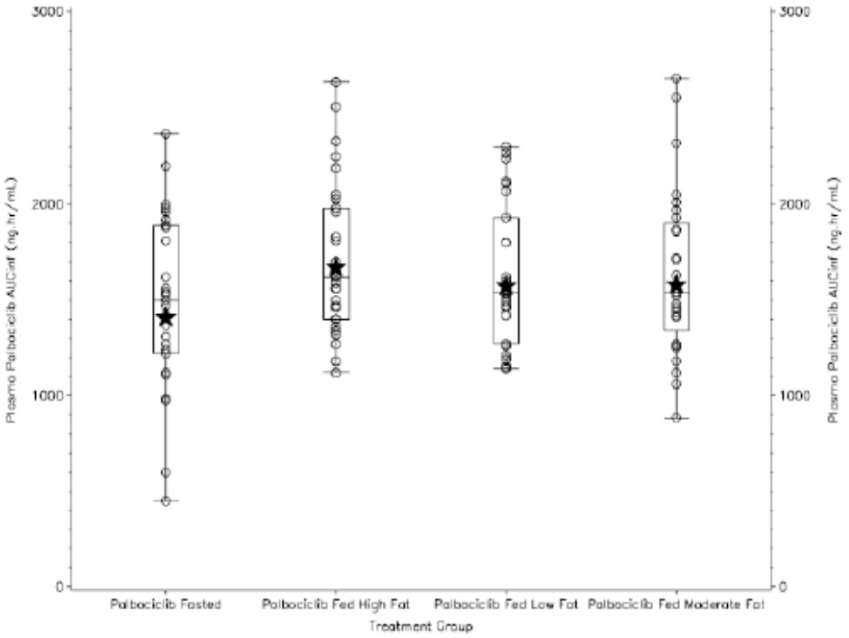
Abbreviations: %CV=percent coefficient of variation; hr=hour(s); N=number of subjects in the treatment arm; n=number of subjects where t½, AUCinf, CL/F and Vz/F were determined; SD=standard deviation.
a. Geometric mean (geometric %CV) for all except: median (range) for Tmax and Tlast; arithmetic mean ± SD for t½.

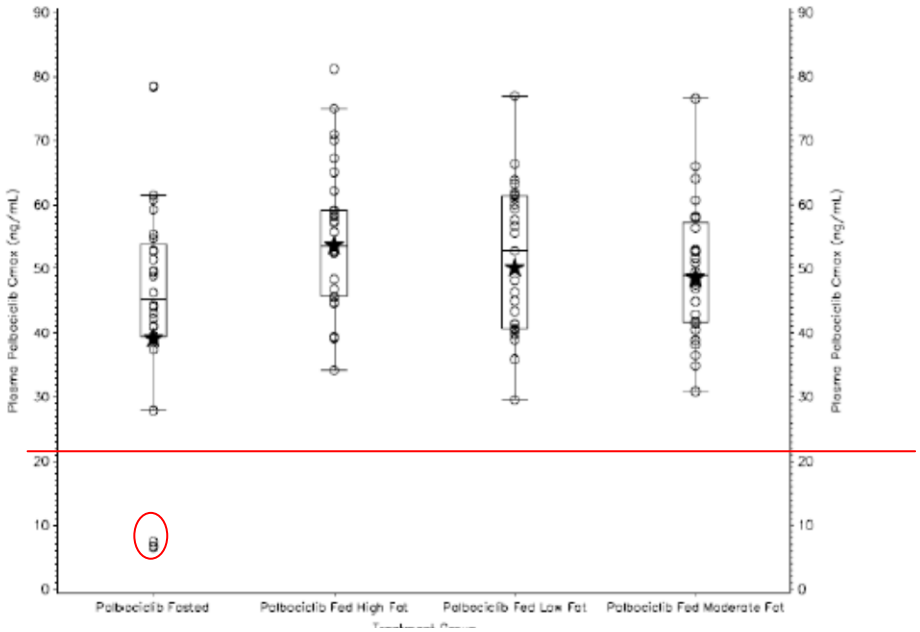
Table 37. Statistical Summary of Treatment Comparison of Plasma Palbociclib ("Low-Liers" Included)

Parameter[a] (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Test	Reference		
Palbociclib Fed High Fat (Test) vs. Palbociclib Fasted (Reference)				
AUC_{inf} (ng•hr/mL)	1627	1349	120.59	(112.61, 129.14)
AUC_{last} (ng•hr/mL)	1587	1242	127.74	(117.15, 139.29)
C_{max} (ng/mL)	52.99	38.46	137.78	(120.55, 157.47)
Palbociclib Fed Low Fat (Test) vs. Palbociclib Fasted (Reference)				
AUC_{inf} (ng•hr/mL)	1509	1349	111.81	(104.29, 119.87)
AUC_{last} (ng•hr/mL)	1462	1242	117.66	(107.74, 128.50)
C_{max} (ng/mL)	48.87	38.46	127.08	(110.92, 145.60)
Palbociclib Fed Moderate Fat (Test) vs. Palbociclib Fasted (Reference)				
AUC_{inf} (ng•hr/mL)	1527	1349	113.13	(105.60, 121.19)
AUC_{last} (ng•hr/mL)	1483	1242	119.36	(109.40, 130.22)
C_{max} (ng/mL)	47.70	38.46	124.04	(108.43, 141.88)

Values have been back-transformed from the log scale. Abbreviations: CI=confidence interval; hr=hour(s). a. The ratios (and 90% CIs) are expressed as percentages.

Figure 15. Individual and Geometric Mean Plasma Palbociclib AUCinf (Upper Panel) and Cmax (Lower Panel) Values by Treatment ("low-liers" included).





Stars represent the geometric mean and open circles represent individual values. Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times interquartile range. The red circle identifies the "low-liers" present when palbociclib freebase is administered after an overnight fasted condition, and the red line identifies the cut-point for identification of "low liers".

Comparative bioavialability of the palbociclib freebase commercial formulation after a moderate-fat meal vs. the palbociclib (b) (4) isethionate formulation administered 1 hour after and 2 hours before two separate moderate-fat meals (similar to administration in the pivotal trial 1003) (Trial 1036):

Trial 1036 evaluated the compared the exposure of the palbociclib commercial freebase formulation (single 125 mg capsule) given 25 minutes after a moderate-fat meal versus the palbociclib (b) (4) isethionate formulation (25 mg and 100 mg capsule) under two different fasted conditions (palbociclib

administration after an overnight fast or palbociclib administration 1 hour after and 2 hours before separate moderate-fat meals) in healthy subjects. Trial 1036 demonstrated comparable exposure between the palbociclib commercial freebase formulation given 25 minutes after a moderate-fat meal and the palbociclib isethionate formulation under a fasted condition similar to that of the pivotal efficacy trial 1003 (Table 38). Trial 1036 supports the recommended administration of the commercial freebase formulation with food.

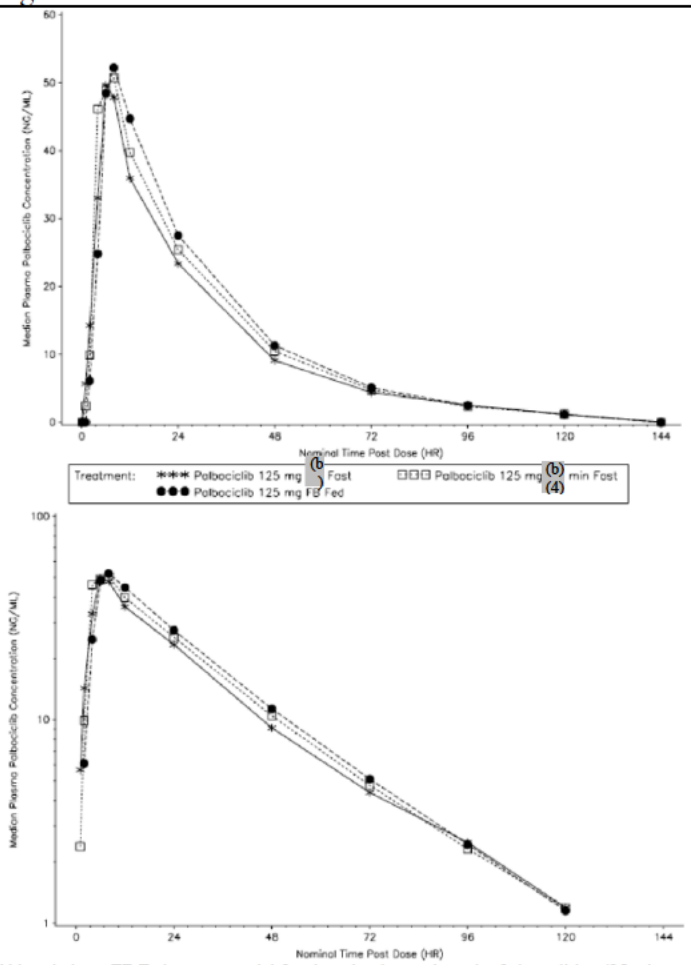
Trial 1036 was a randomized, single-dose, 6-sequence, 3-period crossover study in healthy subjects. Approximately 36 subjects each received 3 single doses of palbociclib 125 mg either as Treatment A (Reference), Treatment B (Reference), or Treatment C (Test) separated by a 10-day washout period.

Treatments were as follows:
Treatment A (Reference): Palbociclib 125 mg as the (b) (4) isethionate formulation (as a 25-mg and a 100-mg hard capsule) under overnight fasted conditions. Following an overnight fast of at least 10 hours, subjects were administered a single 125 mg dose of palbociclib (b) (4) isethionate formulation. No food was allowed for at least 4 hours post dose.
Treatment B (Reference): Palbociclib 125 mg as the (b) (4) isethionate formulation (as a 25-mg and a 100-mg hard capsule) administered under minimal fasted conditions (1 hour after and 2 hours before 2 separate moderate-fat meals). Following an overnight fast of at least 10 hours, subjects were given the first of 2 moderate-fat standard calorie meals (approximately 15% protein, 50% carbohydrate, 35% fat diet of 500-700 calories) 1 hour and 20 minutes before palbociclib (b) (4) isethionate formulation (as a 25-mg and a 100-mg hard capsule) administration, the meal was to be consumed within a 20-minute period with study drug administered approximately 1 hour after completion of the meal. Two (2) hours after palbociclib administration, the second moderate-fat standard calorie meal was to be consumed. Both meals should have been consumed within a 20-minute period. No food was allowed for at least 4 hours after the second moderate-fat meal given post dose.
Treatment C (Test): Palbociclib 125 mg as the commercial freebase hard capsule (a single 125-mg hard capsule) administered 25 minutes after a moderate-fat meal. Following an overnight fast of at least 10 hours, subjects started the recommended moderate-fat standard calorie meal (approximately 15% protein, 50% carbohydrate, 35% fat diet of 500-700 calories) meal 25 minutes prior to administration of palbociclib. This meal was consumed over a 20 minute period with study drug administered approximately 5 minutes after completion of the meal. No food was allowed for at least 4 hours post dose.

For treatment A, B and C, Blood samples for PK analysis of palbociclib were taken pre-dose, and for 144 hours post-dose.

Following administration of single oral doses of palbociclib under Test and Reference conditions at equivalent dose (125 mg), the median plasma concentration-time profiles were similar between the Test and Reference treatments (Figure 14). In general, no apparent difference with respect to the rate of absorption was observed with median Tmax values ranging from 6.01 to 8.00 hours for all treatments (Table 38). Following attainment of Cmax, median plasma palbociclib concentrations declined in parallel across all treatments with an apparent mean elimination t½ value of approximately 22 to 23 hours for all treatments (Table 38 and Figure 16). Inter-subject variability (%CV) for palbociclib AUCinf and Cmax was in the range of 23-33% across all treatments (Table 38).

Figure 16. Median Plasma Palbociclib Concentration-Time Profiles Following Single Oral Doses.



Abbreviations: FB Fed = commercial free base hard capsule under fed condition (25 minutes after a moderate-fat meal) or Treatment C, (b) (4) I Fast = (b) (4) isethionate formulation (as a 25-mg and a 100-mg hard capsule) under fasted condition or Treatment A, (b) (4) I min Fast = (b) (4) iseth ate formulation (as a 25-mg and a 100-mg hard capsule) under minimal fasted condition (1 hour after and 2 hours before 2 separate moderate-fat meals) or Treatment B

Table 38. Summary of Plasma Palbociclib PK Parameter Values Following Single Oral Dosing

Parameter Summary Statistics[a] by Treatment			
Parameter (units)	**Treatment A: Palbociclib 125 mg (b) (4) I Fast**	**Treatment B: Palbociclib 125 mg (b) (4) I min Fast**	**Treatment C: Palbociclib 125 mg FB Fed**
N, n	36, 36	36, 36	35, 35
AUC_{inf} (ng•hr/mL)	1468 (28)	1596 (23)	1624 (26)
AUC_{last} (ng•hr/mL)	1425 (28)	1553 (23)	1580 (27)
T_{last} (hr)	120 (72.0-144)	120 (96.0-144)	120 (96.0-144)
C_{max} (ng/mL)	50.51 (33)	54.34 (25)	52.98 (32)
T_{max} (hr)	6.01 (4.02-12.0)	6.02 (4.00-8.02)	8.00 (6.00-12.0)
$t_{½}$ (hr)	22.7 (4.09)	22.6 (4.45)	22.4 (3.64)
CL/F (L/hr)	85.15 (28)	78.27 (23)	76.93 (26)
V_z/F (L)	2748 (28)	2510 (22)	2453 (26)

Abbreviations %CV = percent coefficient of variation, FB Fed = commercial free base hard capsule under fed condition (25 minutes after a moderate-fat meal), (b) (4) I Fast = (b) (4) sethionate formulation (as a 25-mg and a 100-mg hard capsule) under fasted condition, (b) (4) I min Fast = (b) (4) isethionate formulation (as a 25-mg and a 100-mg hard capsule) under minimal fasted condition (1 hour after and 2 hours before 2 separate moderate-fat meals), hr = hour(s), N = number of subjects in the treatment group, n = number of subjects where t½, AUCinf, CL/F and Vz/F were determined, SD = standard deviation. a. Geometric mean (geometric %CV) for all except median (range) for Tmax and Tlast; arithmetic mean (±SD) for t½.

Table 39. Statistical Summary of Treatment Comparison for Palbociclib.

Parameter (units)	Adjusted Geometric Means: Test	Adjusted Geometric Means: Reference	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Treatment C: Palbociclib 125 mg FB Fed (Test) vs Treatment B: Palbociclib 125 mg (b) (4) I min Fast (Reference)				
AUC_{inf} (ng•hr/mL)	1629	1596	102.06	(98.12, 106.16)
AUC_{last} (ng•hr/mL)	1584	1553	101.98	(97.92, 106.21)
C_{max} (ng/mL)	53.13	54.34	97.78	(93.46, 102.31)
Treatment C: Palbociclib 125 mg FB Fed (Test) vs Treatment A: Palbociclib 125 mg (b) (4) I Fast (Reference)				
AUC_{inf} (ng•hr/mL)	1629	1468	110.93	(106.65, 115.38)
AUC_{last} (ng•hr/mL)	1584	1425	111.15	(106.72, 115.76)
C_{max} (ng/mL)	53.13	50.51	105.20	(100.54, 110.07)
Treatment B: Palbociclib 125 mg (b) (4) I min Fast (Test) vs Treatment A: Palbociclib 125 mg (b) (4) I Fast (Reference)				
AUC_{inf} (ng•hr/mL)	1596	1468	108.69	(104.54, 113.00)
AUC_{last} (ng•hr/mL)	1553	1425	108.99	(104.69, 113.46)
C_{max} (ng/mL)	54.34	50.51	107.58	(102.87, 112.51)

Abbreviations: CI=confidence interval, FB Fed = commercial free base hard capsule under fed condition (25 minutes after a moderate-fat meal), (b) (4) I Fast = (b) (4) isethionate formulation (as a 25-mg and a 100-mg hard capsule) under fasted condition, (b) (4) I min Fast = (b) (4) isethionate formulation (as a 25-mg and a 100-mg hard capsule) under minimal fasted condition (1 hour after and 2 hours before 2 separate moderate-fat meals), vs = versus a The ratios (and 90% CIs) are expressed as percentages

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure *in vivo* performance and quality of the product?

Yes. Refer to the ONDQA Biopharmaceutics review for more details.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes, plasma and urine concentrations of the active parent, palbociclib, were measured in the clinical pharmacology and biopharmaceutics studies. Based on the mass-balance trial (1011), palbociclib was the main circulating moiety in plasma (23.3%), with palbociclib glucuronide accounting for 14.8% (pharmacological activity not assessed) and other minor metabolites accounting for < 10% of circulating radioactivity each.

2.6.2 Which metabolites have been selected for analysis and why?

The plasma PK of the active metabolite PF-05089326 was initially characterized in the mass-balance trial 1011, and accounts for less than 10% of plasma radioactivity.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total plasma concentration of palbociclib was measured in the clinical trials. This was appropriate due to the constant plasma protein binding of palbociclib over the clinically relevant concentration range studied. The average binding of palbociclib to proteins in human plasma was 85.3% (ie, the average fraction unbound in plasma was 0.147) over a concentration range of 0.5 to 5 µg/mL.

2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf)

Methods for the analysis of palbociclib and PF-05089326 in human plasma and urine samples collected during clinical studies are described below. Methods A5489003, A5489006 A5489004 and A54890011 were developed and validated by (b) (4)

Plasma Assays:
An initial LC-MS/MS method was validated to measure palbociclib in human plasma (validation report **A5489003**). Subsequently a new LC-MS/MS method was validated to measure both palbociclib and its lactam metabolite, PF-05089326, in human plasma samples (validation report **5489006**). The first method (A5489003) was applied in trial 1001, 1002, 1003 and 1004. The second method (5489006) was applied in trials 1009, 1010, 1011, 1012, 1015, 1017, 1018, 1020, 1021, 1022, 1026, 1036 and 1008.

Urine Assay:
An initial LC-MS/MS method was validated for human urine (**A5489004**), and was applied to trial 1001. A subsequent LC-MS/MS method was validated for human urine (**A5489011**), and was applied to trial 1011.

Letrozole Plasma Concentrations:
Plasma samples obtained in protocol A5481003 were analyzed for letrozole concentrations by (b) (4) (b) (4) using LC-MS/MS (A5489005). The lower limit of quantitation (LLOQ) was 2.00 ng/mL and the linear calibration range was appropriate at 2.00 ng/mL to 200 ng/mL. The linearity of this method was evaluated by analyzing eight calibration standards over the nominal concentration range of 2.00 to 200 ng/mL using a linear weighted, 1/concentration squared, least-squares regression algorithm to plot the peak area ratio of the analyte to its internal standard versus concentration.

Midazolam and 1'-hydroxymidazolam Plasma Concentrations:
Plasma samples obtained in protocol A5481012 were analyzed for midazolam and 1'-hydroxymidazolam concentrations by (b) (4) using LC-MS/MS (A5489008). The lower limit of quantitation (LLOQ) was 1.00 ng/mL for midazolam and 1'-dydroxymidazolam, and the linear calibration range was appropriate at 0.100 ng/mL to 100 ng/mL. The linearity of this method was evaluated by analyzing ten calibration standards in duplicate over the nominal concentration range of 0.100 to 100 ng/mL using a linear weighted, 1/concentration squared, least-squares regression algorithm to plot the peak area ratio of the analyte to its internal standard versus concentration.

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Method A5489003:
Calibration curves consisting of 12 standards across a range of 2.50 ng/mL to 2500 ng/mL for palbociclib were generated by plotting the peak area ratio of palbociclib to its internal standard using a weighted (1/concentration squared) least squares linear regression. Calibration curve correlation coefficients (r) were ≥0.9982 for palbociclib. Mean inter-assay precision for back-calculated calibration standards was within 7.1% CV and mean inter-assay accuracy ranged from -3.7% to 4.8% of nominal concentration for the palbociclib standards. QC samples at 4 concentration levels spanning the assay range (2.50, 6.00, 150.0, and 2000 ng/mL for palbociclib) were used to evaluate mean inter- and intra-assay precision and accuracy, as summarized in Table 40.

Table 40. Inter-assay and Intra-assay Accuracy and Precision for Bioanalytical Method A5489003

	Palbociclib
Intra-Assay Precision (%CV)	≤ 11.7%
Intra-Assay Accuracy (%RE)	-0.7% to 18.6%
Inter-Assay Precision (%CV)	≤ 10.0%
Inter-Assay Accuracy (%RE)	8.0% to 10.7%

Method A5489006:
Calibration curves consisting of 8 standards across a range of 1.00 ng/mL to 250 ng/mL for palbociclib and 0.100 ng/mL to 25.0 ng/mL for PF-05089326 were generated by plotting the peak area ratio of palbociclib or PF-05089326 to the internal standard using a weighted (1/concentration squared) least squares linear regression. Calibration curve correlation coefficients (r) were ≥ 0.9990 for palbociclib and ≥ 0.9974 for PF-05089326.

Mean inter-assay precision for back-calculated calibration standards was within 2.67% CV for palbociclib and within 8.47% CV for PF-05089326. Mean inter-assay accuracy ranged from -3.51% to 1.84% of nominal concentration for the palbociclib standards, and from -4.19% to 7.39% of nominal concentration for the PF-05089326 standards. QC samples at 4 concentration levels spanning the assay range (1.00, 2.50, 15.0 and 190 ng/mL for palbociclib and 0.100, 0.250, 1.50 and 19.0 ng/mL for PF-05089326)) were used to evaluate mean inter- and intra-assay precision and accuracy, as summarized in Table 41.

Table 41. Inter-assay and Intra-assay Accuracy and Precision for Bioanalytical Method A5489006

	Palbociclib	PF-05089326
Intra-Assay Precision (%CV)	≤ 4.22%	≤5.41%
Intra-Assay Accuracy (%RE)	1.85% to 12.0%	-3.05% to 14.6%
Inter-Assay Precision (%CV)	≤ 3.38%	≤6.91%
Inter-Assay Accuracy (%RE)	4.12% to 8.82%	0.882% to 11.0%

Method A5489004:
Calibration curves consisting of 8 standards across a range of 0.100 µg/mL to 100 µg/mL for palbociclib were generated by plotting the peak area ratio of palbociclib to the internal standard using a weighted (1/concentration squared) least squares linear regression. Calibration curve correlation coefficients (r) were ≥ 0.9957 for palbociclib.

Mean inter-assay precision for back-calculated calibration standards was within 7.0% CV and mean inter-assay accuracy ranged from -6.5% to 8.6% of nominal concentration for the palbociclib standards. QC samples at 5 concentration levels spanning the assay range (0.100, 0.300, 4.00, 10.0 and 80.0 µg/mL for palbociclib) were used to evaluate mean inter- and intra-assay precision and accuracy, as summarized in Table 42.

Table 42. Inter-assay and Intra-assay Accuracy and Precision for Bioanalytical Method A5489004

	Palbociclib
Intra-Assay Precision (%CV)	≤ 7.9%
Intra-Assay Accuracy (%RE)	-9.8% to 18.9%
Inter-Assay Precision (%CV)	≤ 11.0%
Inter-Assay Accuracy (%RE)	-1.5% to 10.6 %

Method A5489011:
Calibration curves consisting of 8 standards across a range of 0.100 µg/mL to 10.0 µg/mL for palbociclib were generated by plotting the peak area ratio of palbociclib to the internal standard using a weighted (1/concentration squared) least squares linear regression. Calibration curve correlation coefficients (r) were ≥ 0.9960 for palbociclib.

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4 APPENDICES

4.1 PHARMACOMETRICS REVIEW

SUMMARY OF FINDINGS

KEY REVIEW QUESTIONS

The purpose of this review is to address the following key questions.

Is the relevant labeling regarding intrinsic factors adequately supported by population PK analysis?

Yes. The labeling related to the following intrinsic factors is adequately supported by on population PK analysis.

Renal impairment: No significant relationship between clearance and creatinine clearance was identified based on population PK analysis (81 patients with normal renal function, 74 patients with mild renal impairment, 29 patients with moderate renal impairment and no patients with severe renal impairment). This is consistent with renal elimination being a minor clearance pathway of palbociclib. Therefore, no dose adjustment is recommended for patients with mild and moderate renal impairment.

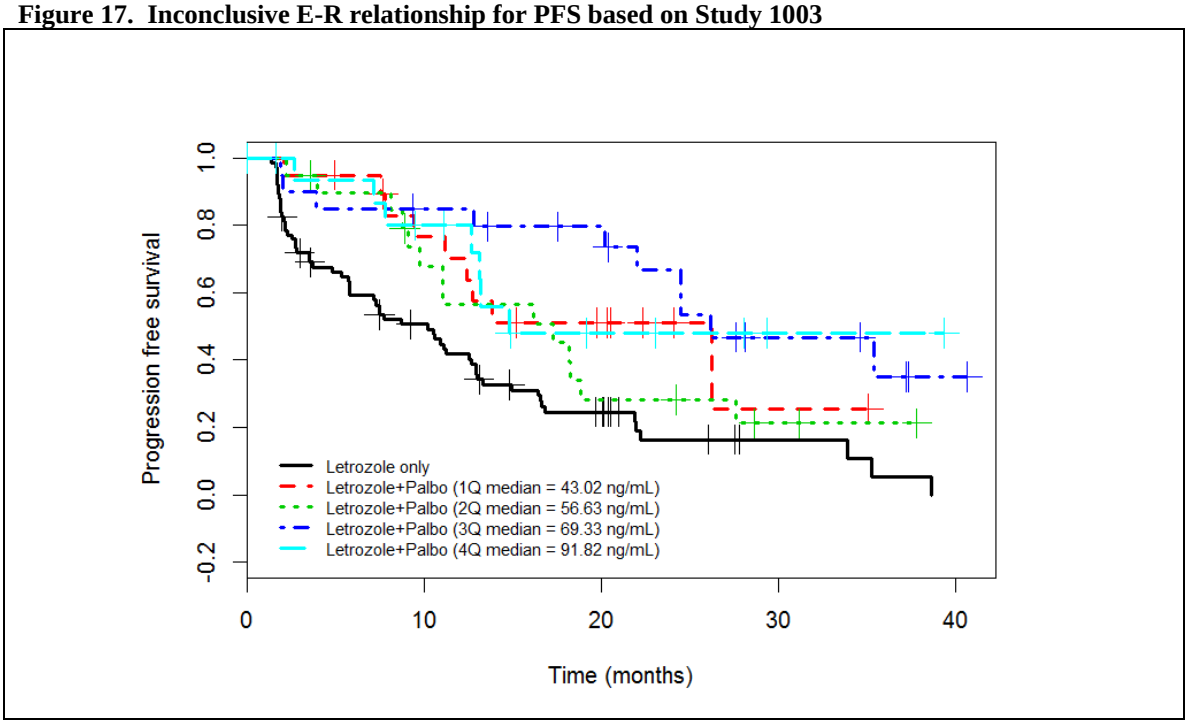
Hepatic impairment: No significant relationship between clearance and liver function was identified based on population PK analysis (142 patients with normal liver function, 40 patients with mild hepatic impairment, 1 patient with moderate hepatic impairment and no patients with severe hepatic impairment). Therefore, No dose adjustment is recommended for patients with mild hepatic impairment.

Other factors: No dose adjustment is recommended with respect to gender, body weight and age. Gender was not identified as significant covariate in population PK analysis (50 male and 133 female patients). Body weight (range: 37.9-123 kg) and age (range: 22-89 years) were significant covariates on clearance. In comparison with a typical subject at a median age of 61 years and a median body weight of 73.7 kg, clearance was increased by 14.7% at an age of 45 years and decreased by 8.33% at an age of 74 years. For body weight, clearance was decreased by 13.2% and increased by 14.2% at a weight of 55 kg and 97 kg, respectively. Therefore, body weight and age have no clinically significant effect on exposure of palbociclib. In addition, no meaningful effect of tumor burden (i.e., baseline tumor size) on palbociclib PK was observed.

What are the characteristics of exposure-response (E-R) relationship for efficacy?

The E-R relationship for efficacy remains inconclusive due to the limited data (n=81) with a fix dose of 125 mg in study 1003. Based on reviewer's analysis, there is no clear trend of better PFS with increasing exposure (Figure 17) following the proposed dose. Similarly, a consistent E-R relationship for efficacy was not established by sponsor's analysis using multivariate cox proportional hazard model and parametric time-to-event model. Therefore, due to the limited data in the E-R analysis and potential confounding effects of other risk factors, a reliable estimate of effect of palbociclib exposure on efficacy cannot be achieved. Therefore, a definitive conclusion on E-R relationship for efficacy cannot be made at this time.

Figure 17. Inconclusive E-R relationship for PFS based on Study 1003

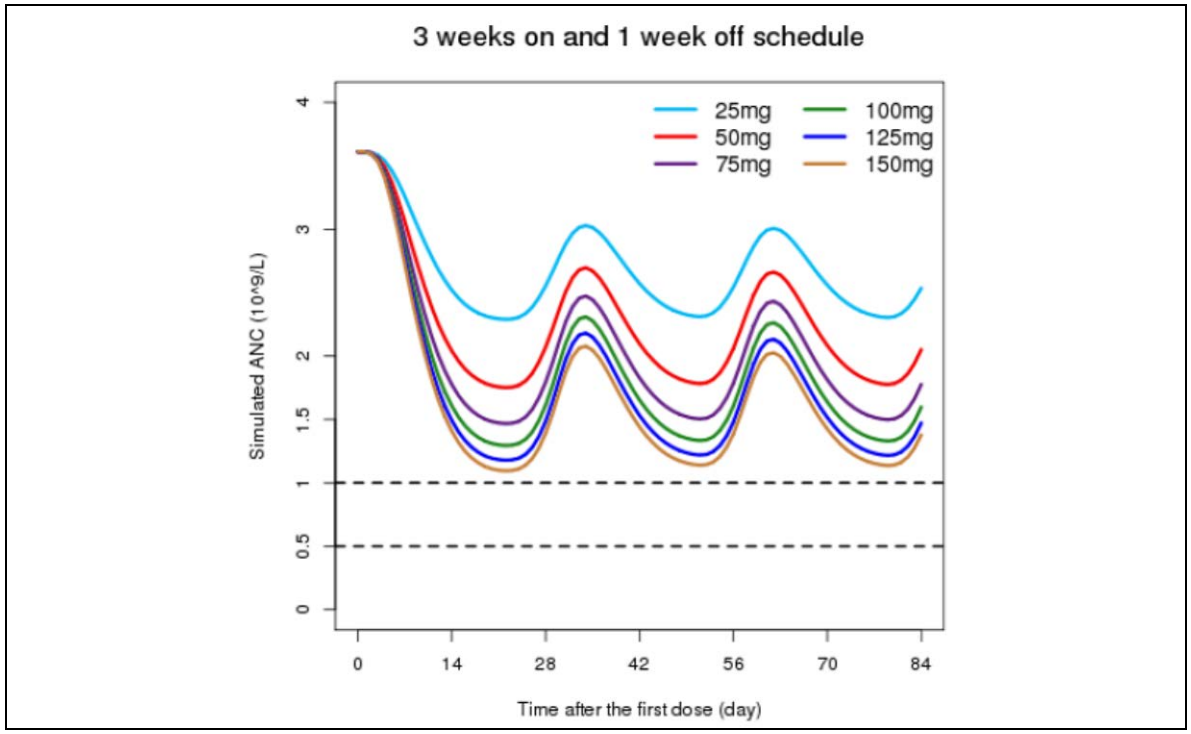


Sources: FDA Reviewer's analysis

Does E-R relationship for neutrophil response support the proposed dose modification based on hematologic toxicity (e.g., neutropenia)?

Yes. More reduction in absolute neutrophil count (ANC) appears to be associated with increasing palbociclib exposure. The relationship between palbociclib exposure and neutrophil count change over the time was adequately described by a semi-mechanistic population PK/PD modeling by sponsor. Longitudinal neutrophil changes at different doses with 3 weeks on and 1 week off schedule were simulated using sponsor's model (Figure 18), suggesting lower dose/exposure will lead to less neutrophil reduction. This supports the proposed dose modification in the label for neutropenia management.

Figure 18. Simulated longitudinal ANC profiles at different dose (3 weeks on and 1 week off schedule)

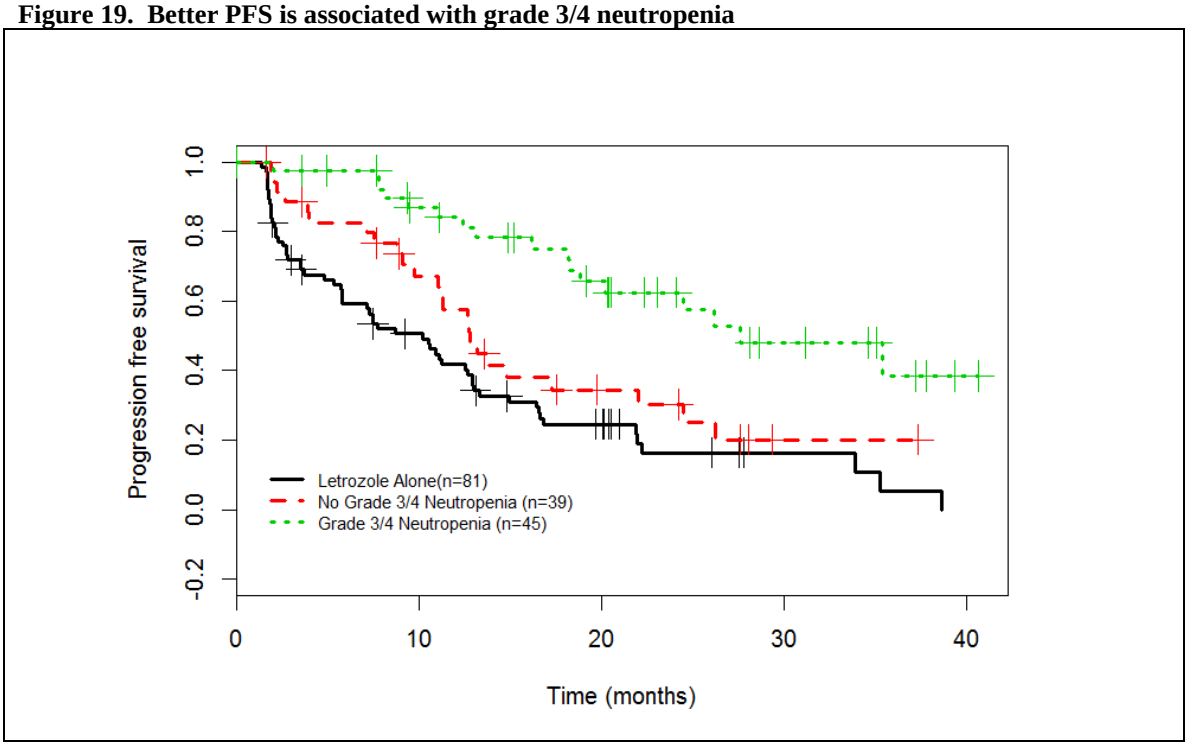


Sources: Sponsor's population modeling analysis report (PMAR-EQDD-A548b-DP4-271), Page 67

Is there an association between neutropenia and efficacy (i.e., PFS)?

An apparent association between neutrophil response and PFS was identified based on reviewer's analysis. It appeared that patients with grade 3 or 4 neutropenia had better PFS than those without grade 3 or 4 neutropenia (Figure 19, p=0.0046). Multivariate analysis using cox proportional hazard model was conducted and led to similar conclusion with a hazard ratio of 0.502 (i.e., hazard ratio: w/ grade 3/4 neutropenia to wo/ grade 3/4 neutropenia, p=0.046), after adjusting for other prognostic factors, including baseline tumor size, baseline Aspartate aminotransferase (AST) and baseline lymphocyte count. A consistent relationship between neutropenia and PFS was also identified by additional analysis controlling for potential confounders (see details in reviewer's analysis). However, given the exploratory nature of all these analyses and the limited data, the result should be interpreted with caution. In future studies (e.g., the confirmatory trials) effort needs to be made to further examine the association between neutropenia and PFS.

Figure 19. Better PFS is associated with grade 3/4 neutropenia



Sources: FDA Reviewer's analysis

RECOMMENDATIONS

The Division of Pharmacometrics in Office of Clinical Pharmacology has reviewed the information contained in NDA 20-7103. This NDA is considered acceptable from a pharmacometrics perspective.

LABEL STATEMENTS

Please refer to Section 3 - Detailed Labeling Recommendations in clinical pharmacology review.

RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK analysis

Sponsor's population PK analysis was based on pooled data (1933 non-missing PK samples available from 183 patients) from Studies 1001,1002 and 1003. In these studies, the isethionate salt capsule formulation of palbociclib was used. The patients were characterized by a wide range of ages (22 to 89 years) and relatively wide range of body weight (37.9 to 123 kg). Palbociclib PK was well characterized by a 2-compartment model with first-order absorption and absorption lag time. The parameter estimates of final population PK model are summarized in Table 44.

Table 44: Parameter estimates of final population PK model

Final Model (Model #8, OFV= -1507.93)						
Parameter	**Estimate**	**RSE %**	**SE**	**95% Confidence Interval (CI)**		**Shrinkage %**
CL/F (L/hr)	60.2	3.31%	1.99	56.3	64.1	16.00%
V_2/F (L)	2710	4.46%	121	2473	2947	38.17%
Q /F (L/hr)	10.6	15.47%	1.64	7.39	13.81	34.23%
V_3/F (L)	61300	30.34%	18,600	24844	97756	--
Ka (1/hr)	0.367	8.39%	0.0308	0.307	0.427	25.28%
Lag (hr)	0.658	4.24%	0.0279	0.603	0.713	--
F_1 (fixed)	1	--	--	--	--	--
Food effect on Lag	0.288	36.11%	0.104	0.084	0.492	--
Food effect on F_1	0.160	58.38%	0.0934	-0.023	0.343	--
Age effect on CL/F	-0.45	18.53%	0.0834	-0.614	-0.287	--
BWT effect on V_2/F	0.00906	25.28%	0.00229	0.00457	0.0135	--
BWT effect on CL/F	0.484	29.75%	0.144	0.202	0.766	--
CL/F ω^2 (%CV)	0.131 (36.19%)	15.50%	0.0203	0.091(30.17%)	0.171 (41.35%)	--
V_2/F ω^2 (%CV)	0.091 (30.15%)	24.53%	0.0223	0.047 (21.73%)	0.135 (36.69%)	--
Q/F ω^2 (%CV)	1.59 (126.10%)	21.82%	0.347	0.910 (95.39%)	2.27 (150.67%)	--
Ka ω^2 (%CV)	0.699 (83.61%)	20.46%	0.143	0.419 (64.73%)	0.979 (98.94%)	--
Thetarized Sigma	0.317	4.38%	0.0139	0.290	0.344	10.41%

Sources: Sponsor's population modeling analysis report (PMAR-EQDD-A548b-DP4-269), Page 52

Sponsor's conclusion based on population PK analysis:

1. In cancer patients where palbociclib was formulated as isethionate salt capsules, the relative bioavailability and absorption lag time were increased by 16.0% and 28.8% respectively in the fed condition (palbociclib taken with high-fat meal) compared to other fasted conditions.
2. Co-administration of acid reducing agents with the palbociclib isethionate salt capsules did not have a significant effect on the relative bioavailability or absorption of palbociclib.
3. Body weight and age were significant covariates on clearance. In comparison with a typical subject at a median age of 61 years and a median body weight of 73.7 kg, clearance was increased by 14.7% at an age of 45 years and decreased by 8.33% at an age of 74 years. For body weight, clearance was decreased by 13.2% and increased by 14.2% at a weight of 55 kg and 97 kg, respectively. Therefore, these covariates were not considered clinically significant.
4. No significant relationship between clearance and creatinine clearance was identified (81 patients with normal renal function, 74 patients with mild renal impairment, 29 patients with moderate renal impairment and no patients with severe renal impairment). Therefore, no dose adjustment is recommended for patients with mild and moderate renal impairment.
5. No significant relationship between clearance and liver function was identified (142 patients with normal liver function, 40 patients with mild hepatic impairment, 1 patient with moderate hepatic impairment and no patients with severe hepatic impairment). Therefore, No dose adjustment is recommended for patients with mild hepatic impairment.

Reviewer's Comments on population PK analysis:

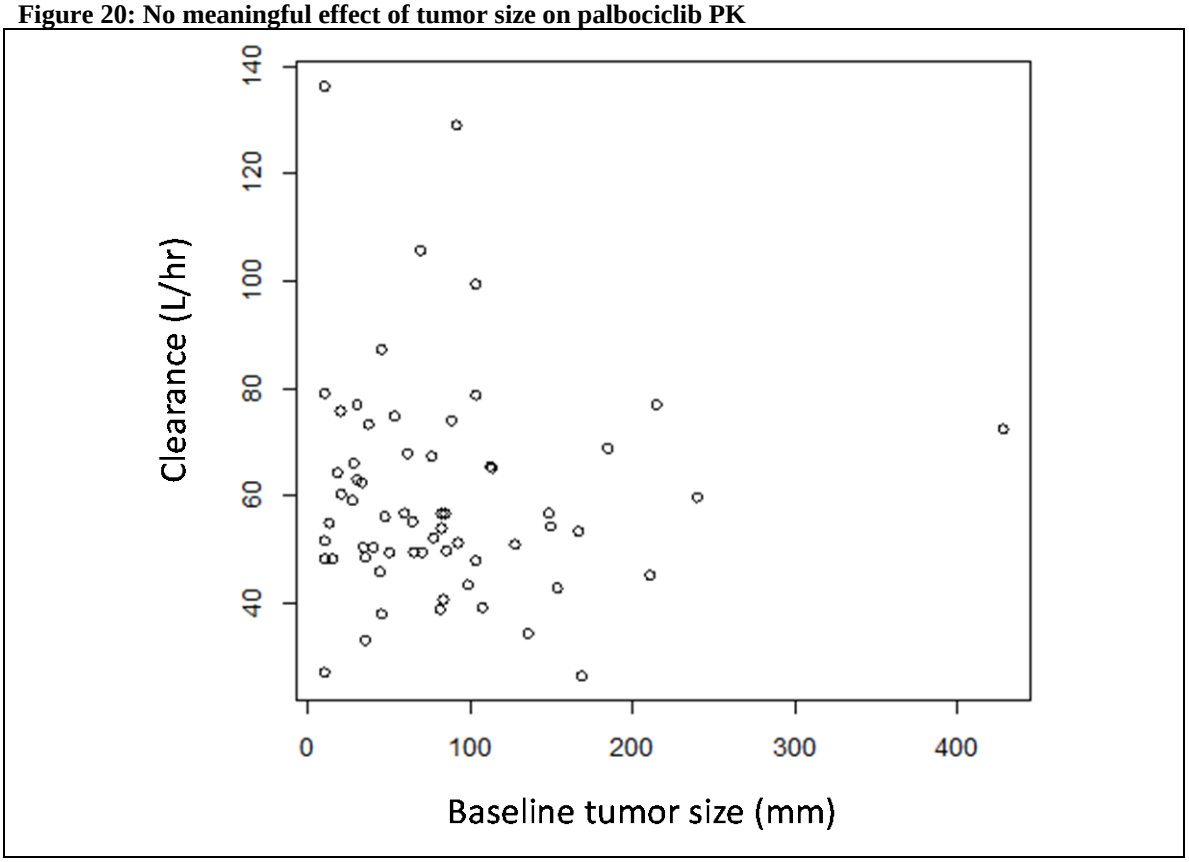
1. Reviewer agrees with sponsor's conclusions in general. The final model adequately captured the observed data and all the PK parameters were estimated with acceptable precision. The predictive capability of the final PK model was sufficiently validated.

2. Sponsor's conclusions regarding food effect and acid reducing agents seem reasonable (b) (4) [redacted]

3. This population PK model can provide reliable post hoc exposure predictions that will be used in subsequent E-R analyses given small shrinkage in PK parameters and adequate model performance in describing the observed data.

*4. No meaningful effect of tumor burden (i.e., baseline tumor size) on palbociclib PK was observed (*Figure 20*).*

Figure 20: No meaningful effect of tumor size on palbociclib PK



Sources: FDA Reviewer's analysis

2.2 E-R for efficacy

Data from study 1003 were used to perform an E-R analyses for efficacy (PFS) in patients with advanced breast cancer. A total of 162 patients were included E-R analysis, including 81 in the letrozole alone arm and 81 in the letrozole plus palbociclib arm. Exposure variables were the average palbociclib concentration (Cavg) value over an entire treatment duration for each patient using the formula below.

C_{avg}=Average daily dose intensity (ADI_{day})/(CL/F)/24

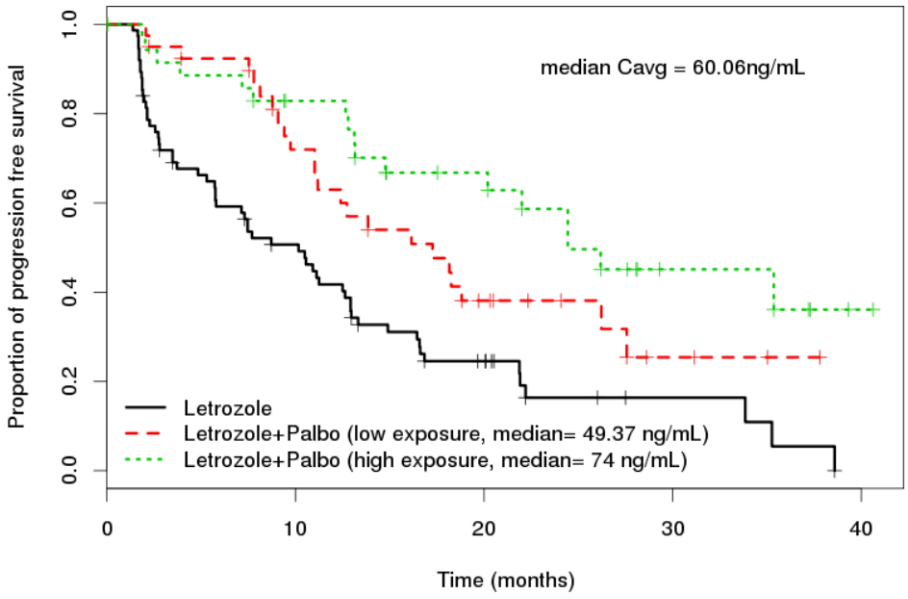
ADI_{day} is the ratio of cumulative palbociclib dose during treatment to the duration of the treatment (days).

Kaplan Meier (KM) analysis, cox proportional analysis and parametric time-to-event model were conducted to explore the relationship between palbociclib exposure and PFS and to identify potential prognostic factors (covariates) for PFS. The tested covariates included palbociclib exposure, either Cavg or the low and the high exposure group, age, baseline body weight, baseline tumor size, ECOG, disease-free interval, baseline albumin, urea nitrogen, alkaline phosphatase, ALT, AST, bilirubin, lactase dehydrogenase, lymphocyte count, neutrophil count, CCND1 amplification, p16 loss, CYP19A1

polymorphism and CCND1 polymorphism.

Preliminary results from KM analysis showed a trend of better PFS for patients with higher exposure (Figure 21).

Figure 21: Kaplan Meier Plot of Letrozole Alone, the Low, and the High Palbociclib



Sources: Sponsor's population modeling analysis report (PMAR-EQDD-A548b-DP4-387), Page 38

Sponsor further conducted cox proportional hazard model and parametric time-to-event model to characterize the E-R relationship. The results from univariate and multivariate cox proportional analysis are summarized in Table 45 and Table 46 . The results based on data from pooled data from letrozole alone arm and combination arm suggested that better PFS is associated with higher palbociclib exposure (Table 45). However, the analysis based on data from combination arm only didn't identify such association (Table 46). In light of the inconsistent conclusions regarding E-R relationship identified with different data sets, a definitive conclusion about E-R relationship for PFS cannot be drawn.

Table 45: Multivariate Analysis of Cox Proportional Model – the Data From Letrozole Alone and Palbociclib Plus Letrozole Arms

Variable	Coefficient	Hazard Ratio (95% CI)	p-value
C_{avg} (ng/mL)	-0.0149	0.985 (0.978, 0.993)	6.73×10^{-5}
Baseline AST (U/L)	0.0154	1.02 (1.01, 1.03)	0.00134
Baseline tumor size (mm)	0.00401	1.00 (1.00, 1.01)	0.0188
Baseline lymphocyte (10^6/mL)	-0.704	0.495 (0.305, 0.803)	0.00443

Sources: Sponsor's population modeling analysis report (PMAR-EQDD-A548b-DP4-387), Page 7

Table 46: Multivariate Analysis of Cox Proportional Model – the Data from Palbociclib Plus Letrozole Arms

Variable	Coefficient	Hazard Ratio (95% CI)	p-value
C_{avg} [a] (ng/mL)	-6.74×10^{-5}	1.00 (0.981, 1.020)	0.995
Baseline AST (U/L)	0.0187	1.019(1.005, 1.033)	0.00914
Baseline tumor size (mm)	0.0068	1.007 (1.002, 1.012)	0.0109
Baseline lymphocyte (10^6/mL)	-1.333	0.263 (0.113, 0.617)	0.00214

Sources: Sponsor's population modeling analysis report (PMAR-EQDD-A548b-DP4-387), Page 8

Sponsor also conducted additional analyses using cox proportional hazard model with palbociclib concentration as time-varying covariate and parametric time-to-event model with log-normal distribution for the PFS event time. Similarly, inconsistency regarding the E-R relationship for PFS was also found in the results based on these analyses with pooled data from both arms and data from combination arm only.

Reviewer's Comments: Extensive analysis with various modeling approach was conducted by sponsor to characterize the E-R relationship for efficacy (PFS). A consistently positive E-R relationship for PFS was not identified in sponsor's analysis using multivariate cox proportional hazard model and parametric time-to-event model. Reviewer's analysis also failed to reveal a clear E-R relationship for PFS
(Figure 17). Therefore, due to the limited data in the E-R analysis, a reliable estimate of effect of palbociclib exposure on efficacy cannot be achieved and a definitive conclusion on E-R relationship for efficacy cannot be made at this time. Future analysis with the data from phase 3 trials will be of great value to elucidate the E-R relationship for efficacy.

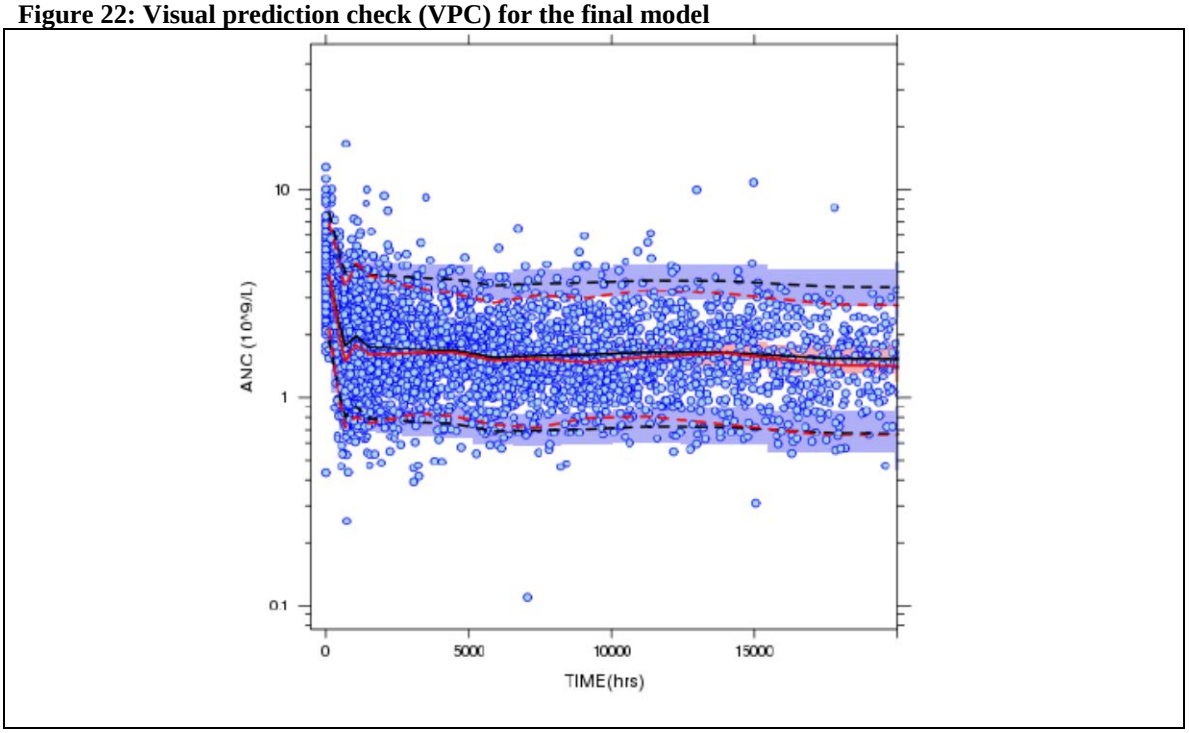
2.3 PK/PD modeling for neutropenia

Data pooled from Studies 1001, 1002, and 1003 were used to establish a population PK-PD model that describes the longitudinal observations of absolute neutrophil count (ANC) in patients with advanced cancer on treatment with palbociclib. The population PK-PD analysis data comprised of 3872 ANC observations available from 185 patients treated with palbociclib, including 74 patients in Study 1001, 16 patients in Study 1002 and 95 patients in Study 1003.

The individual PK parameters were obtained from the population PK modeling. The sequential linked PK-PD analysis was conducted based on the following strategy: semimechanistic physiological model development, random effects model development, inclusion of covariates, final model development, assessment of model adequacy, and validation of the final model.

The relationship between plasma concentration of palbociclib and absolute neutrophil count was adequately described by a semi-mechanistic physiological myelosuppression PKPD model (Figure 22). Decreased longitudinal neutrophil level was attributed to increased palbociclib exposure.

Figure 22: Visual prediction check (VPC) for the final model



Sources: Sponsor's population modeling analysis report (PMAR-EQDD-A548b-DP4-271), Figure 24, Page 50

Reviewer's Comments: *The final model adequately captured the observed data and all the model parameters were estimated with acceptable precision. The predictive capability of the final model was sufficiently validated. The modeling results suggested lowering dose/exposure will lead to less neutrophil reduction (*Figure 18*). The finding supports the proposed dose modification in the label for neutropenia management.*

REVIEWER'S ANALYSIS

INTRODUCTION

Preliminary results from sponsor's univariate cox proportional analysis showed that the early neutrophil response was significant associated with PFS response (p=0.0038). One of the potential explanation would be that it was the palbociclib exposure that drives both neutrophil and tumor response. Herein, an independent analysis was performed by reviewer to further elucidate the association between the PFS and neutrophil response by taking other potential prognostic factors into account.

METHODS

Kaplan Meier (KM) analysis, cox proportional analyses were conducted with data from palbociclib plus letrozole arm (n=84) in trial 1003 to elucidate the relationship between neutrophil response and PFS. The prognostic factors (covariates) for PFS identified by sponsor's analysis (baseline tumor size (SLD), baseline AST and baseline lymphocyte count) were taken into account in reviewer's analysis.

Data Sets

Data sets used are summarized in Table 47.

Table 47. Analysis Data Sets

Study Number	Name	Link to EDR
PMAR 387	ef1003.xpt	\\cdsesub1\evsprod\nda207103\0000\m5\datasets\pmar-387-efficacy\analysis\legacy\datasets\ef1003.xpt
PMAR 387	neudat.xpt	\\cdsesub1\evsprod\nda207103\0000\m5\datasets\pmar-387-efficacy\analysis\legacy\datasets\neudat.xpt
PMAR 387	pkpara.xpt	\\cdsesub1\evsprod\nda207103\0000\m5\datasets\pmar-387-efficacy\analysis\legacy\datasets\pkpara.xpt

Software

R 3.1.1 was used for analyses.

RESULTS AND DISCUSSIONS

As shown in the K-M analysis (Figure 19), patients with grade 3 or 4 neutropenia appeared to have better PFS than patients without it. Furthermore, such trend of better PFS in patients with grade 3 or 4 neutropenia was consistently identified by K-M analysis after controlling the difference in exposure, tumor size (Figure 23 and Figure 24). A univariate and multivariate cox proportional hazard model was also conducted to estimate the effect of neutropenia on the PFS with and without taking into account effects of other prognostic factors. Prognostic factors identified by multivariate cox proportional hazard model included baseline tumor (SLD), baseline AST, and baseline lymphocyte count with decreasing order of magnitude when their distribution ranges were considered. Of note, Figure 23 showed that higher PFS benefit was observed in patients with low exposure and grade 3 or 4 neutropenia than in patients with high exposure but without grade 3 or 4 neutropenia. Both univariate and multivariate cox analysis reached similar conclusion regarding the apparent association between neutropenia and PFS (Table 48).

It is biologically plausible that tumor cells in patients who had neutropenia were more sensitive to the CDK inhibitory effect of palbociclib in the G1 to S transition of the cell proliferation cycle, hence had better PFS. However, given the exploratory nature of all these analyses and the limited data, the result should be interpreted with caution. Data from the ongoing confirmatory trials will be of great value to further examine the association between neutropenia and PFS.

Figure 23: K-M Analysis by controlling exposure

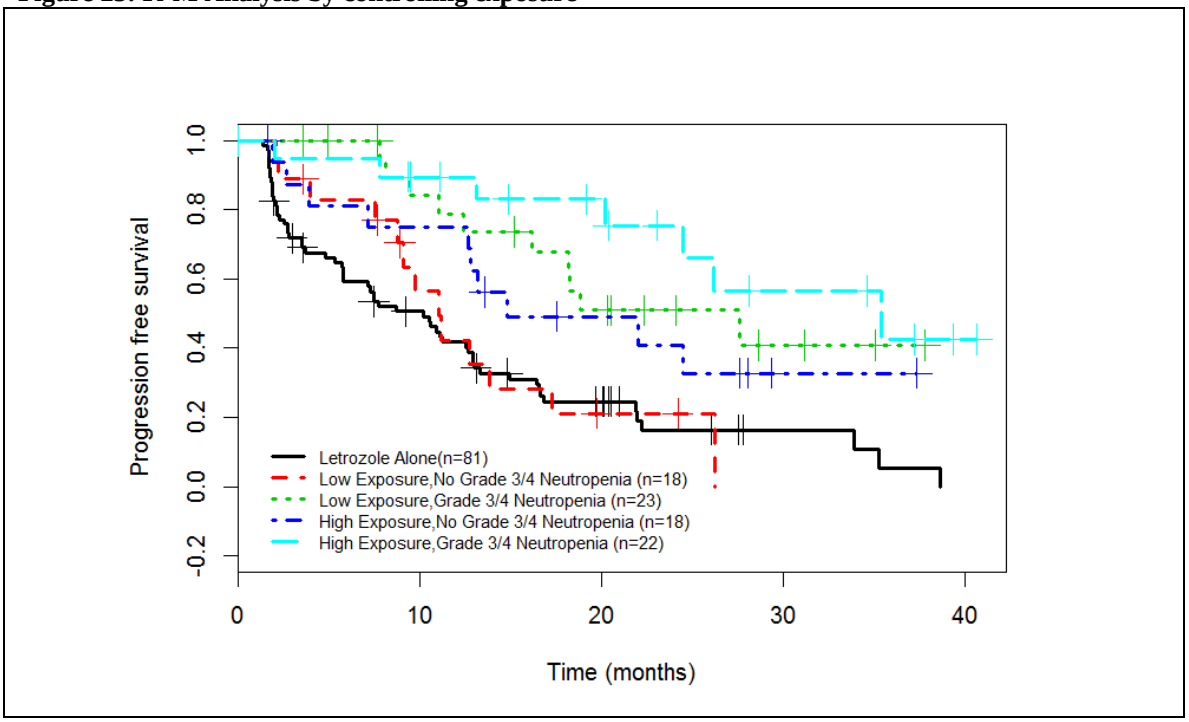


Figure 24: K-M analysis by controlling baseline tumor size (SLD)

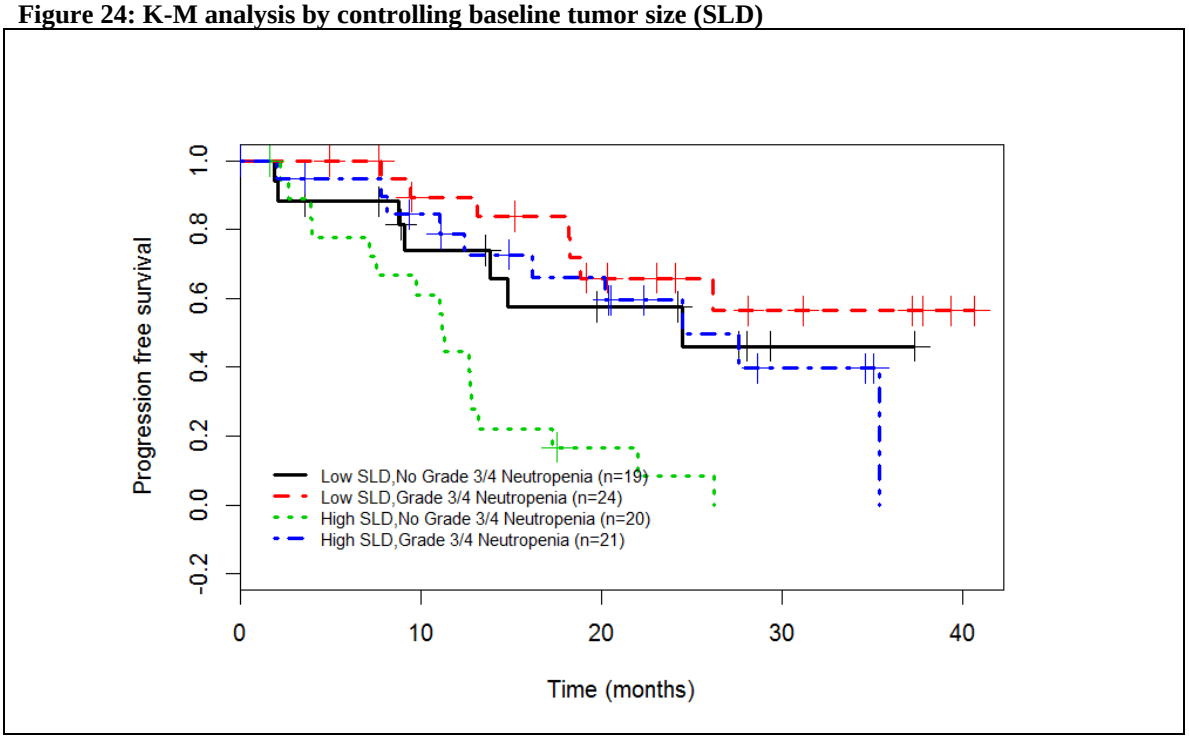


Table 48: Univariate and multivariate cox proportional analysis - the data from palbociclib plus letrozole Arms (n=84)

	Univariate Analysis			*Multivariate Analysis*		
Covariate	**Coefficient**	**Hazard Ratio (95% CI)**	**p-value**	**Coefficient**	**Hazard Ratio (95% CI)**	**p-value**
Grade 3 or 4 Neutropenia (Yes/No)	-0.908	0.403 (0.22, 0.76)	0.0046	-0.6894	0.502 (0.26, 0.98)	0.046
Baseline Lymphocytes (10^6/mL)	-	-	-	-0.8625	0. 422 (0.22, 0.81)	0.0092
Baseline AST(U/L)	-	-	-	0.0134	1.014 (0.99, 1.03)	0.0520
Baseline tumor size (mm)	-	-	-	0.0052	1.005 (0.99, 1.01)	0.0570

LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
Reviewer_2.r	Code for KM and cox proportional hazard analysis	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Palbociclib_NDA 207103 JYU\ER_Analyses\reviewer\reviewer_2.r

4.2 GENOMICS REVIEW

SUMMARY

Palbociclib is an oral, small molecule inhibitor of cyclin dependent kinase (CDK) 4 and CDK6 proposed 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. Nonclinical studies analyzing differentially expressed genes between palbociclib-sensitive and -resistant breast cancer cell lines suggested that increased retinoblastoma (RB1) and cyclin-D1 (CCND1) and decreased cyclin dependent kinase inhibitor 2A (CDKN2A) were associated with sensitivity to palbociclib [PMID: 19874578], and sensitive cell lines mostly represented the luminal/ER-positive subtype. These nonclinical results and the mechanism of palbociclib informed the final design of the Phase 2 portion of the pivotal Phase 1/2 trial, A5481003, which evaluated investigator-assessed progression-free survival (PFS) in 165 ER-positive, HER2-negative advanced breast cancer patients that were randomly assigned in a 1:1 ratio to receive palbociclib plus letrozole or letrozole alone. The trial was conducted in two parts: Part 1 enrolled 66 patients regardless of tumor CCND1 and/or CDKN2A status (i.e., biomarker positive, negative or unknown) and Part 2 enrolled 99 patients whose tumors tested positive for CCND1 gene amplification, loss of CDKN2A, or both, as measured by fluorescence in situ hybridization (FISH). An interim, retrospective analysis of investigator-assessed PFS by composite CCND1/CDKN2A biomarker status conducted on Part 1 data did not find a correlation between biomarker status and outcomes. For the biomarker positive subgroup, the median PFS was 26.1 months in the palbociclib plus letrozole arm vs. 7.5 months in letrozole arm [HR 0.2 (95% CI: 0.07-0.71)] and for the biomarker negative subgroup, the median PFS was 35.3 months in the palbociclib plus letrozole arm vs. 5.7 months in the letrozole arm [HR 0.2 (95% CI: 0.07-0.71)]. As such, enrollment in Part 2 was terminated after accrual of 99 patients and the protocol was then amended to evaluate clinical benefit in all patients randomized in both Parts 1 and 2. For the two parts combined, the median PFS by investigator assessment was 20.2 months vs. 10.2 months, favoring the palbociclib plus letrozole arm [HR 0.488 (95% CI: 0.319-0.748); 1-sided p=0.0004]. Approximately 87% of biomarker positive patients had CCND1-amplified tumors, while 28% had tumors with CDKN2A loss (with or without concomitant CCND1 amplification) in Parts 1 and 2 combined. Except for two patients in the letrozole arm in Part 1, biomarker-positive patients with tumors positive for CDKN2A loss were only observed in Part 2. It is not clear whether both genetic events (i.e., CCND1 amplification and CDKN2A loss) would equally affect prognosis or sensitivity to therapy. Exploratory analyses conducted by the review team suggest that patients with tumors positive for CDKN2A loss may derive less benefit from palbociclib plus letrozole vs. letrozole alone. The proposed indication for palbociclib is not limited to patients who test positive for CCDN1 amplification and/or CDKN2A loss. Given the PFS benefit and preliminary clinical evidence that the composite biomarker (i.e., CCND1/CDKN2A) does not robustly differentiate responders beyond ER positivity, the proposed indication in ER-positive/HER2-negative breast cancer (b) (4) appears acceptable pending further assessment of CDKN2A loss on palbociclib responses. As a post-marketing commitment, the applicant should formally evaluate the effect of CDKN2A and other potential biomarkers of palbociclib response (e.g., RB1 status may be a critical determinant of response based on palbociclib's mechanism) in ongoing and planned trials (e.g., PALOMA-2 [A5481008]).

1 BACKGROUND

Palbociclib is an oral, small molecule inhibitor of CDK4 and CDK6 (CDK4/6) proposed in combination with letrozole for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease.

CDK4/6 are heterodimeric complexes composed of a catalytic kinase subunit and a regulatory D-type cyclin subunit (CCND1, D2, D3). CDK4/6 promote cell cycle progression through phosphorylation of substrates, including the tumor suppressor retinoblastoma 1 (RB1, also known as Rb). Therefore, the activity of CDK4/6 is tightly regulated through several mechanisms including the abundance of the D-type cyclin regulatory subunits (which activate CDK4/6) as well as the abundance of opposing CDK4/6 inhibitory proteins such as CDKN2A (also known as p16). CDKN2A binds directly to CDK4/6, blocking RB1 phosphorylation and subsequent G1-S transition [PMID: 16603719, 21734724]. In accordance with its key role, the p16-cyclin D/CDK4/6-RB1 pathway is commonly deregulated in cancer [PMID: 24136988, 16603719]. Various molecular alterations can disrupt this pathway and potentially lead to aberrant CDK4/6 activity, including amplification and/or overexpression of CCND1, which is commonly associated with ER-positive breast cancer, and functional loss of CDKN2A. Furthermore, estrogen effects on cell cycle are linked to CCND1 expression [PMID: 23864650].

Nonclinical studies analyzing differentially expressed genes between palbociclib-sensitive and -resistant breast cancer cell lines suggested that high expression of RB1 and CCND1, and low expression of CDKN2A, were associated with sensitivity to palbociclib [PMID: 19874578]. Also, sensitive cell lines mostly represented the luminal/ER-positive subtype. These results supported the inclusion of a biomarker-selected population, specifically those with CCND1 amplification or CDKN2A loss, in the PALOMA-1 (A5481003) trial of palbociclib plus letrozole in ER-positive/HER2-negative advanced breast cancer supporting this NDA submission.

In contrast to how Part 2 of the pivotal trial was conducted, the proposed indication for palbociclib is not confined to a biomarker-defined population. Similarly, limited data are available for palbociclib treatment effects based on tumor RB1 status, which may be a critical determinant of response based on palbociclib mechanism of action. As such, the purpose of this review is to evaluate the appropriateness of the to-be-treated population in relation to the molecular inclusion criteria in the pivotal clinical trial, and whether additional studies are indicated to further characterize heterogeneity in treatment response across subgroups defined by molecular characteristics.

2 SUBMISSION CONTENTS RELATED TO GENOMICS

2.1 Clinical Studies

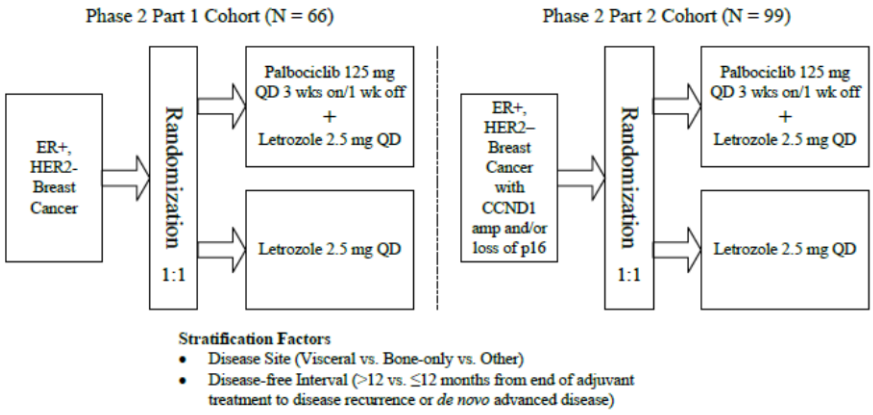
A5481003 (PALOMA-1): The clinical efficacy of palbociclib supporting NDA 207103 is based on the Phase 2 portion of the pivotal trial A5481003 entitled “Phase 1/2, Open-Label, Randomized Study of the Safety, Efficacy, and Pharmacokinetics of Letrozole plus PD 0332991 [Oral CDK 4/6 Inhibitor] and Letrozole Single Agent for the First-Line Treatment of ER-Positive, HER2-Negative Advanced Breast Cancer in Postmenopausal Women”.

- *Reviewer comment: Data from the Phase 1 portion (N=12), which was designed to assess the safety and tolerability of the combination of letrozole and palbociclib as well as to evaluate drug-drug interaction (DDI) potential of the combination, were not reviewed.*

The Phase 2 portion of trial A5481003 initially planned for enrollment of 150 postmenopausal women with ER-positive, HER2-negative advanced breast cancer. Patients were randomly assigned in a 1:1 fashion to receive open-label palbociclib plus letrozole (Arm A) or letrozole alone (Arm B). Emerging nonclinical data suggested that increased RB1 and CCND1 and decreased CDKN2A could serve as potential biomarkers of sensitivity to palbociclib. As a result, the applicant amended the Phase 2 portion of the trial protocol to include two parts (Figure 1): in Part 1 (Ph2P1; planned N~60), tumor CCND1 amplification and CDKN2A loss were retrospectively assessed from available samples; in Part 2 (Ph2P2; planned N~150), enrollment was limited to patients whose tumors had CCND1 amplification and/or CDKN2A loss (Figure 1). Detection of CCND1 amplification and/or CDKN2A loss was determined by central testing of fresh or archived tumor samples using fluorescence in situ hybridization (FISH) with the following cutoffs and definitions:

a. Biomarker positive was defined as ER-positive, HER2-negative advanced breast cancer with CCND1/ chromosome enumeration probe (CEP)11≥1.5 and/or CDKN2A/CEP9<0.8
b. Biomarker negative was defined as ER-positive, HER2-negative advanced breast cancer with CCND1/CEP11<1.5 and CDKN2A/CEP9 ≥0.8

Figure 1: Trial A5481003 – Final Design of the Phase 2 Portion



Source: Applicant's Figure 1; A5481003 report body

- *Reviewer comment: The cutoff selected to define CCND1 amplification positivity (CCND1/CEP11 ratio ≥1.5) appears to be low compared to published articles assessing CCND1 amplification by FISH. The applicant indicated in their response to Genomics IR (12 November 2014, SN0040) that a low cutoff point was used to include ER-positive/HER2-negative advanced breast cancer patients with any potential signal of CCND1 amplification in the A5481003 trial with the intent of refining the cutoff in a later-phase trial.*

An interim analysis of Ph2P1data showed clinical activity of palbociclib in combination with letrozole regardless or biomarker (CCND1/CDKN2A) status. Enrollment in Ph2P2 was then terminated after 99 patients had accrued to Part 2 and the protocol was amended to determine the clinical benefit of the combination in patients randomized in both Ph2P1and Ph2P2 combined with secondary subgroup analysis in Ph2P1 and Ph2P2 separately. The primary efficacy endpoint of the Phase 2 portion was investigator-assessed PFS according to RECIST v1.0. The data cutoff for final analysis was 29 November 2013.

Additional exploratory biomarkers retrospectively assessed by the applicant in available samples included the following:

- Blood (germline DNA): Single nucleotide polymorphisms (SNPs) in CYP19A1 (rs4646) and CCND1 (rs9344, G/A870) genes
- Tumor: Ki67, CCND1 and RB1 protein expression.

The final biomarker analysis sets are summarized in Table 1. Although planned, CDK4 and CDK6 were not analyzed.

Table 1: Biomarker Analysis Sets in the A5481003 Phase 2 Portion

	Phase 2 (Ph2P1+Ph2P2)		Ph2P1		Ph2P2	
Analysis Set	Palbociclib + Letrozole	Letrozole	Palbociclib+ Letrozole	Letrozole	Palbociclib+ Letrozole	Letrozole
ITT Analysis Population	84	81	34	32	50	49
Biomarker Analysis Sets						
Polymorphism	76	74	30	28	46	46
Copy Number	72	72	22	24	50	48
Protein biomarkers	45	35	12	16	33	19
Ki67	74	71	24	26	50	45

Source: Modified from applicant's Table 13, A5481003 report body; ITT=Intent-to-treat; Ki67= Nuclear protein identified by the Ki67 monoclonal antibody; Ph2P1=Phase 2 Part 1; Ph2P2=Phase 2 Part 2; Ph2P1+Ph2P2=Phase 2 combined

3 KEY QUESTIONS AND SUMMARY OF FINDINGS

3.1 Is palbociclib appropriate for all patients with ER-positive, HER2-negative advanced breast cancer based on a clinical trial primarily conducted in patients with CCND1 amplification and/or CDKN2A loss?

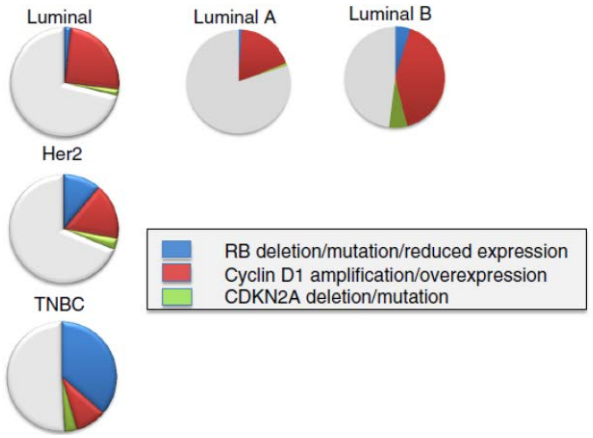
In contrast to how Part 2 of the pivotal trial was conducted, the proposed indication for palbociclib is not limited to patients who test positive for CCND1 amplification and/or CDKN2A loss. Given the PFS benefit and preliminary clinical evidence that the composite biomarker (i.e., CCND1/CDKN2A) does not robustly differentiate responders beyond ER positivity, the proposed indication in ER-positive/HER2-negative breast cancer (b) (4) appears acceptable pending further assessment of CDKN2A loss on palbociclib responses. As a post-marketing commitment, the applicant should formally evaluate the effect of CDKN2A and other potential biomarkers of palbociclib response (e.g., RB1 status may be a critical determinant of response based on palbociclib's mechanism) in ongoing and planned trials (e.g., PALOMA-2 [A5481008]).

3.1.1 Relevance of the p16-cyclin D/CDK4/6-RB1 pathway in luminal/ER positive breast cancer

The p16-cyclin D/CDK4/6-RB1 pathway is commonly deregulated in cancer [PMID: 24136988, 16603719]. Various molecular alterations can disrupt this pathway and potentially lead to aberrant CDK4/6 activity, including functional loss of CDKN2A and amplification and/or overexpression of CCND1. CDKN2A is a tumor suppressor found to be inactivated in different tumors through deletion, which has been reported in 4.2% (COSMIC at cancer.sanger.ac.uk/cosmic) to 42% of breast cancers, methylation (28-31%) or point mutation (infrequent) [PMID: 21619050, 7550353, 18239974]. Similarly, CCND1 is a recognized oncogene found to be overexpressed in 50-70% of breast tumors through amplification (15-20% of breast tumors), or more rarely by mutation or as a consequence of dysfunctional mitogenic signaling [PMID: 21734724, 23336272]. The observed frequencies for these alterations, however, can be higher or lower within specific breast cancer patient populations, or due to differences in methods and cutoffs.

The majority of ER-positive breast cancer overlaps with the luminal breast cancer subtype (luminal/ER-positive), which is highly heterogeneous in terms of gene expression, mutation spectrum and changes in copy number [PMID: 23000897, 24624545]. Within the luminal subtype there is further heterogeneity, as CCND1 amplification (58% in luminal B vs. 29% in luminal A) and loss of CDK2NA or RB1 are more commonly observed in the luminal B compared to the luminal A subtype (Figure 2). Across subtypes, RB1 loss has been observed at higher frequency in triple-negative breast cancer (TNBC). However, any breast cancer can potentially exhibit loss of RB1 or CDKN2A, or amplification of CCND1 [PMID: 25223380]. It is currently believed that RB1-positive tumors are sensitive to CDK inhibition, while tumors lacking RB1 are resistant. Additional biomarkers of response to CDK inhibitors have not yet been identified.

Figure 2: Mechanisms of p16-cyclin D/CDK4/6-RB1 Pathway Disruption Across Breast Cancer Subtypes



Source: figure 4 from PMID: 25223380; "The retinoblastoma tumor suppressor pathway in different breast cancer subtypes via TCGA." The pathway was evaluated for both genetic alterations and altered expression on TCGA data. TNBC=triple-negative breast cancer; TCGA= The Cancer Genome Atlas; RB=RB1, retinoblastoma 1; CDKN2A= cyclin-dependent kinase inhibitor 2A.

It is also important to consider that CCND1 has both catalytic and non-catalytic, CDK- independent functions. Some argue that targeting CDK4/6 activity alone may only be partially effective in CCND1-dependent tumors [PMID: 21734724]. Similarly, CDKN2A may function both through CDK4/6-dependent and -independent mechanisms to regulate the cell cycle [PMID: 24136988]. Additionally, RB1 phosphorylation can be regulated by other mechanisms beyond CDK4/6 [PMID: 25223380], underscoring the complexity of these cell cycle regulators.

3.1.2 PFS and CCND1 and CDKN2A biomarker status

3.1.2.1 Topline results of the A5481003 Phase 2 portion, Parts 1 and 2

Based on the applicant's analysis, in the overall Phase 2 dataset (Ph2P1+Ph2P2), the median PFS was 20.2 months (95% CI: 13.8-27.5) in the palbociclib plus letrozole arm vs. 10.2 months (95% CI: 5.7-12.6) in the letrozole arm favoring palbociclib plus letrozole [HR 0.488 (95% CI: 0.319-0.748); stratified 1-sided p=0.0004]. For Part 1, the median PFS in the palbociclib plus letrozole arm was 26.1 months (95% CI: 11.2-NR) in the palbociclib plus letrozole arm vs. 5.7 months (95% CI: 2.6-10.5) in the letrozole arm [HR 0.299 (95% CI: 0.156-0.572); 1-sided p-value of <0.0001]. For Part 2, the median PFS was 18.1 months (95% CI: 13.1-27.5) in the palbociclib plus letrozole arm vs. 11.1 months (95% CI: 7.1-16.4) in the letrozole arm [HR 0.508 (95% CI: 0.303-0.853); 1-sided p-value=0.0046]. For full efficacy analyses of the ITT population, refer to Clinical review (Dr. Julia Beaver).

3.1.2.2 Distribution of CCND1amplification and CDKN2A loss in the A5481003 Phase 2 portion, Parts 1 and 2

In the Phase 2 portion of the A5481003 trial (Parts 1 and 2), 165 patients were randomized (84 to combination and 81 to letrozole alone) at 50 sites in the U.S. and other 11 countries. In Part 2, a total of 319 patients were screened, 220 were excluded and 99 patients were randomly assigned to treatment. Of the 220 excluded patients, 165 patients did not meet the biomarker positivity inclusion criterion, i.e., CCND1 amplification and/or loss of CDKN2A as determined by the central laboratory (response to clinical IR; 10 November 2014, SN 0037).

- *Reviewer comment: The screen failure rate based on biomarker status is within the expected range based on reported frequencies for the molecular alterations in the literature and inclusive assay cutoffs used by the applicant.*

In Part 1, CCND1 and CDKN2A status was retrospectively determined in 46 out of 66 randomized patients who had available tumor samples for analysis (22 in the palbociclib plus letrozole arm and the 24 in the letrozole arm). All patients classified as biomarker positive (N=21) had CCND1-amplified tumors and only 2 patients also had tumors positive for CDKN2A loss. In the biomarker-selected Part 2, most patients similarly had CCND1-amplified tumors, although 19 patients in the combination arm and 12 patients in the letrozole arm had tumors with CDKN2A loss (with or without concomitant CCND1 amplification) (Table 2).

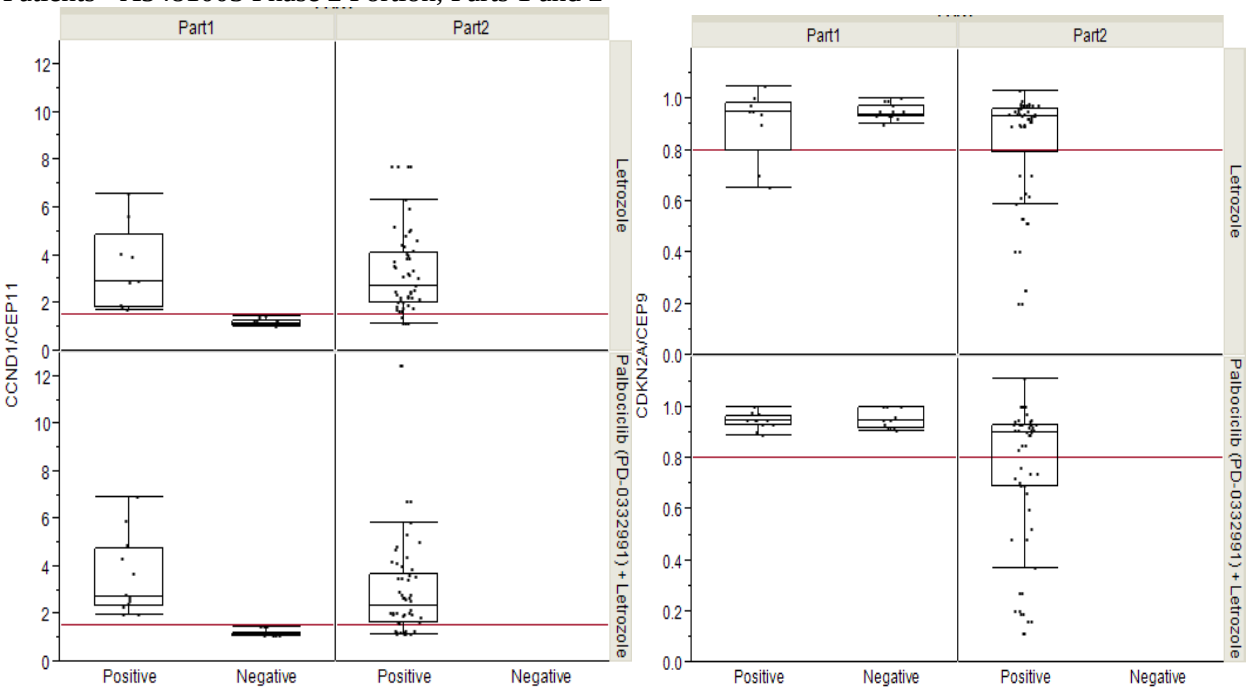
Table 2: CCND1 and CDKN2A Status - A5481003 Phase 2 Portion, Parts 1 and 2

	Biomarker Status	CCND1 amplification only		CDKN2A loss only		Both CCND1amplification and CDKN2A loss		Total Biomarker CCND1 amplification and/or CDKN2A loss	
		Palbociclib + letrozole	Letrozole	Palbociclib + letrozole	Letrozole	Palbociclib + letrozole	Letrozole	Palbociclib + letrozole	Letrozole
Part 1	Positive	12	7	0	0	0	2	12	9
	Negative							10	15
	Unknown							12	8
Part 2	Positive	31	37*****	11	4	8	8	50	49*****

***1** patient in the letrozole arm was not treated; Biomarker Positive: CCND1/CEP11≥1.5 and/or CDKN2A/CEP9<0.8, Biomarker Negative: CCND1/CEP11<1.5 and CDKN2A/CEP9 ≥0.8. CCND1=Cyclin D1; CDKN2A= Cyclin-dependent kinase inhibitor 2A.*

As shown in the figure below, the distribution and range of FISH ratios especially for CDKN2A loss was different in Parts 1 and 2 (Figure 3).

Figure 3: Distribution of CCND1 and CDKN2A FISH Ratios in Biomarker Positive and Negative Patients - A5481003 Phase 2 Portion, Parts 1 and 2



Source: Reviewer analyses; Biomarker Positive: CCND1/CEP11 ≥1.5 or CDKN2A/CEP9 <0.8, Biomarker Negative: CCND1/CEP11 <1.5 and CDKN2A/CEP9 ≥0.8; cutoffs for genetic amplification (1.5) and loss (0.8) indicated as a horizontal red line. FISH: fluorescence in situ hybridization; CCND1=Cyclin D1; CDKN2A= Cyclin-dependent kinase inhibitor 2A; CEP=chromosome enumeration probe; 20 patients had biomarker unknown status in Part 1 and were not represented.

3.1.2.2 PFS according to CCND1amplification and CDKN2A loss in the A5481003 Phase 2 Portion

An interim retrospective analysis of biomarker status on Part 1 data showed clinical activity of palbociclib in combination with letrozole in both biomarker positive and negative subgroups (Table 3). Of note, although not statistically significant, the median PFS of the biomarker negative subgroup was longer than that of the biomarker positive subgroup in the combination arm and shorter in the letrozole arm.

Table 3: PFS by Biomarker Status and Treatment - A5481003 Phase 2 Portion, Part 1

	Median PFS (Months)			
	Palbociclib + Letrozole	Letrozole	Log-rank p-value[a]	Hazard Ratio[b]
Positive				
N	12	9		21
Estimate	26.1	7.5		0.2
80% CI	12.65, NR	2.27, 12.48		0.11, 0.48
95% CI	11.01, NR	1.77, 16.82		0.07, 0.71
Negative				
N	10	15		25
Estimate	35.3	5.7	0.006	0.2
80% CI	18.23, NR	2.73, 8.71		0.11, 0.48
95% CI	8.11, NR	2.14, 10.55		0.07, 0.71
Unknown				
N	12	8		20
Estimate	9.1	NR		0.9
80% CI	3.88, 24.41	1.68, NR		0.32, 2.63
95% CI	1.87, NR	1.68, NR		0.18, 4.61

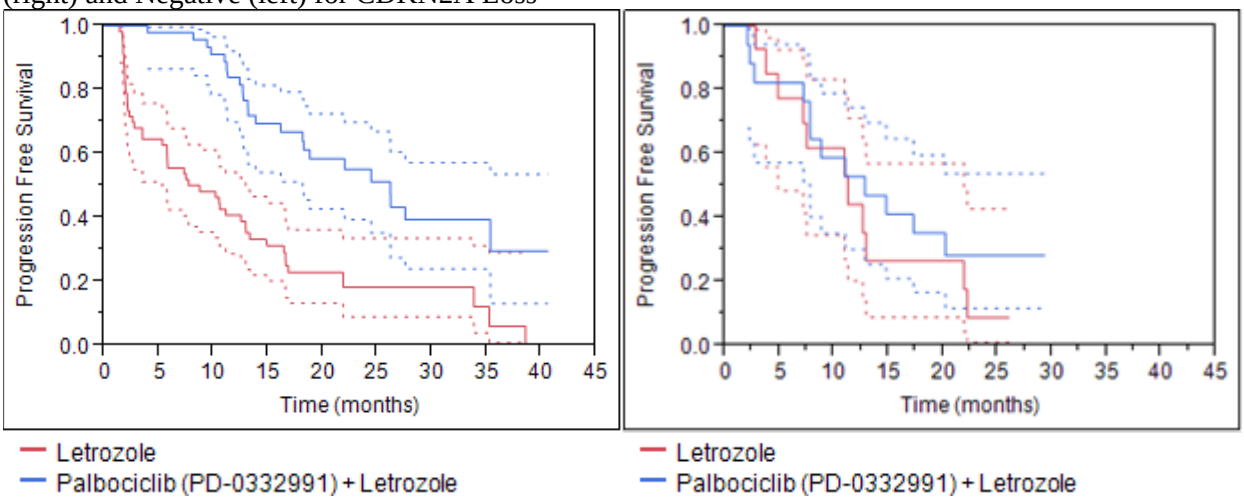
Source: Applicant's Table 44, A5481003 report body; exploratory analyses; Positive: CCND1/CEP11 ≥1.5 and/or CDKN2A/CEP9 <0.8, Negative: CCND1/CEP11<1.5 and CDKN2A/CEP9 ≥0.8. "a Log-rank p-values produced only when N≥10 in both comparison groups. b Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of Palbociclib + Letrozole". CCND1=Cyclin D1; CDKN2A= Cyclin-dependent kinase inhibitor 2A; CI=Confidence interval; NR=Not reached; PFS=Progression-free survival.

Also, the applicant reports that results were similar when different cutoff points for CCND1 amplification (e.g., CCND1/CEP11 ratios ≥2, ≥3, and ≥4) were used in trial A5481003. These analyses were reproduced by the clinical and statistical review team (refer to Clinical review for details; Dr. Julia Beaver).

- *Reviewer comment: The Phase 2 trial was mostly confined to biomarker positive patients whose tumors were CCND1-amplified. Except for two biomarker positive patients in the letrozole arm in Part 1, patients with tumors positive for CDKN2A loss were only observed in Part 2. This subset of patients was therefore underrepresented in Part 1 interim analysis that suggested a lack of correlation between CCND1/CDKN2A status and outcomes. It is not clear whether both genetic events (i.e., CCND1 amplification and CDKN2A loss) would equally affect prognosis or sensitivity to therapy.*

The review team conducted exploratory analyses of investigator-assessed PFS by CDKN2A loss (as defined by the applicant). The results suggest that patients with tumors positive for CDKN2A loss may derive less benefit from adding palbociblib to letrozole (Figure 4).

Figure 4: Kaplan-Meier Plot of Investigator-Assessed PFS: Subset of Patients with Tumors Positive (right) and Negative (left) for CDKN2A Loss



Source: Reviewer analyses (exploratory); Positive for CDKN2A loss: CDKN2A/CEP9 ratio <0.8, Negative for CDKN2A loss: CDKN2A/CEP9 ratio ≥0.8; CDKN2A= Cyclin-dependent kinase inhibitor 2A; A5481003 Phase 2 portion, Parts 1 and 2; Dotted lines represent 95% confidence intervals.

- *Reviewer comment: The unexpected findings for patients with tumors positive for CDKN2A loss may be related to the presence of unknown tumor genetic events and/or compensatory signaling mechanisms that modify the molecular phenotype and influence response to therapy. Alternatively these findings may be related to the small sample sizes, imbalances and exploratory nature of the analyses. As a post-marketing commitment, the applicant should formally evaluate the effect of CDKN2A, RB1, and other potential biomarkers of palbociclib response in ongoing and planned trials (e.g., PALOMA-2 [A5481008]). Of note, in a glioma cell line model, CDKN2A/B deletion was associated with resistance to palbociclib, while CDKN2A/B and CDKN2C co-deletion was associated to sensitivity [PMID: 20534551].*

3.1.3 Additional exploratory biomarkers

The applicant conducted additional assessments to explore whether baseline levels of selected cell cycle markers in tumor tissue and presence of germline polymorphisms correlate with palbociclib plus letrozole efficacy. The results presented below (except for those in Table 6) reflect the applicant's analyses.

- *Reviewer comment: Concerning the exploratory analyses summarized below, incomplete sample acquisition, analyses limited to a group of selected biomarkers (e.g., gain of CDK4 which is reported in 25% in luminal B and 14% in luminal A [PMID:23000897]was planned but not analyzed) and inclusive assay cutoffs may have impacted the ability to detect differences across biomarker-defined subgroups. Also, tumor samples could be archived or fresh and the impact of sample storage or prior treatment on selected tumor markers was not evaluated. The applicant informs that the cell cycle-relevant biomarkers' effect on palbociclib plus letrozole clinical efficacy will be further tested in the current ongoing Phase 3 studies.*

3.1.3.1 Ki67 (proliferation marker)

Tumor tissue was available for Ki67 expression analysis by immunohistochemistry (IHC) for 145 of the 165 randomized patients (Table 1). Approximately 65% of patients in the palbociclib plus letrozole arm and 56% in the letrozole arm had Ki67-expressing tumors (high level), using a >20% cutoff as

recommended by the test manufacturer. The differences in PFS were not statistically significant based on the applicant analyses (Table 4). Similar results were observed in the individual Parts 1 and 2 (data not shown).

Table 4: Investigator-Assessed PFS for Ki67 ≤20% and >20%, A5481003 Phase 2 Portion

	Palbociclib + Letrozole				Letrozole			
	Median PFS (Months)				Median PFS (Months)			
	Ki67≤20%	Ki67>20%	Log-rank p-value[a]	Hazard Ratio[b]	Ki67≤20%	Ki67>20%	Log-rank p-value[a]	Hazard Ratio[b]
Phase 2 (Ph2P1+Ph2P2)								
N	26	48		74	31	40		71
Estimate	26.1	18.2	0.332	0.7	9.4	11.1	0.773	0.9
80% CI	16.13, NR	13.83, 24.41		0.44, 1.12	5.75, 12.91	7.29, 12.61		0.65, 1.32
95% CI	11.30, NR	12.78, 27.53		0.34, 1.44	4.83, 14.88	5.29, 13.30		0.54, 1.59

Source: Applicant's table 48, A5481003 report body; only results from Phase 2 combined are depicted. "a Log-rank p-values produced only when N≥10 in both comparison groups. b Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of a Ki67 value ≤20%". CI=Confidence interval; Ki67=Nuclear protein identified by the Ki67 monoclonal antibody; PFS=Progression-free survival; Ph2P1=Phase 2 Part 1; Ph2P2=Phase 2 Part 2; Ph2P1+Ph2P2=Phase 2 combined; Phase 2: Ki67 Analysis Set.

3.1.3.2 CCND1 and RB1 protein expression

Tumor tissue was available for analysis of CCND1 and RB1 protein expression by IHC for 80 of the 165 randomized patients (Table 1). The following definitions of expression were applied: Positive: any expression; Negative: no detectable expression. Over 90% of patients had CCND1- and RB1-expressing tumors (Ph2P1+Ph2P2 combined) with very few tumors having undetectable CCND1 (N=6) or RB1 (N=4) (Table 5). In Phase 2 combined (Ph2P1+Ph2P2), the median CCND1values (percentage of positive cells) were 85.0% and 80.0% in the palbociclib plus letrozole and letrozole arms, respectively. The median RB1 values were 80% and 70% in the palbociclib plus letrozole and letrozole arms, respectively; this apparent imbalance was present in both Parts 1 and 2 (87.5% vs 72.5% in Part 1 and 70.0% vs 55.0% in Part 2).

Table 5: Frequency of Tumor RB1and CCND1 Expression, A5481003 Phase 2 Portion

	Phase 2 (Ph2P1+Ph2P2)		Ph2P1		Ph2P2	
	Palbociclib + Letrozole (N=45	Letrozole (N=35)	Palbociclib + Letrozole (N=12)	Letrozole (N=16)	Palbociclib + Letrozole (N=33)	Letrozole (N=19)
Gene	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Cyclin D1						
Positive	41 (91.1)	32 (91.4)	10 (83.3)	16 (100.0)	31 (93.9)	16 (84.2)
Negative	3 (6.7)	3 (8.6)	2 (16.7)	0	1 (3.0)	3 (15.8)
Rb						
Positive	41 (91.1)	32 (91.4)	10 (83.3)	16 (100.0)	31 (93.9)	16 (84.2)
Negative	2 (4.4)	2 (5.7)	2 (16.7)	0	0	2 (10.5)

Source: Applicant's table 49, A5481003 report body; Rb =RB1; retinoblastoma 1; CCND1-cyclin D1; Ph2P1=Phase 2 Part 1; Ph2P2=Phase 2 Part 2; Ph2P1+Ph2P2=Phase 2 combined; Phase 2: Protein Biomarkers Analysis Set.

The reviewer conducted exploratory analyses of investigator-assessed PFS by RB1 expression (as defined by the applicant). Although the intermediate expression subgroup does appear to have shorter median PFS compared to the high expression, the effect of palbociclib plus letrozole over letrozole seems to have remained the same regardless of RB1 expression.

Table 6: Investigator-Assessed PFS for RB1 Expression, A5481003 Phase 2 Portion

		Palbociclib+Letrozole		Letrozole	
Biomarker	Biomarker Status	Events (n/N)	Median PFS	Events (n/N)	Median PFS
RB1	High	17/28	18.8 (11.0-27.5)	18/21	5.7 (2.1-14.9)
	Intermediate	7/13	13.8 (3.9-NC)	9/11	2.7 (1.7-12.5)

Source: Reviewer analyses (exploratory); High: > 50% of positive cells, Intermediate: ≤50% positive cells; RB1=retinoblastoma 1; PFS=progression-free survival; A5481003 Phase 2 portion, Parts 1 and 2. Only 4 patients were negative for RB1 expression (2 in each treatment arm) and are not represented.

- *Reviewer comment: Most tested tumor samples were positive (any expression signal) for CCND1 and RB1expression. Observed frequencies may be inflated because of the inclusive cutoffs used to distinguish marker positive and marker negative (i.e., positive was defined as <u>any</u> expression). It is also unclear from results in Table 5 how RB1 expression translates into functional RB1 activity. Small sample sizes may have contributed for some of the apparent imbalances. Regarding RB1, discordant data have been associated to technical difficulties in measuring RB1 expression by immunohistochemistry and to a lack of correlation between allele loss and protein expression [PMID: 21260944]. The ability to correctly identify functional RB1 is important since CDK inhibitors are not expected to be active in RB1-deficient tumors. Of note, the biological consequences of high levels of CCND1 protein expression due to CCND1 gene amplification may not be equivalent to high levels of CCND1 protein expression due to other mechanisms.*

<u>3.1.3.3 Germline SNPs</u>

Assessments of the following SNPs were carried out on germline DNA extracted from peripheral blood:

- Cytochrome P450, family 19, subfamily A, polypeptide 1 (*CYP19A1*) gene polymorphism <u>rs4646</u> (3' untranslated region, A/C (FWD)); MAF/Minor Allele Count A=0.3357/1681[dbSNP at http://www.ncbi.nlm.nih.gov/projects/SNP; accessed December 2014]. CYP19A1 encodes aromatase. The variant polymorphism has been associated with either improved response in advanced breast cancer [PMID: 18245543] or poor response to neoadjuvant letrozole in early breast cancer [PMID: 20144226].

- *CCND1* gene polymorphism <u>rs9344</u> (synonymous codon, A/G (FWD)); MAF/Minor Allele Count: A=0.4135/2071 [dbSNP at http://www.ncbi.nlm.nih.gov/projects/SNP; accessed December 2014]. CCND1 rs9344 polymorphism leads to alternate splicing of CCND1 mRNA into two transcripts. The altered transcript-b is primarily encoded by the variant allele A and results in increased CCND1 because of a prolonged half-life [PMID: 23567490].

Homozygous Wild-Type vs. Variant (heterozygous or variant homozygous) genotypes were defined as C/C vs. C/A or A/A for CYP19A1 (rs4646) and G/G vs. G/A or A/A for CCND1 (rs9344), respectively. Observed genotype frequencies are depicted in Table 7.

Table 7: Frequency of CYP19A1 (rs4646) and CCND1 (rs9344) genotypes - A5481003 Phase 2 Portion

		Phase 2 (Ph2P1+Ph2P2)		Ph2P1		Ph2P2	
		Palbociclib + Letrozole (N=76)	Letrozole (N=74)	Palbociclib + Letrozole (N=30)	Letrozole (N=28)	Palbociclib + Letrozole (N=46)	Letrozole (N=46)
Gene	Genotype	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
CYP19A1	A/A	6 (7.9)	4 (5.4)	3 (10.0)	3 (10.7)	3 (6.5)	1 (2.2)
	C/A	26 (34.2)	27 (36.5)	10 (33.3)	12 (42.9)	16 (34.8)	15 (32.6)
	C/C	44 (57.9)	43 (58.1)	17 (56.7)	13 (46.4)	27 (58.7)	30 (65.2)
CCND1	A/A	20 (26.3)	21 (28.4)	10 (33.3)	11 (39.3)	10 (21.7)	10 (21.7)
	G/A	36 (47.4)	35 (47.3)	13 (43.3)	12 (42.9)	23 (50.0)	23 (50.0)
	G/G	20 (26.3)	18 (24.3)	7 (23.3)	5 (17.9)	13 (28.3)	13 (28.3)

Source: Applicant's Table 45, A5481003 report body; CYP19A1= cytochrome P450, family 19, subfamily A, polypeptide 1 (CYP19A1); CCND1=Cyclin D1; Ph2P1=Phase 2 Part 1; Ph2P2=Phase 2 Part 2; Ph2P1+Ph2P2=Phase 2 combined; Phase 2: Polymorphism Analysis Set.

The applicant did not observe a statistically significant difference in PFS between patients with different CYP19A1 or CCND1genotypes in either treatment arm (results not shown). In Phase 2 (Ph2P1+Ph2P2), regardless of CYP19A1 or CCND1 genotypes, investigator-assessed PFS was statistically significantly longer in the palbociclib plus letrozole arm compared with the letrozole arm (results not shown).

4 SUMMARY AND CONCLUSIONS

The p16-cyclin D/Cdk4-RB1 pathway can be disrupted in different ways. It is important to consider how the specific genetic event(s) and/or affected pathway node(s) collectively shape the tumor molecular phenotype and (potentially) influence the response to therapy [PMID: 20534551].

In Part 2, biomarker positivity for the purpose of trial inclusion was based on either CCND1 amplification or CDKN2A loss (or both) as a composite biomarker. Most patients were CCND1-amplified. Only two patients in Part 1 had tumors positive for CDKN2A loss. It is not clear whether CCND1 amplification and CDKN2A loss would equally affect prognosis or sensitivity to therapy.

So far, positive predictors of response to palbociclib plus letrozole have not been identified beyond ER positivity. Contrary to the expectation, exploratory analyses suggest that patients with tumors positive for CDKN2A loss may derive less benefit from adding palbociclib to letrozole. The applicant should formally evaluate the effect of CDKN2A, RB1, and of other potential biomarkers of palbociclib response in ongoing and planned trials (e.g., PALOMA-2 [A5481008]).

The A5481003 trial is an early trial which included exploration of potential prognostic and predictive biomarkers of response to palbociclib plus letrozole (supported by nonclinical data and published literature). According with the applicant's analyses, the assessed exploratory biomarkers including germline polymorphisms (CYP19A1, CCND1) and tumor Ki67, did not show significant differences in PFS between treatment arms.

5 RECOMMENDATIONS

5.1 Labeling

None

5.2 Post-marketing studies

The applicant should formally evaluate the effect of CDKN2A, RB1, and other potential biomarkers of palbociclib response in ongoing and planned trials (e.g., PALOMA-2 [A5481008]).

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/s/

JEANNE FOURIE ZIRKELBACH
01/15/2015

JINGYU YU
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ROSANE CHARLAB ORBACH
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LIANG ZHAO
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QI LIU
01/15/2015

NAM ATIQUR RAHMAN
01/15/2015
I concurr with the review team's recommendation.

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 207103	**Reviewer:** Minerva Hughes, Ph.D.	
Submission Date:	15 August 2014		
Division:	Division of Oncology Drug Products 1	**Team Leader:** Angelica Dorantes, Ph.D.	
		Acting Supervisor: Paul Seo, Ph.D.	
Sponsor:	Pfizer	**Secondary Reviewer:** Elsbeth Chikhale, Ph.D. (Acting Team Leader)	
Trade Name:	Ibrance	**Date Assigned:**	23 July 2014
		Primary Review: **PDUFA Date:**	15 January 2015 13 April 2015
Generic Name:	Palbociclib	**Date of Review:**	6 Jan 2015
Indication:	Use in combination w/letrozole for ER-positive, HER2 negative breast cancer	**Type of Submission:** **505(b)(1)** Priority NDA NME NDA Fast Track/Breakthrough Drug	
Dosage Form/Strengths	Capsule (75, 100, and 125 mg)		
Route of Administration	Oral		

Biopharmaceutics Review Focus:

- Relative bioavailability/bioequivalence studies for formulation changes (b) (4) which is reviewed by Clinical Pharmacology)
- Dissolution method and acceptance criteria
- Manufacturing process impact on dissolution (quality-risks)

SUMMARY OF IMPORTANT BIOPHARMACEUTICS FINDINGS

General

NDA 207103 seeks accelerated approval for the use of palbociclib (a new molecular entity) in combination with letrozole, for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease. The proposed drug product is an immediate release hard-gelatin capsule formulation that will be available in three strengths: 75 mg, 100 mg, and 125 mg.

Bioequivalence Studies

As per the MOU between Biopharmaceutics and Clinical Pharmacology, the pivotal relative bioavailability study, Study 1036, will be reviewed by Clinical Pharmacology. This 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 to demonstrate the following:

- The initial Phase 3 free-base formulation is bioequivalent to the proposed commercial

product.

- Variations in the drug substance particle size up to (b) (4) µm (b) (4) demonstrate acceptable clinical performance for the product's intended use.
- A mean dissolution of Q= (b) (4)% in 30 minutes ensures adequate drug exposure and is an acceptable quality control limit.

Dissolution Specification

The following dissolution method and acceptance criterion are acceptable:

Dissolution Method	
Apparatus	USP 2
Medium	0.1 N HCl
Agitation speed	50 rpm
Temperature	37 ºC
Sampling Times	30 minutes
Analytical Method	UV detection
Acceptance Criterion	Q = 80% in 30 min

CONSULTS

None.

QUALITY RISK ASSESSMENT

The full quality risk assessment is summarized in the Product Quality review by Dr. Joyce Crich. From a Biopharmaceutics perspective, the critical process parameters impacting dissolution are as follows: (1) (b) (4) To a lesser extent, (b) (4) could influence dissolution; however, the proposed controls appear reasonable to ensure a low risk of adverse dissolution effects.

PHASE 4 COMMITMENTS

None.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 207103 for Ibrance (palbociclib) is recommended for approval.

Signature Block

Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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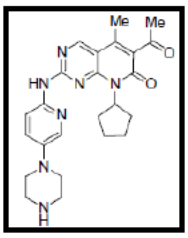
BIOPHARMACEUTICS REVIEW

1 GENERAL ATTRIBUTES

1.1 *What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?*

The proposed drug substance palbociclib is a small molecule with the following structure and chemical formula.



Chemical structure of palbociclib; $C_{24}H_{29}N_7O_2$; 447.5 g/mol

Palbociclib is manufactured as a yellow to orange powder. It is fairly (b) (4) (b) (4). The (b) (4) was selected for development. Two other forms were identified during development (b) (4). No (b) (4) was found. (b) (4)

The proposed drug product is formulated as hard gelatin, opaque capsules using a (b) (4) in dosage strengths of 75 mg, 100 mg, and 125 mg. The qualitative and quantitative composition is illustrated below for the 125 mg strength as representative of all three strengths.

Name of Ingredients	Reference to Standard	Function	Unit Formula	
			Unit (mg)	%
Blend Composition				
Palbociclib	Pfizer	Drug Substance	125.000[1]	(b) (4)
Microcrystalline Cellulose (b) (4)	USP/NF, Ph Eur., JP	(b) (4)		(b) (4)
Lactose Monohydrate	USP/NF, Ph Eur., JP			
Sodium Starch Glycolate (Type A)	USP/NF, Ph Eur., JP			
Colloidal Silicon Dioxide	USP/NF, Ph Eur., JP			
Magnesium Stearate	USP/NF, Ph Eur., JP			
Total (b) (4) Fill Weight				
Hard Gelatin Capsule Shell				
Capsule Shells (Size #0, Caramel/Caramel HG Capsules)[3]	Pfizer	(b) (4)	1 capsule	
Body (Caramel)				
Gelatin	USP/NF, Ph Eur., JP	(b) (4)		(b) (4)
Red Iron Oxide (b) (4)	USP/NF, JP	Colorant		
Yellow Iron Oxide (b) (4)	USP/NF, JP	Colorant		
Titanium Dioxide (b) (4)	USP/NF, Ph Eur., JP	(b) (4)		
Cap (Caramel)				
Gelatin	USP/NF, Ph Eur., JP	(b) (4)		
Red Iron Oxide (b) (4)	USP/NF, JP	Colorant		
Yellow Iron Oxide (b) (4)	USP/NF, JP	Colorant		
Titanium Dioxide (b) (4)	USP/NF, Ph Eur., JP	(b) (4)		
Approximate Weight of Capsule Shell				
Print Ink[3]				
Approximate Weight of Ink on Capsule Shell				

(footnotes omitted)

1.2 *What are the proposed mechanism(s) of action and therapeutic indication(s)?*

Palbociclib is a first-in-class cyclin-dependent kinase (CDK) 4/6 inhibitor. The drug is intended to be used in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)/ErbB2-negative advanced breast cancer.

1.3 *What are the proposed dosage(s) and route(s) of administration?*

The proposed dose is 125 mg taken orally, once daily, for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. The drug should be taken with food and with letrozole 2.5 mg. The 100 mg and 75 mg strengths are available for dose modifications for individual safety and tolerability.

1.4 *Is there any information on BCS classification? What claim does the applicant make based on BCS classification? What data are available to support this claim?*

A BCS class (b) (4) is reported by the Applicant. The drug solubility information provided is consistent with a (b) (4) compound. However, the Applicant notes that palbociclib would be classified as a (b) (4) drug because (b) (4) (b) (4) Therefore a BCS (b) (4) classification is reported by the Applicant. From the Biopharmaceutics perspective, a BCS (b) (4) classification appears more consistent with regulatory standards.

A consensus regarding a BCS (b) (4) versus BCS (b) (4) designation is not needed to support NDA approval and thus, no additional discussions are warranted with the Applicant.

2 GENERAL BIOPHARMACEUTICS (IN VIVO)

2.1 CLINICAL STUDIES

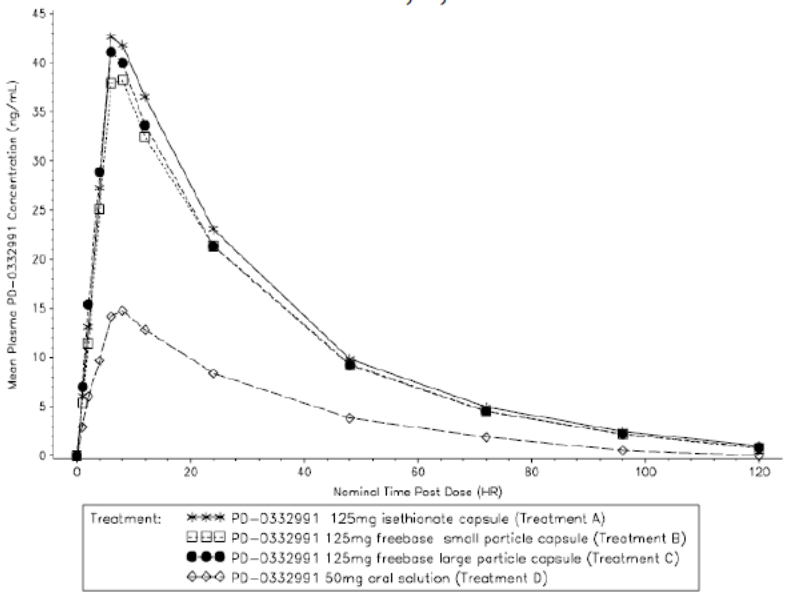
2.1.1 What are the design features of the biopharmaceutics studies used to support the proposed to-be-marketed formulation? Summary of individual study reviews provided.

Eight (8) biopharmaceutics studies have been conducted in healthy volunteers to assess absolute bioavailability (BA) (Study 1015), relative BA and bioequivalence (BE) (Studies 1009, 1020, 1022, 1036, and 1040), food effect (Study 1021), and antacid effect (Study 1018).

This Biopharmaceutics Review includes an evaluation of Studies 1009 (partial), 1020 (partial), 1022 and 1040.[1] All other studies are addressed by Dr. Jeanne Fourie Zirkelbach (Clinical Pharmacology), as per the September 2013 MOU and

[1] Study 1040 is not summarized in the Summary of Biopharmaceutics or Clinical Pharmacology sections of the NDA; however, the study was completed to evaluate drug particle size and dissolution effects on bioavailability under fed conditions. Palbociclib was initially dosed under fasting conditions in clinical studies, but the change from the isethionate salt to free base capsules amplified a group of low responders, and the new proposed dosing is with food.

application related communications between the Office of Clinical Pharmacology and Biopharmaceutics. Of note, the relative BA Study 1036 is the most critical study supporting approval (see Clinical Pharmacology Review).

Relative BA Study 1009 (particle size effects only)	
STUDY DESIGN	An open-label, randomized, 4-period, 4-treatment, 4-sequence, crossover, single-dose study to evaluate the bioavailability of free base capsule or oral solution palbociclib formulations relative to isethionate capsule administered in the fasted state to healthy adult volunteers.
METHODOLOGY	Twenty-four (24) subjects were enrolled to obtain at least 20 evaluable subjects who completed the study. Each subject received 4 treatments (A, B, C and D) with a washout period of at least 10 days between each dose. Subjects who withdrew were not replaced unless the number of completed subjects fell below 20. The treatment allocation was as follows: • Treatment A (ref): a 125 mg single dose of isethionate hard capsules (1 x 100 mg and 1 x 25 mg) • Treatment B: a 125 mg freebase hard capsule, the (b) (4) initial Phase 3 formulation (b) (4)-µm particle size) • Treatment C: a 125 mg freebase hard capsule, the (b) (4) initial Phase 3 formulation ((b) (4)-µm particle size) • Treatment D: a 50 mg oral solution.
NUMBER OF SUBJECTS/DEMOGRAPHICS	All subjects were male, of which 10 were white, 13 were black and 1 was of other race (24 total). The mean age was 38.7 years (range: 24 years to 55 years). The mean weight and BMI were 81.1 kg (range: 59.3 kg to 102.0 kg) and 26.1 kg/m^2 (range: 20.3 kg/m^2 to 30.5 kg/m^2), respectively.
SUMMARY OF RESULTS	**Mean Plasma Concentration Profiles Following Single Oral Doses of Treatments A, B, C and D** 

Relative BA Study 1009 (particle size effects only)

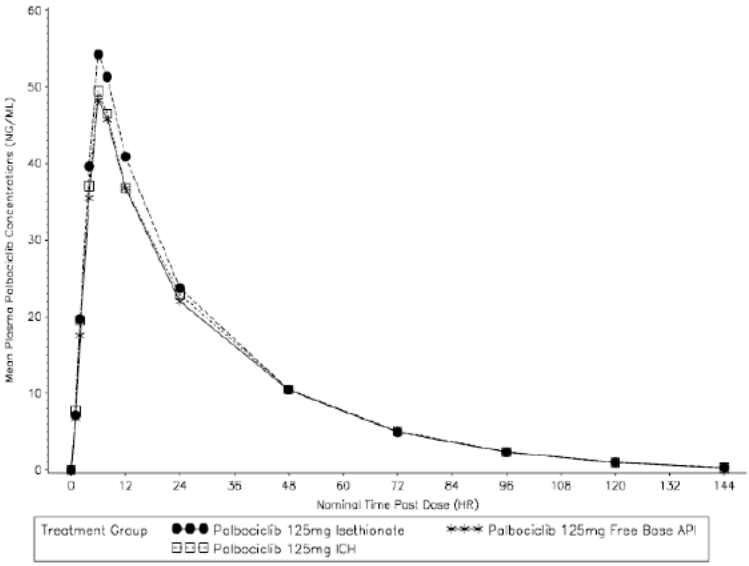
Parameters (units)	Parameter Summary Statistics[a] by Treatment Treatment A: 125 mg Isethionate Capsule	Treatment B: 125 mg Freebase Small Particle Capsule	Treatment C: 125 mg Freebase Large Particle Capsule	Treatment D: 50 mg Oral Solution
N, n	24, 24	24, 23	24, 24	24, 23
AUC_{inf}DN125 (ng•hr/mL)	1388 (24)	1322 (22)	1267 (38)	1302 (22)
AUC_{last}DN125 (ng•hr/mL)	1337 (25)	1168 (48)	1213 (41)	1156 (26)
AUC_{inf} (ng•hr/mL)	1388 (24)	1322 (22)	1267 (38)	520.8 (22)
AUC_{last} (ng•hr/mL)	1337 (25)	1168 (48)	1213 (41)	462.0 (26)
C_{max}DN125 (ng/mL)	43.29 (24)	36.35 (58)	39.44 (52)	37.09 (27)
C_{max} (ng/mL)	43.29 (24)	36.35 (58)	39.44 (52)	14.82 (27)
T_{max} (hr)	6.01 (5.98-12.0)	8.00 (5.98-12.0)	8.00 (4.00-12.0)	8.00 (6.00-12.0)
CL/F (L/hr)	90.07 (24)	94.56 (22)	98.76 (38)	96.00 (21)
Vz/F (L)	2880 (19)	3049 (25)	3175 (46)	3123 (23)
$t_{½}$ (hr)	22.40 (±3.329)	22.60 (±3.457)	22.57 (±3.688)	22.72 (±2.812)

Palbociclib Bioequivalence Analyses (Reported)

Parameters (units)	Adjusted Geometric Means Test	Reference	Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CIs for Ratio
Treatment B (Test) versus Treatment A (Reference)				
AUC_{inf}DN125 (ng•hr/mL)	1301	1388	93.75	(86.55, 101.55)
AUC_{last}DN125 (ng•hr/mL)	1168	1337	87.32	(78.21, 97.48)
C_{max}DN125 (ng/mL)	36.35	43.29	83.97	(73.91, 95.39)
Treatment C (Test) versus Treatment A (Reference)				
AUC_{inf}DN125 (ng•hr/mL)	1267	1388	91.29	(84.37, 98.77)
AUC_{last}DN125 (ng•hr/mL)	1213	1337	90.69	(81.23, 101.25)
C_{max}DN125 (ng/mL)	39.44	43.29	91.11	(80.20, 103.51)
Treatment D (Test) versus Treatment A (Reference)				
AUC_{inf}DN125 (ng•hr/mL)	1288	1388	92.78	(85.65, 100.50)
AUC_{last}DN125 (ng•hr/mL)	1156	1337	86.42	(77.40, 96.48)
C_{max}DN125 (ng/mL)	37.09	43.29	85.68	(75.42, 97.34)

SUMMARY OF SAFETY[2]	There were no deaths, serious adverse events (SAEs), severe adverse events (AEs), dose reductions or permanent discontinuations due to AEs in Study 1009. One (1) subject temporarily discontinued the study treatment due to a treatment emergent adverse event (TEAE) that was considered not treatment related. The 24 subjects reported a total of 50 TEAEs (all causality), 38 of which were considered treatment related.
Reviewer's Assessment	*Study 1009 provides a satisfactory overview of the preliminary considerations for implementing a drug substance (salt to free base) change to the palbociclib formulation* (b) (4) *There were no major changes to the conduct of the study and planned analyses since the final plan and all PK data were included in the analysis. The lactam metabolite PF-05089326 was also monitored, but was not deemed relevant for understanding formulation effects on drug exposures.* (b) (4)

[2] Drug safety is fully evaluated by the assigned Clinical Reviewer.

Relative BA Study 1020 (Initial Phase 3/Commercial Product)	
STUDY DESIGN	An open label 6-sequence 3-period crossover study of palbociclib (PD-0332991) in healthy volunteers to establish the bioequivalence of the Phase 1/2 and Phase 3 formulation to the palbociclib ICH formulation under fasted conditions.
METHODOLOGY	A total of 73 subjects were enrolled to complete the PK collection portion of each study period. Each subject was to receive 3 treatments (A, B, and C) with a washout period of at least 10 days between each treatment. Following treatment administration, subjects underwent PK sampling for 144 hours. The 3 treatments were as follows: • Treatment A (ref 1): single dose of palbociclib 125 mg (as a 25-mg capsule and a 100-mg hard capsules) with the isethionate salt form as used in the Phase 1/2 Studies A5481001, A5481002 and A5481003. • Treatment B (ref 2): single dose of palbociclib 125 mg (as a 125-mg single capsule) made with a free base API as a (b) (4) in a hard capsule as used in the Phase 3 Study A5481008. • Treatment C (test): single dose of palbociclib 125 mg (as a 125-mg single capsule) ICH formulation (final commercial formulation).
NUMBER OF SUBJECTS/DEMOGRAPHICS	Of the 73 subjects enrolled in this study, 71 were male and 2 were female. The mean age was 34.5 years and the majority were Black (42 subjects). The weight of subjects ranged from 55.9 to 107.0 kg and height ranged from 160.5 to 192.0 cm. The BMI ranged from 19.8 to 30.5 kg/m^2. All treated subjects were analyzed for PK and safety. There were 5 discontinuations in this study (2 subjects in Treatment A, 2 subjects in Treatment B, and 1 subject in Treatment C).
SUMMARY OF RESULTS	**Mean Plasma Palbociclib Concentration-Time Profiles** 

Relative BA Study 1020 (Initial Phase 3/Commercial Product)

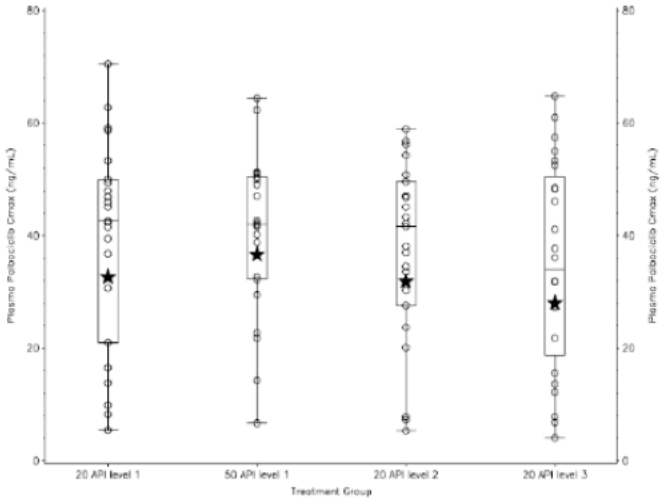
Parameter Summary Statistics[a] by Treatment

Parameter (units)	Treatment A Palbociclib 125 mg Isethionate	Treatment B Palbociclib 125 mg Free Base API	Treatment C Palbociclib 125 mg ICH
N, n	71, 71	71, 70	71, 70
AUC_{inf} (ng•hr/mL)	1521 (25)	1398 (36)	1427 (36)
AUC_{last} (ng•hr/mL)	1472 (26)	1330 (39)	1355 (40)
T_{last} (hr)	119 (71.5-145)	119 (71.6-145)	119 (48.0-145)
C_{max} (ng/mL)	53.63 (25)	44.82 (54)	45.24 (61)
T_{max} (hr)	6.00 (4.00-8.02)	6.00 (4.00-48.0)	6.00 (4.00-48.0)
$t_{½}$ (hr)	22.36 ± 4.76	22.66 ± 4.84	22.23 ± 4.67
CL/F (L/hr)	82.17 (25)	89.41 (36)	87.58 (36)
V_z/F (L)	2596 (23)	2866 (37)	2751 (38)

Palbociclib Bioequivalence Analyses (Reported)

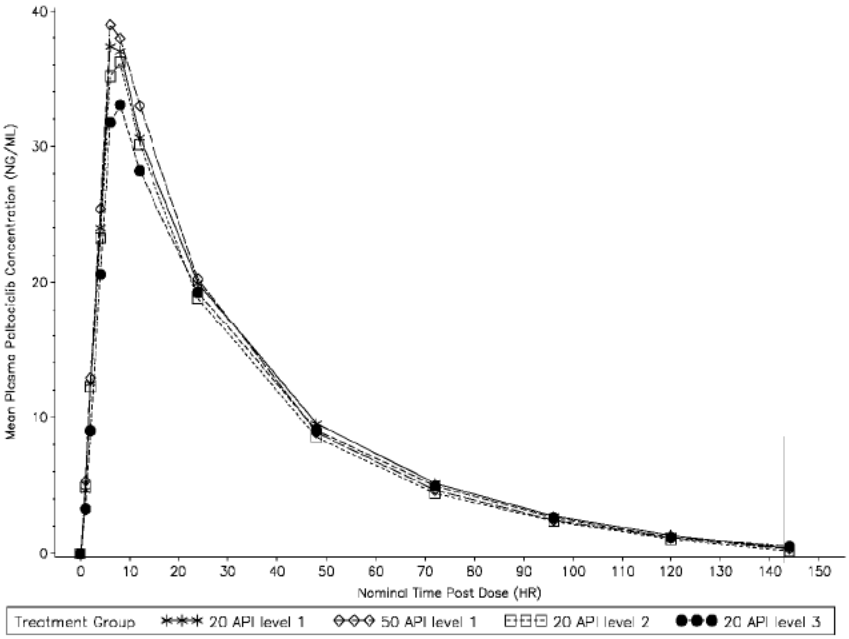
Parameter (units)	Adjusted Geometric Means: Test	Adjusted Geometric Means: Reference	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Palbociclib 125 mg ICH (Test, Treatment C) vs Palbociclib 125 mg Free Base API (Reference 2, Treatment B)				
AUC_{inf} (ng•hr/mL)	1437	1389	103.44	(98.14, 109.03)
AUC_{last} (ng•hr/mL)	1363	1329	102.54	(96.57, 108.87)
C_{max} (ng/mL)	45.39	44.83	101.24	(91.19, 112.39)
Palbociclib 125 mg ICH (Test, Treatment C) vs Palbociclib 125 mg Isethionate (Reference 1, Treatment A)				
AUC_{inf} (ng•hr/mL)	1437	1516	94.80	(89.97, 99.90)
AUC_{last} (ng•hr/mL)	1363	1466	92.94	(87.53, 98.69)
C_{max} (ng/mL)	45.39	53.54	84.78	(76.36, 94.12)

SUMMARY OF SAFETY	There were no deaths, discontinuations or dose reductions, SAEs, or severe AEs reported in this study. Nine (9) TEAEs were reported in 8 subjects after palbociclib 125 mg isethionate treatment, of which 6 AEs were considered treatment-related by the investigator. Seven (7) TEAEs were reported in 7 subjects after palbociclib 125 mg free base API treatment, of which 4 AEs were considered treatment-related by the investigator. Thirteen (13) TEAEs were reported in 9 subjects after palbociclib 125 mg ICH treatment, of which 6 AEs were considered treatment-related by the investigator.
Reviewer's Assessment (Initial Phase 3 and Final Commercial Product)	*Study 1020 was initially designed as the pivotal BE study supporting a formulation change from the isethionate salt to the free base drug substance. However, the 90% confidence intervals for the Cmax parameter did not fall within the 80-125% BE limit. The observed %CV for the commercial ICH formulation (final capsules) was unexpectedly high at* (b) (4) *compared with* (b) (4) *for the isethionate capsules. Further investigations by the Applicant identified a group of low responders in the free-base formulation groups. The reason for the observed "low-liers" is thought to be associated with the more pH-dependent dissolution profile of palbociclib free base capsules compared with that of the isethionate capsules. Because BE was not demonstrated, additional studies were completed to support approval of the free base capsule (see Clinical Pharmacology Review).* *This BE study was reviewed by Biopharmaceutics to confirm the changes to the manufacturing process and formulation* (b) (4) *for the initial Phase 3 and to be marketed product. With respect to this formulation change, bioequivalence was adequately demonstrated.*

Relative BA Study 1022 (Particle size/Dissolution Effects)	
STUDY DESIGN	An open-label, randomized, single-dose, 4-sequence, 4-period crossover study in healthy volunteers to investigate the influence of drug substance particle size (b) (4) and (b) (4)-µm) and dissolution level (Levels 1 to 3) on the bioavailability of palbociclib 125-mg, formulated as the free base in hard capsules under fasted condition in healthy volunteers.
METHODOLOGY	A total of 24 subjects were planned in the study to ensure a minimum of 20 completers. Each subject received 4 treatments (A, B, C and D) with a washout period of at least 10 days between successive treatments. The four treatment groups were as follows: • Treatment A (ref): 125-mg single dose of palbociclib, (b) (4)µm (20-µm per A5481022 protocol) API particle size and dissolution Level , (b) (4)% in (b) (4) minutes (b) (4)-µm API Level 1). • Treatment B: 125-mg single dose of palbociclib, (b) (4)-µm (50-µm per A5481022 protocol) API particle size and dissolution Level 1, (b) (4)% in (b) (4) minutes ((b) (4)-µm API Level 1). • Treatment C: 125-mg single dose of palbociclib, (b) (4)-µm (20-µm per A5481022 protocol) API particle size and dissolution Level 2, (b) (4)% in (b) (4) minutes ((b) (4)-µm API Level 2). • Treatment D: 125-mg single dose of palbociclib, (b) (4)-µm (20-µm per A5481022 protocol) API particle size and dissolution Level 3, (b) (4)% in (b) (4) mintues ((b) (4)-µm API Level 3).
NUMBER OF SUBJECTS/DEMOGRAPHICS	All 24 subjects were healthy male volunteers. Eleven (11) subjects were black, 9 subjects were white, and 4 subjects were of other ethnic origin. The mean age was 39.6 years (range 21 to 55 years) and the mean BMI was 27.6 kg/m^2 (range 21.0 to 30.5 kg/m^2). There was one study discontinuation; one subject after completing Period 1 in Treatment D.
SUMMARY OF RESULTS	**Individual and Geometric Mean Plasma Cmax Values by Treatment** 

Relative BA Study 1022 (Particle size/Dissolution Effects)

Mean Plasma Palbociclib Concentration-Time Profiles



Palbociclib Bioequivalence Analyses (Reported)

Parameter (units)	Adjusted Geometric Means: Test	Adjusted Geometric Means: Reference	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Palbociclib 125 mg (b) (4) API Level 1 (Test) versus Palbociclib 125 mg API Level 1 (Reference)			
AUC_{inf} (ng•hr/mL)	1263	1242	101.66	(91.90, 112.46)
AUC_{last} (ng•hr/mL)	1207	1187	101.66	(90.86, 113.75)
C_{max} (ng/mL)	37.23	33.46	111.29	(91.48, 135.41)
	Palbociclib 125 mg (b) (4) API Level 2 (Test) versus Palbociclib 125 mg API Level 1 (Reference)			
AUC_{inf} (ng•hr/mL)	1152	1242	92.73	(83.82, 102.58)
AUC_{last} (ng•hr/mL)	1092	1187	91.98	(82.20, 102.92)
C_{max} (ng/mL)	32.29	33.46	96.51	(79.32, 117.42)
	Palbociclib 125 mg (b) (4) API Level 3 (Test) versus Palbociclib 125 mg API Level 1 (Reference)			
AUC_{inf} (ng•hr/mL)	1152	1242	92.72	(83.70, 102.71)
AUC_{last} (ng•hr/mL)	1065	1187	89.66	(80.15, 100.30)
C_{max} (ng/mL)	28.03	33.46	83.77	(68.90, 101.86)

SUMMARY OF SAFETY	No deaths occurred during this study. No subjects experienced an SAE, a severe AE, a discontinuation from the study due to an AE, or a dose reduction or a temporary discontinuation of study drug due to an AE. The majority of AEs were assessed as being not related to treatment. All AEs were considered mild in severity, with the exception of 1 moderate AE of prolonged QT interval (time from ECG Q wave to the end of the T wave corresponding to electrical systole) which was reported following administration of palbociclib 125 mg (b) (4) µm API Level 3.
Reviewer's Assessment (Dissolution/Particle Size Effects)	*Under fasted conditions, the capsule dissolution rate appeared to have the greatest impact on observed Cmax values. None of the altered formulations (larger particle size or slower dissolution rate) met the bioequivalence criterion, though the mean values appeared comparable (i.e., +/- (b) (4) %) and the box plot distributions spanned similar ranges. As evidenced in previous*

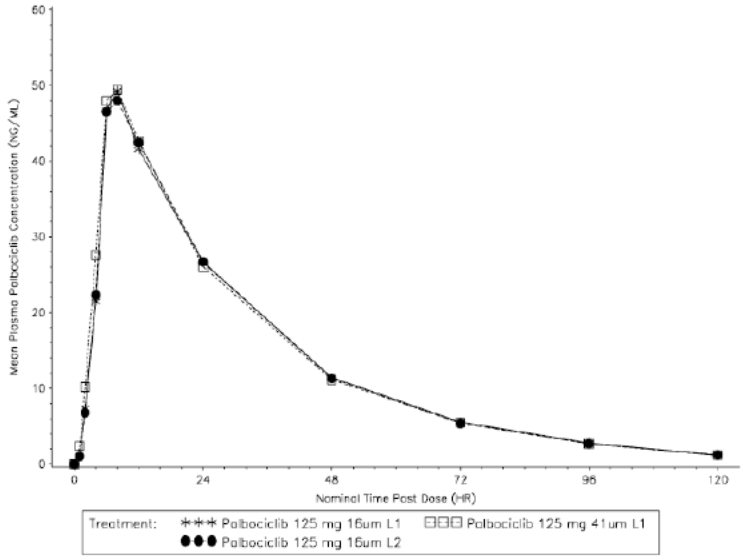
Relative BA Study 1022 (Particle size/Dissolution Effects)	
	relative BA studies under fasted conditions, a number of subjects had low drug exposures that likely contributed to high %CVs, which was most pronounced for Cmax (%CV range of 55%-88%) and thus, potentially impacted the bioequivalence assessment. Per discussions with Dr. Fourie Zirkelbach, however, Cmax is not linked to safety or efficacy for this drug and small differences are not expected to have any clinical significance. The observed difference in Cmax between the Level 1 and Level 2 dissolution is similar to that observed with the change in drug substance in Study 1020; a difference that was found clinically acceptable and appropriately addressed with food administration (see Clinical Pharmacology review). Study 1022 was repeated under fed conditions (see Study 1040) to reduce the confounding variability and demonstrate sameness under the intended use conditions. Generally, fasted conditions are deemed more appropriate for evaluating formulation changes. However, from a clinical risk perspective, the drug product will be administered with food and thus, Study 1040 provides a better indicator of clinical risks with respect to particle size and dissolution effects.

	Relative BA Study 1040 (particle size/dissolution)
STUDY DESIGN	An open-label, 6-sequence, 3-period, crossover study of palbociclib in healthy volunteers to estimate relative bioavailability of 3 palbociclib formulations under fed conditions.
METHODOLOGY	A total of 30 subjects were planned in the study to ensure a minimum of 24 completers. Each subject received 3 treatments (A, B, and C) with a washout period of at least 10 days between successive treatments. The three treatment groups were as follows: • Treatment A (ref): 125-mg single dose of palbociclib, 16-µm (API particle size and dissolution Level 1 (16-µm API Level 1). • Treatment B: 125-mg single dose of palbociclib, 41-µm API particle size and dissolution Level 1 (41-µm API Level 1). • Treatment C: 125-mg single dose of palbociclib, 16-µm API particle size and dissolution Level 2 (16-µm API Level 2). Subjects were given a moderate-fat standard-calorie meal (approximately 15% protein, 50% carbohydrate, 35% fat diet of 500-700 calories) approximately 30 minutes prior to dosing.
NUMBER OF SUBJECTS/DEMOGRAPHICS	A total of 30 subjects were assigned to study treatment, and all 30 subjects received study treatments and completed the study. There were no study discontinuations. All 30 subjects were healthy male volunteers. Eighteen (18) subjects were Black, 5 were White, 1 was Asian, and 6 were of other ethnic origin. The mean age was 38.5 years (range 23 to 55 years), and the mean BMI was 26.8 kg/m^2 (range 20.6 to 30.0 kg/m^2).

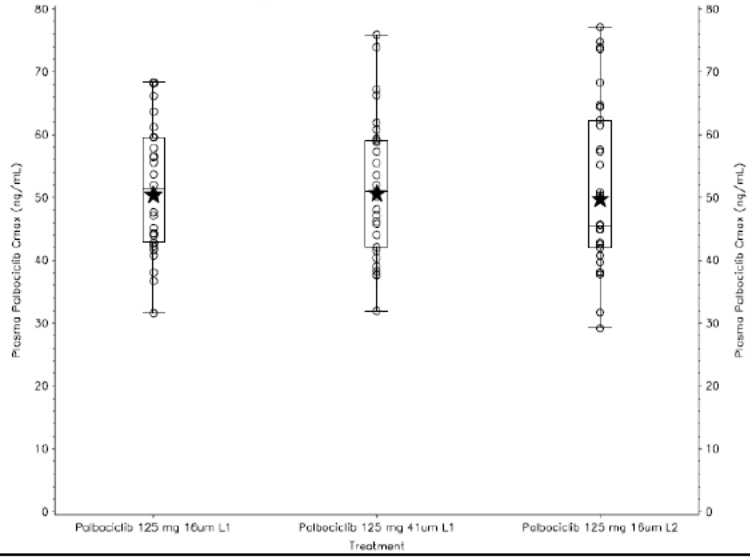
Relative BA Study 1040 (particle size/dissolution)

SUMMARY OF RESULTS

Mean Plasma Palbociclib Concentration-Time Profiles



Individual and Geometric Mean Plasma Cmax Values by Treatment



Palbociclib Bioequivalence Analyses (Reported)

Parameter (units)	Adjusted Geometric Means: Test	Adjusted Geometric Means: Reference	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Palbociclib 125 mg 41 µm L1 (Test) versus Palbociclib 125 mg 16 µm L1 (Reference)				
AUC_{inf} (ng•hr/mL)	1569	1569	100.00	(96.87, 103.23)
AUC_{last} (ng•hr/mL)	1511	1515	99.77	(96.44, 103.22)
C_{max} (ng/mL)	50.61	50.42	100.38	(95.97, 104.99)
Palbociclib 125 mg 16 µm L2 (Test) versus Palbociclib 125 mg 16 µm L1 (Reference)				
AUC_{inf} (ng•hr/mL)	1558	1569	99.31	(96.20, 102.52)
AUC_{last} (ng•hr/mL)	1507	1515	99.47	(96.15, 102.91)
C_{max} (ng/mL)	49.76	50.42	98.68	(94.35, 103.22)

Relative BA Study 1040 (particle size/dissolution)	
SUMMARY OF SAFETY	There were no deaths, SAEs, severe AEs, discontinuations or dose reductions due to AEs reported in this study. Overall, about half of the TEAEs were reported as treatment-related. All TEAEs were considered mild in severity.
Reviewer's Evaluation	*There were no unusual changes to the study protocol or data exclusions impacting data review. Administering palbociclib with food appeared to yield more uniform drug exposure kinetics and eliminated the presence of a subgroup of low responders that lead to high variability in Study 1022. In this study, the %CV for Cmax was 21-27% compared with up to 88% under fasted conditions. Bioequivalence was demonstrated as per the standard BE criterion. As such, Study 1040 provided adequate support for the proposed drug substance particle size acceptance criterion of NMT (b) (4) µm (b) (4) and dissolution final sampling at (b) (4) minutes.*

2.1.2 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

The proposed commercial formulation and the formulation used in the pivotal Phase 1/2 studies supporting bioequivalence did not meet the standard criteria for bioequivalence under fasting conditions. The additional biopharmaceutics and clinical pharmacology studies completed to support approval, in spite of the bioequivalence deficiencies, are addressed by Dr. Jeanne Fourie Zirkelbach (see Clinical Pharmacology review).

2.1.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Refer to the Clinical Pharmacology Review by Dr. Jeanne Fourie Zirkelbach for an assessment of the food effect studies and dosing recommendations.

Study 1021 evaluated the effects of food on the drug exposure kinetics using the commercial free base formulation – 125 mg (i.e., the final to-be marketed formulation). The AUC and Cmax parameters were higher in subjects who were fed a high-fat meal compared with subjects who were fasting. The Applicant attributes the different response with food to the presence of so called "low-liers," a subset of individuals with substantially lower exposure when palbociclib free base capsules were administered after an overnight fast.

2.2 BIOANALYTICAL METHOD SECTION

2.2.1 How are the active moieties and/or metabolites identified and measured in the plasma in the biopharmaceutics studies?

Human plasma samples (EDTA treated) were analyzed for the parent drug palbociclib, which is the active species.

2.2.2 What bioanalytical methods are used to assess concentrations?

All PK samples were sent to [redacted] (b) (4) for analysis using a validated HPLC-MS/MS method (VR A5489006)

2.2.2.1 What is the range of the standard curve? How does it relate to the requirements for the clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification (LLOQ/ULOQ, and assay validation parameter: accuracy, precision, selectivity, sample stability, etc.?

Study 1009

- Calibration standard responses were linear over the range of 1.00 to 250 ng/mL (PD-0332991) and 0.100 to 25.0 ng/mL (PF-05089326) by using a weighted (l/concentration^2) linear least squares regression. The lower limit of quantification (LLOQ) was 1.00 ng/mL for PD-0332991(palbociclib) and 0.100 ng/mL for PF-05089326 (major metabolite). Clinical specimens with plasma PD-0332991 and PF-05089326 concentrations below the LLOQ were reported as below LLOQ. The between-day assay accuracy, expressed as percent relative error (%RE), for quality control (QC) concentrations, ranged from -6.47% to 2.85% for the low, medium, medium-high and high QC samples for PD-0332991. Assay precision, expressed as the between-day percent coefficients of variation (%CV) of the mean estimated concentrations of QC samples was ≤5.94% for low (2.50 ng/mL), medium (15.0 ng/mL), medium-high (40.0 ng/mL), and high (190 ng/mL) concentrations.

  The between-day assay accuracy, expressed as %RE, for QC concentrations, ranged from -10.0% to 2.89% for the low, medium, medium-high and high QC samples for PF-05089326. Assay precision, expressed as the between-day %CV of the mean estimated concentrations of QC samples was ≤8.57% for low (0.250 ng/mL), medium (1.50 ng/mL), medium-high (4.00 ng/mL), and high (19.0 ng/mL) concentrations.

Study 1020

- The same HPLC-MS/MS method (VR A5489006) was used for analysis.

Study 1022

- The same HPLC-MS/MS method (VR A5489006) was used for analysis.

Study 1040

- The same HPLC-MS/MS method (VR A5489006) was used for analysis.

2.2.2.2 Are the Inspection reports of the BE study acceptable?

Study site inspections were not completed for the BE/BA studies reviewed in this report as these studies were not considered the pivotal studies for approval. Thus, a for-cause approach for inspections was applied and there were no for cause issues noted during the review.

3 GENERAL BIOPHARMACEUTICS (IN VITRO)

3.1 DISSOLUTION INFORMATION

3.2 DISSOLUTION METHOD

3.2.1 What is the proposed dissolution method?

(b) (4)

[redacted]

(b) (4)

[redacted]

3.2.5 Is the proposed dissolution method biorelavant? What data are available to support this claim?

No. The proposed dissolution method is not biorelavant.

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3.2.6 Is the proposed method acceptable? If not, what are the deficiencies?

Yes. The proposed dissolution method is acceptable. It is acknowledged that the proposed dissolution method supports (b) (4) dissolution of the palbociclib capsules, (b) (4) This limitation is understood given the relationship between solution pH and drug solubility, and the Applicant is proposing relatively mild testing conditions. Moreover, the Applicant has demonstrated acceptable clinical equivalence across a range of dissolution profiles to permit a clinical risk-based approach to evaluating the proposed dissolution method. The proposed dissolution method could distinguish bio-inequivalent capsules (e.g., Level 1 and Level 3 dissolution), which is a critical attribute for any dissolution method that is not always evaluated.

3.3 ACCEPTANCE CRITERIA

3.3.1 What are the proposed dissolution acceptance criteria for this product?

The proposed dissolution acceptance criterion is Q = (b) (4)% in 30 minutes.

3.3.2 What data are available to support the criteria?

The justification for the proposed dissolution acceptance criterion is based on data from (b) (4) drug product batches manufactured with the palbociclib free-base drug substance and intended for registration stability and clinical use (post approval Phase 3). The comprehensive mean dissolution profiles supporting the proposed acceptance criterion are illustrated below for each capsule strength.

Figure 3.2.P.5.6-2. Comprehensive Dissolution Profiles of 75-mg Capsules (mean)

(b) (4)

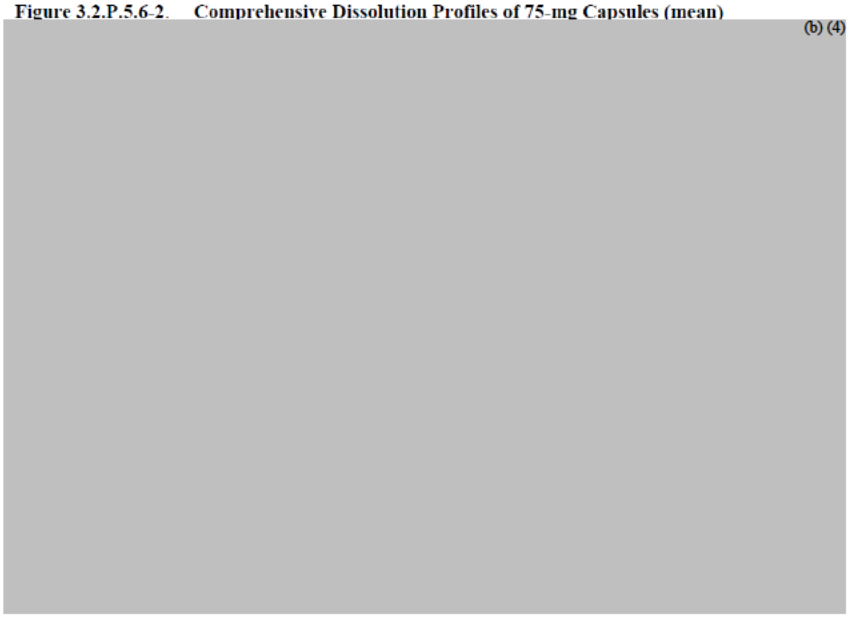


Figure 3.2.P.5.6-3. Comprehensive Dissolution Profiles of 100-mg Capsules (mean)

Figure 3.2.P.5.6-4. Comprehensive Dissolution Profiles of 125-mg Capsules (mean)

The summary stability data (initia (b) (4) and 12 months) is also tabulated below.

Acceptance Criteria	NLT % (Q) in 30 minutes			
Test Procedure	TM-1877A			
	Strength:	75 mg	100 mg	125 mg
Ranges [a]	Initial	(b) (4)		
	25 °C/60% RH			
	30 °C/75% RH			
	40 °C/75% RH			

[a] Ranges represent individual dissolution results

There were no observed trends in the dissolution stability data through 12 months of storage. It is noted that a few batches required stage 2 and at least one batch required stage 3 testing at various time points. Individual units had dissolution values as low as (b) (4)%, which is likely due to (b) (4) discussed further in Section 4.4.2 of this Review. However, all drug product lots complied with USP <711> criteria for allowable variation at stage 1, 2, and 3 dissolution testing.

3.3.3 *Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?*

The capsules used for the clinical studies supporting NDA approval (Phase 1/2) used the isethionate salt form (b) (4) Batch analyses data for the isethionate capsules include only disintegration testing. The dissolution criterion is established based on the registration batches and the commercial free base capsules used in the post-marketing Phase 3 clinical study, which is ongoing.

3.3.4 *Are mean (n =12) dissolution profile data used for the setting of the acceptance criteria?*

Yes.

3.3.5 *Are the acceptance criteria acceptable? If not, what are the recommended criteria?*

Yes, the proposed acceptance criterion is acceptable. Dissolution profile sampling was done at (b) (4) 30, and (b) (4) minutes. The mean and individual dissolution values at (b) (4) minutes (see Table 3.2.P.5.6-10 in NDA) indicate that (b) (4) minutes is not an appropriate final sampling time point. There are no data for the (b) (4) minute sampling time points; however, the apparent variability at (b) (4) minutes (b) (4) does indicate a potential for undesired variability issues at a final sampling time point of (b) (4) minutes. Further, relative bioavailability studies suggest that there is likely no difference in clinical performance between (b) (4)% in (b) (4) minutes versus 30 minutes. In consideration of the in vitro and in vivo data, final sampling at 30 minutes is adequate to assure consistent product quality.

4 DISSOLUTION APPLICATIONS

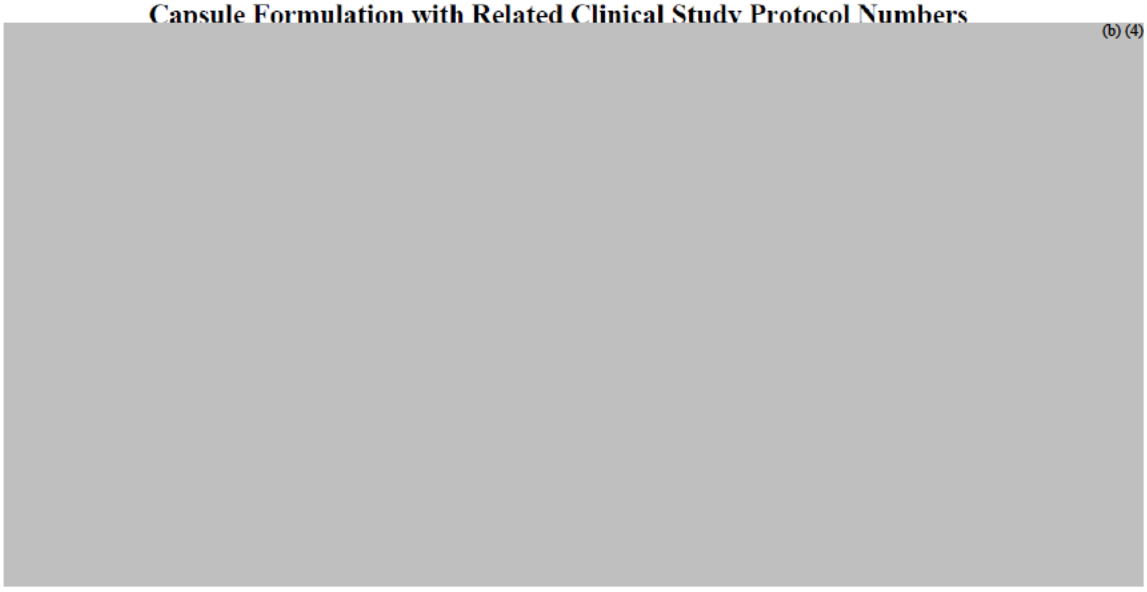
4.1 FORMULATION CHANGES

4.1.1 *Is the to-be-marketed formulation the same as the formulation used in the pivotal clinical or bioequivalence studies? If not, is dissolution used to bridge the data?*

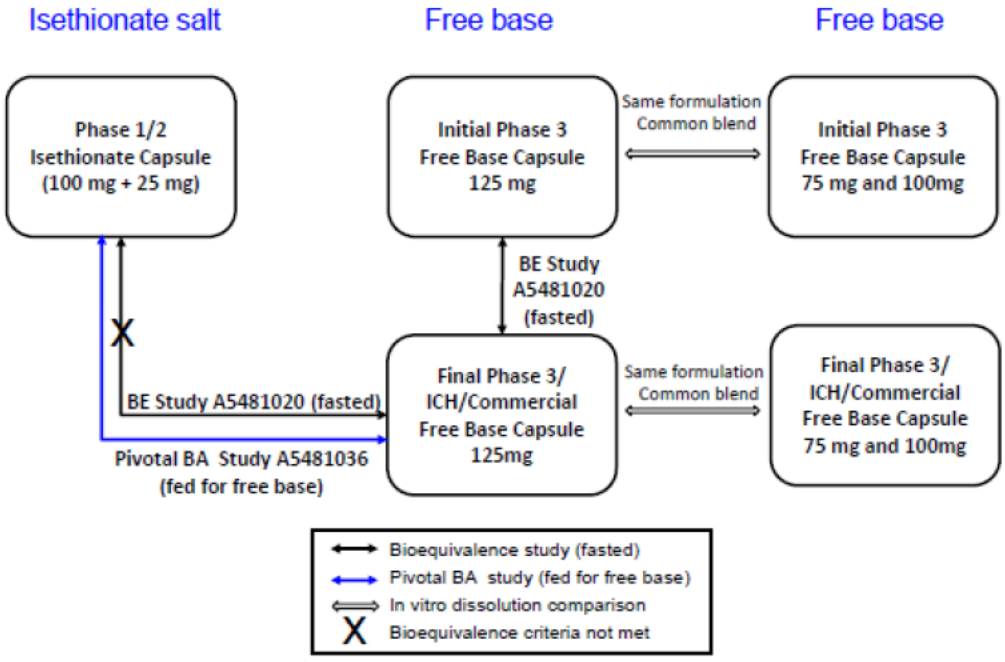
No. The clinical trial material used in the pivotal Phase 1/2 efficacy study (Study 1003), the results of which are the basis for NDA approval, (b) (4) However, the to-be-marketed formulation was used in the pivotal relative bioavailability study, Study 1036. The proposed commercial free base capsules are also being used in the ongoing Phase 3 post approval study. A tabular summary of the formulations used throughout clinical development is presented below.

Table 2. Comparison of Clinical Capsule Formulations and Proposed Commercial Capsule Formulation with Related Clinical Study Protocol Numbers

(b) (4)



An overview of the bridging scheme to link the Phase 1/2 isethionate capsules to the to-be-marketed free base capsules is illustrated below.



BA=bioavailability; BE=bioequivalence; ICH=International Conference on Harmonization (registration stability)

The relative BA/BE studies evaluated by Biopharmaceutics were discussed previously.

4.1.2 *Is the finished tablet* (b) (4) *Do the dissolution data comparing the* (b) (4) *?*

No. The drug product is a capsule formulation.

4.2 BIOWAIVERS

4.2.1 Is there a waiver request for in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?

No. Because the relative bioavailability studies used only the 125 mg free base capsule, an implied biowaiver request may be perceived for the 100 mg and 75 mg capsules. However, all free base capsule strengths are being used in the ongoing Phase 3 confirmatory clinical study. In addition, the 125 mg, 100 mg, and 75 mg, are manufactured using a (b) (4) (b) (4) Thus, the strengths are and BA/BE studies using only the higher strength are generally acceptable, provided that the in vitro dissolution data are comparable across all strengths. The comparative mean dissolution profiles in pH (b) (4) and (b) (4) media are illustrated below for all three strengths.

Comparative Dissolution of Palbociclib 75 mg, 100 mg, and 125 mg Strength Final Phase 3/Commercial Free Base Capsules in Different pH Media

(b) (4)

(b) (4)

4.2.2 Is there any IVIVR or IVIVC information submitted? What is the regulatory application of the IVIVR/IVIVC in the submission? What data are provided to support the acceptability of the IVIVR or IVIVC model?

Not applicable.

4.3 SURROGATES IN LIEU OF DISSOLUTION

4.3.1 Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support the approval of the proposed surrogate test?

No.

4.4 DISSOLUTION AND QBD

4.4.1 Does the application contain QbD elements? If yes, is dissolution identified as a CQA for defining design space?

No.

4.4.2 Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?

There were no DOE studies. From a formulation development perspective, excipient effects on drug product performance were evaluated using classical product development studies, which included varying suppliers, quantities, type, and using multiple lots to account for intra-grade and lot-to-lot variability among the excipients. Based on the study results, the Applicant concluded that excipient grades that meet the compendia specification would be sufficient to ensure acceptable drug product performance.

The drug product manufacturing process includes a (b) (4) Optimal processes and parameters were defined based on small scale lab experiments, prior knowledge, and experience with similar (b) (4) drug products. Process understanding was achieved through multivariate and univariate analysis of small scale development trials, and computational modeling tools (high level summaries in the NDA). Based on all the batch data and process knowledge gained, the following product quality attributes have a moderate or higher impact on dissolution and critical controls have been implemented (see the CMC Product Quality Review by Joyce Crich for full details).

Product Quality Attribute	Quality Risks
Excipients	Moderate
Drug Substance Particle Size	Moderate
(b) (4)	Moderate
	High

During the registration stability and Phase 3 clinical supply campaigns, an edge of failure for dissolution was identified during (b) (4) The impact on dissolution was only observed at (b) (4) and the failure has been attributed to (b) (4). Of note, initial process optimization studies utilized disintegration testing, which did not highlight the dissolution issues noted after the registration campaign was completed. An (b) (4)% cut-off was implemented as an

interim measure on clinical supply batches, while investigative studies continued to identify the root cause and remediation measures. The cut-off applied only to clinical supplies; the entire lot was used for release and stability testing. The summary (b) (4) dissolution data for the 125 mg capsules exhibiting (b) (4)

(b) (4)

Investigative studies suggested that the root cause of the dissolution failures was due to (b) (4) Refer to the CMC review by Dr. Crich for an assessment and recommendations regarding the acceptability of the (b) (4) and controls for the commercial process.

From the Biopharmaceutics perspective, these data suggest that the effects of (b) (4) In addition, the proposed dissolution method (b) (4)

It is noted that a (b) (4) (b) (4)

4.4.3 What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

Not applicable.

4.4.4 Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

No.

5 LABELING

As per the current MOU between Biopharmaceutics and Clinical Pharmacology, the biopharmaceutics labeling issues are addressed by Clinical Pharmacology.

6 INFORMATION REQUESTS DURING THE REVIEW

Biopharmaceutics specific information requests were not submitted during the review. However, there were several biopharmaceutics related comments included in CMC information requests regarding the (b) (4) ***dissolution failures as part of a team based evaluation of the Applicant's control strategy. Review feedback was provided to the CMC review team (Joyce Crich) and incorporated in the above QBR, where appropriate.***

NDA FILING AND REVIEW FORM

Office of Clinical Pharmacology			
General Information About the Submission			
NDA Number	NDA 207103 IND 69324	**Brand Name**	Ibrance®
OCP Division	DCP V	**Generic Name**	Palbociclib (PD 0332991, PF-00080665) capsules
OND Division	OHOP/DOP1	**Drug Class**	Cyclin-dependent kinases (CDK) 4 and 6 inhibitor.
OCP Reviewer	Jeanne Fourie Zirkelbach, Ph.D.	**Indication(s)**	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 who have not received previous systemic treatment for their advanced disease.
OCP Team Leader	Qi Liu, Ph.D.	**Dosage Form**	75 mg, 100 mg and 125 mg palbociclib capsules
Sponsor	Pfizer Inc.	**Route of Administration**	oral
Date of Submission	8/15/14	**Priority Classification**	Priority Review (8 months)
PDUFA Due Date	4/15/15		

Clinical Pharmacology Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Submitted in Wave 2 –Aug 13.
Reference Bioanalytical and Analytical Methods	X	11		-Determine plasma palbociclib concentrations. -Determine plasma palbociclib lactam active metabolite (PF-05089326). -Determine urine palbociclib concentrations. -Determine plasma letrozole concentrations. -Determine plasma midazolam and hydroxymidazolam concentrations. -Determine plasma tamoxifen, n-desmethyltamoxifen, 4-OH tamoxifen and desmethyl-4OH-tamoxofen concentrations.
I. Clinical Pharmacology				
Mass balance:	x	1		1011 ADME in healthy volunteers

Metabolic profiling	x	3		PD-0332991_05Mar13_095443 Reaction Phenotyping of PD-0332991 Using Human Hepatocytes Relay Method PD-0332991_18Sep13_170350 In Vitro Recombinant Sulfotransferase (SULT) Reaction Phenotyping of PD-0332991 Sulfonation and Enzyme Kinetic Parameters in Human Liver S9, Cytosol, and SULT2A1 PD-332991_10Sep13_193503 Metabolism of PD-0332991 in Rat, Dog, and Human Hepatocytes
Isozyme characterization:				
Active Metabolites				PF-05089326 In vitro studies done as described in document.
Transporters	x	1		PD-332991/25MAR09/142925-Permeability and Transport Evaluation of PD-0332991
Blood/plasma ratio:	x	1		RR764-04302- Definitive Red Blood Cell (RBC) Distribution of PD-0332991-0054 in Human Whole Blood.
Plasma protein binding:	x	2		RR764-04174-Protein Binding of PF-05089326 in Human Plasma PF-05089326_17Dec12_104347-Protein Binding of PF-05089326 in Human Plasma
Pharmacokinetics (e.g., Phase I)				
Healthy volunteers	x	11		1011, 1012, 1017, 1018, 1026, 1009, 1015, 1020, 1021, 1022, 1036
single dose:	x			
multiple dose:	x			
Patients-	x	3		1001, 1002, 1003 and 1010 (Japanese Patients).
single dose:	X			
multiple dose:	X			
Dose proportionality -	X			1001
Drug-drug interaction studies	x	4		Healthy volunteer DDI: 1012(midazolam), 1017 (rifampin), 1018(rabeprazole), 1026(tamoxifen)
In-vivo effects on primary drug:				1017, 1018, 1026
In-vivo effects of primary drug on other drugs:				1012

In-vitro:	x	9		*PD-0332991_27MAY10_181141 Effect of PD-0332991 on Human Drug Metabolizing Enzymes In Vitro* *PD-332991/05SEP09/130322 Effect of PF-05089326, a Metabolite of PD-332991, on Human Drug Metabolizing Enzymes In Vitro* *PF-00080665_15Feb13_165849 In Vitro Evaluation of PF-00080665 as an Inhibitor of UDP Glucuronosyltransferase (UGT) Enzyme Activities in Human Liver Microsomes* (b) (4) *123065 In Vitro Investigation of the Potential for PF-00080665 to Induce Cytochrome P450 (CYP1A2, CYP2B6, CYP2C8, and CYP3A4) in Cultured Cryopreserved Human Hepatocytes* (b) (4) *28428 or 12_03731 In Vitro Studies of Selected Test Articles With the Human BSEP (ABCB11/sPgp) Transporter in the Vesicular Transport Inhibition Assay* (b) (4) *28429 or 12_03729 In Vitro Interaction Studies of Selected Test Articles With Human Renal Uptake Transporters* (b) (4) *128430 or 12_03729 In Vitro Interaction Studies of PF-00080665 (PD-0332991) With the Human OATP1B1 and OATP1B3 Uptake Transporters* (b) (4) *128431 or 12-03730 The In Vitro Study of BCRP BCG2) Inhibition by PF-00080665-73-0006 (PD-0332991) in MDCKII-BCRP Cells* *PF-00080665_06Dec12_163603 The In Vitro Study of MDR1 (ABCB1) Inhibition by PF-00080665 (PD-0332991) in MDCKII-MDR1 Cells*
Subpopulation studies -				
Body size				PMAR269: POP PK report – Includes 1001, 1002 and 1003 using Isethionate salt formulation.
gender:				
geriatrics:				
renal impairment:	x	1		
Race/Ethnicity:				
hepatic impairment:	x	1		PMAR269: POP PK report – Includes 1001, 1002 and 1003 using Isethionate salt formulation.
pediatrics:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:	X	3		SAFETY (1001, 1002, 1003): PMAR-EQDD-A548b-DP4-271 (neutropenia) and PMAR-EQDD-A548b-DP4-286 (thrombocytopenia) EFFICACY (1003): PMAR-EQDD-A548b-DP4-387
Population Analyses -				
Data rich:	X	1		PMAR269: POP PK report – Includes 1001, 1002 and 1003 using Isethionate salt formulation.

Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	x	1		1015
Relative bioavailability -	x	3		1009, 1022, 1036
solution as reference:				1009
alternate formulation as reference:				1022, 1036
Bioequivalence studies -	X	1		1020
traditional design; single / multi dose:				1020
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1		2021
QT_C studies	X	1		PMAR-287-PK-ECG –exposure response analysis using 1003
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

CC: DHP: (CSO – A Tilley; MTL –P Cortazar; MO –L Amiri-Kordastani)
OCP: (Reviewer – J Fourie Zirkelbach and Jerry Yu; TL – Q Liu and Liang Zhao; DDD-B Booth; DD - A Rahman)

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	x			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			

14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Waiver.
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

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

Please identify and list any potential review issues to be forwarded to the Applicant: N/A

Clinical Pharmacology - NDA Filing Memo

NDA: 207103, Original Submission, IND: 69,324
Compound: Ibrance (Palbociclib) capsules
Sponsor: Pfizer Inc.
Filing Date: Aug 15, 2014
Reviewer: Jeanne Fourie Zirkelbach, PhD

Previous Regulatory History:

- **SDN 294 (preNDA):** In trial **A5481003** to support the initial NDA, the phase 2 *isethionate salt* capsule formulation was administered under a *fasted condition.* The isethionate salt formulation (b) (4) and the sponsor developed the *commercial free base* formulation for the initial approval. The sponsor provided brief summary statements from the pivotal BE trial **(A5481020)** indicating that *in the fasted state, the isethionate salt was not bioequivalent to the commercial free base formulation. However, when the commercial free base formulation was administered with food, it showed equivalent exposure to the isethionate salt formulation under a fasted condition (trial **A54811036**).*
- **SDN 325 PreNDA: Based on a PreNDA agreement with FDA the following studies will be submitted on Sept 15th during the Original NDA review period:**
  - **A5481038– "**A Phase 1, Open-Label, 3-Period Crossover Study Of The Effect Of An Antacid, A Proton Pump Inhibitor And An H2-Receptor Antagonist On Palbociclib (PD-0332991) Bioavailability Under Fed Conditions In Healthy Volunteers**".**
  - **A5481040- "**A Phase 1, Open-Label, 6 Sequence, 3 Period, Crossover Study Of Palbociclib (PD-0332991) In Healthy Volunteers To Estimate The Relative Bioavailability Of 3 Palbociclib Formulations".

Studies of ER-positive breast cancer cell lines indicated that estrogens and antiestrogens act on sensitive populations of cells in early to mid-G1 phase. The G1/S transition is under the control of CDKs activated by specific regulatory cyclins. CDK4 and CDK6 are activated by binding to D-type cyclins and act early in G1 phase.

Palbociclib is a highly selective, reversible inhibitor of CDK 4 and 6. Letrozole is an oral nonsteroidal aromatase inhibitor that is approved for the first line treatment of postmenopausal women with hormone receptor-positive advanced breast cancer.

Applicant Efficacy Summary and Dose Rationale:
A Phase 1 study (A5481001) evaluating palbociclib as an oral single agent was conducted to investigate safety, pharmacokinetics (PK), and efficacy in patients with advanced solid tumors or lymphomas. This study included a dose-escalation component and evaluated 2 different oral dosing schedules: 3 week continuous QD therapy with 1 week off therapy (Schedule 3/1) and 2 week continuous QD therapy with 1 week off therapy (Schedule 2/1). The recommended Phase 2 dose (RP2D) for Schedule 3/1 and Schedule 2/1 was determined to be 125 mg QD and 200 mg QD, respectively.

From the first in patient Study 1001, the safety profiles at the maximum tolerated dose (MTD) of the Schedule 2/1 (14 days on treatment/7 days off treatment) and schedule 3/1 (21 days on treatment/7 days off treatment) were generally comparable. However, as a greater

proportion of patients on the Schedule 2/1 had treatment-related treatment emergent adverse events compared to those of Schedule 3/1, and a greater long-term antitumor activity was observed with Schedule 3/1, the Schedule 3/1 regimen was selected for further clinical development. In Study 1003, Phase 1, 12 patients were enrolled and treated. The Recommended Phase 2 Dose (RP2D) for the palbociclib plus letrozole combination was confirmed to be palbociclib 125 mg orally once daily (QD) for 3 weeks followed by 1 week off treatment in combination with the recommended dose of letrozole 2.5 mg orally QD continuously.

Trial 5481003 is an open-label, randomized, Phase 1/2 study to assess the efficacy, safety and pharmacokinetics of palbociclib in combination with letrozole and letrozole alone for the first-line treatment of ER-positive, HER2-negative advanced breast cancer in postmenopausal women.

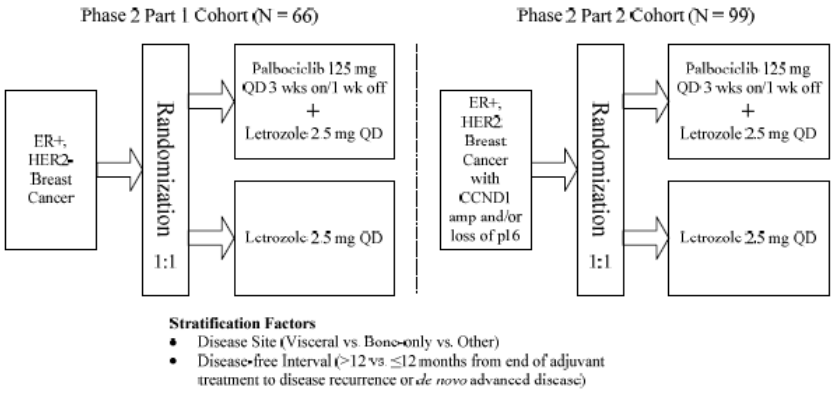
The evidence for the clinical efficacy of palbociclib plus letrozole is derived from pivotal Study A5481003 (referred to as Study 1003, or PALOMA). Study 1003 was an open-label, randomized, Phase 1/2 clinical study to assess the efficacy, safety and PK of palbociclib (isethionate salt formulation) in combination with letrozole and letrozole alone for the first-line treatment of ER-positive, human epidermal growth factor receptor 2 (HER2/ErbB2)-negative advanced breast cancer (ie, locally advanced and metastatic disease) in postmenopausal women. Letrozole was selected as background treatment, as it is approved, commercially available, well known and considered a standard of care for the first-line antihormonal treatment of patients with ER-positive advanced breast cancer. This study had a Phase 1 portion (N=12) to evaluate the safety and tolerability of the combination and to exclude a drug-drug interaction with the combination. The Phase 1 portion of the study was followed by a randomized multicenter Phase 2 portion (N=165) to assess the efficacy and safety of palbociclib plus letrozole compared with letrozole alone in the first-line treatment of ER-positive, HER2-negative postmenopausal women with advanced breast cancer.

The Phase 2 portion of Study 1003 consisted of 2 parts:
Phase 2 Part 1 (Ph2P1) enrolled postmenopausal women with ER-positive, HER2-negative advanced breast cancer (cell-cycle relevant biomarker-unselected). Phase 2 Part 2 (Ph2P2) enrolled a prospectively defined, cell-cycle relevant biomarker-positive (BM-positive) population of postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had tumors demonstrating CCND1 gene amplification (CCND1/CEP11 ratio $\geq$1.5) and/or loss of the CDKN2A gene (CDKN2A/CEP9 ratio <0.8), representing 15% to 20% of human breast cancer. The Phase 2 portion of Study 1003 was analyzed overall (Ph2P1+Ph2P2) as well as by individual part (Ph2P1 [N=66] and Ph2P2 [N=99]).

In trial 1003, the addition of palbociclib to letrozole resulted in statistically significant and robust improvement in progression-free survival (PFS) (hazard ratio [HR]=0.488; 95% confidence interval [CI]: 0.319-0.748; 1-sided p=0.0004), representing a 51% reduction in the risk of disease progression or death. The median PFS was 20.2 months (95% CI: 13.8-27.5 months) in the palbociclib plus letrozole arm and 10.2 months (95% CI: 5.7-12.6 months) in the letrozole arm. The significant improvement in PFS observed with palbociclib plus letrozole was consistent across both the cell cycle-relevant biomarker-unselected patient population (Ph2P1:

HR=0.299; 95% CI: 0.156-0.572; 1-sided p=0.0001) and the cell cycle-relevant biomarker selected patient population (Ph2P2: HR=0.508; 95% CI: 0.303-0.853; 1-sided p=0.0046).

Figure 1. Study A5481003 - Phase 2 Design



Applicant Safety Summary:
Of the 255 patients with malignant disease who received at least 1 dose of palbociclib, 101 patients were postmenopausal women with advanced breast cancer who received palbociclib (125 mg QD on Schedule 3/1) in combination with letrozole (2.5 mg QD continuously) in pivotal Study A5481003 ([Study 1003] N=95) and Part 2 of ongoing Study A5481010 ([Study 1010] N=6), comprising the target population and the recommended dosing regimen for palbociclib treatment.

The most frequently reported (≥20%) TEAEs in the palbociclib plus letrozole arm of the Phase 2 portion of Study 1003 were Neutropenia, Leukopenia, Fatigue, Anaemia, Nausea, Arthralgia, Alopecia, Diarrhoea, and Hot flush. The most common TEAEs were generally consistent with those in Studies 1001 and 1002 where palbociclib was administered as a single agent.

In Study 1003, the median time from first dose to first episode of NEUTROPENIA (all grades) was 20 days (based on AE data). Despite the Grade 3/4 Neutropenia (48.2% [Grade 3] and 6.0% [Grade 4]) seen in the palbociclib plus letrozole arm, no cases of Febrile neutropenia, Neutropenic sepsis, or Neutropenic infection were reported in Study 1003. Episodes of Grade 3/4 Neutropenia were generally managed through dose reduction and/or dose delay and most resolved by the patient's next assessment. While a higher rate of infections was observed in patients who received palbociclib plus letrozole, no patients were permanently discontinued from study treatment or died due to an infection-related event in Study 1003.

Applicant QT Summary: Palbociclib does not appear to have a concentration dependent effect on heart rate.
A slight positive linear relationship between palbociclib concentration and QTcS was observed; however, at the mean or median maximal steady-state palbociclib concentrations following administration of therapeutic doses in cancer patients, the upper bound of the one-sided 95% confidence interval for the increase in QTcS did not exceed the threshold of 10 msec,

thus suggesting QT prolongation is not a major safety concern for palbociclib at the recommended therapeutic dose.

Applicant PK Summary: Palbociclib (isethionate salt and free base) PK profiles and parameters appeared to be generally comparable across studies conducted in a total of 271 healthy subjects. After a single oral 125-mg dose of palbociclib, the median T_{max} was observed between 6 hours and 8 hours after oral dosing. Following attainment of C_{max}, plasma palbociclib concentrations declined in a multi-exponential manner, with mean $t_{½}$ values ranging between 20.9 hours and 25.9 hours. The palbociclib geometric mean plasma C_{max} values ranged from approximately 28.0 ng/mL and 56.1 ng/mL, while the geometric mean AUC_{inf} values ranged from 1087 ng•hr/mL to 1716 ng•hr/mL for the full data sets. The palbociclib geometric mean V_z/F values estimated for the full data sets ranged between 2290 L and 4007 L, which is significantly greater than total body water (42 L), indicating that palbociclib extensively distributes to peripheral tissues. The palbociclib geometric mean CL/F values estimated for the full data sets ranged between 72.9 L/hr and 115 L/hr.

Applicant Population PK (PMAR269: POP PK report):
The Applicant analysis concluded that palbociclib PK was well characterized by a 2-compartment model with the mean apparent oral clearance and volume of distribution of central compartment estimated to be 60.2 L/hr (36.2% for inter-patient variability) and 2710 L (30.2% for interpatient variability), respectively. The first-order absorption rate constant and absorption lag time were estimated to be 0.367 1/hr (83.6% for inter-patient variability) and 0.658 hr, respectively.

- In these 3 studies in cancer patients where palbociclib was formulated as isethionate salt capsules, the relative bioavailability and absorption lag time were increased by 16.0% and 28.8% respectively in the fed condition (palbociclib taken with high-fat meal) compared to fasted conditions.
- Baseline body weight (range: 37.9-123 kg) and age (range: 22-89 years) were significant covariates on CL/F, and baseline body weight was a significant covariate on V_2/F. However, these covariates were not considered clinically significant.
- Based on the current analysis that included 142 patients with normal liver function, 40 patients with mild hepatic impairment and 1 patient with moderate hepatic impairment, the liver enzymes including baseline alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and total bilirubin values were not significant covariates on CL/F of palbociclib. No dose adjustment is recommended for patients with mild hepatic impairment as defined based on the NCI scale.
- Based on the current analysis that included 81 patients with normal renal function, 73 patients with mild renal impairment and 29 patients with moderate renal impairment, creatinine clearance (range: 29-185 mL/min) was not a significant covariate on CL/F of palbociclib. This is consistent with renal elimination being a minor clearance pathway of palbociclib. Therefore, no dose adjustment is recommended for patients with mild and moderate renal impairment.
- Co-administration of acid reducing agents, including proton pump inhibitors, H_2 receptor antagonist and other types of antacids with the palbociclib isethionate salt capsules did not have a significant effect on the relative bioavailability or absorption of palbociclib.

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/s/

JEANNE FOURIE ZIRKELBACH
09/11/2014

QI LIU
09/12/2014