15 September 2016
EMA/652627/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

IBRANCE

International non-proprietary name: palbociclib

Procedure No. EMEA/H/C/003853/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AAPH	auto-oxidation, 2,2'-Azobis(2-methylpropionamidine) dihydrochloride
AT	all treated as treated (population)
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
API	Active Pharmaceutical Ingredient
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC24	AUC from time 0 to 24 hours
AUCinf	AUC from time 0 to infinity
AV	Average value
BCRP	breast cancer resistance protein
BICR	Blinded Independent Central Review
BM-negative	biomarker-negative
BM-positive	biomarker-positive
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BT	blinded treatment
CABG	coronary artery bypass graft
CBR	clinical benefit response
CDC	Centers for Disease Control and Prevention
CCND1	cyclin D
CDK	cyclin-dependent kinase
CDKN2A	cyclin-dependent kinase inhibitor 2A (also known as p16INK4A), the product of the CDKN2A gene
chemo	chemotherapy
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organization of Medical Sciences
Cmax	maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CPP	Critical process parameter
CQA	Critical Quality Attribute
CR	complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
dL	deciliter
DLT	dose-limiting toxicity
DoE	Design of experiments
DOR	duration of objective response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
E-DMC	External Data Monitoring Committee
ER	(o)estrogen receptor
F	fulvestrant
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
g	gram
GC	Gas Chromatography
GI	gastrointestinal
HDPE	High Density Polyethylene
HER2	human epidermal growth factor receptor 2
Hg	Hydrargyrum (Mercury)
HPLC	High performance liquid chromatography
HR	hazard ratio
HR	hormone receptor
hr	hour
IC50	concentration associated with 50% inhibition
ICH	International Conference on Harmonisation

IHC	immunohistochemistry
IIR	Investigator-Initiated Research
IPC	In-process control ITT intent-to-treat (population)
IR	Infrared
IU	International Unit
kg	kilogram
Ki67	nuclear protein identified by the Ki67 monoclonal antibody
KF	Karl Fischer titration
L	iter or letrozole
LDH	lactate dehydrogenase
LDPE	Low density polyethylene
m	meter
Max	maximum
mBPI-sf	modified Brief Pain Inventory- short form
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
Min	minimum
mL	millilitre
mm	millimeter
mRNA	messenger ribonucleic acid
MS	Mass Spectrometry
msec	millisecond
MTD	maximum tolerated dose
n	number of patients meeting prespecified criteria
N	total number of patients
NA	not applicable
NCI	National Cancer Institute
ng	nanogram
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOR	Normal Operating Range
NR	not reached
NSCLC	nonsmall cell lung cancer
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OR	objective response
ORR	objective response rate
OS	overall survival
OTR	outside the toxicity range
PACMP	Post-approval change management protocol
PALOMA	Palbociclib Ongoing Trials in the Management of Breast Cancer
PAR	Proven Acceptable Range
PCTFE	Polychlorotrifluoroethylene
PD	pharmacodynamic
PD	progressive disease
PD-0332991	palbociclib
PFS	progression-free survival
P-gp	P-glycoprotein
Ph1P1	Phase 1 Part 1
Ph1P2	Phase 1 Part 2
Ph2P1	Phase 2 Part 1
Ph2P2	Phase 2 Part 2
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PP	Polypropylene
PPI	proton pump inhibitor
PR	partial response
pRb	retinoblastoma susceptibility gene product
PRO	patient-reported outcomes
PS	performance status
PT	preferred term
PVC	Poly vinyl chloride
QD	once daily
QT	time from the beginning of the QRS complex to the end of the T wave as shown on the electrocardiogram
QTc QT	interval corrected for heart rate

QTcB QT	interval corrected for heart rate using Bazett's correction factor
QTcF QT	interval corrected for heart rate using Fridericia's correction factor
QTcS QT	interval corrected for heart rate using a study-specific correction factor
QTPP	Quality target product profile
RAR	Response assessment report
RB / Rb	retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
RH	Relative Humidity
RP2D	recommended Phase 2 dose
RP-HPLC	Reversed-phase high performance liquid chromatography
RR	time from the peak of 1 QRS complex to the peak of the next as shown on the electrocardiogram
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
sCSR	Supplemental Clinical Study Report
SD	stable disease
sec	second
SOC	system organ class
Std	Dev standard deviation
TCGA	The Cancer Genome Atlas
TEAE	treatment-emergent adverse event
TTP	time to progression
U	Units
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
URT	upper respiratory tract
US	United States
USP	United States Pharmacopoeia
UT	urinary tract
UV	Ultraviolet
WBC	White blood cell
X-ray	roentgenology
µM	micromolar

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Limited submitted on 30 July 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Ibrance, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 September 2013.

The applicant applied for the following indication:

IBRANCE in combination with endocrine therapy is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced/metastatic breast cancer:
- with letrozole as initial endocrine-based therapy in postmenopausal women
- with fulvestrant in women who have received prior therapy

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that palbociclib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance palbociclib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on15/11/2012, 25/7/2013, 27/6/2013 and 24/7/2013. The Scientific Advice was given to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Pierre Demolis

- The application was received by the EMA on 30 July 2015.
- The procedure started on 20 August 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 November 2015.
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 November 2015.
- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 23 November 2015.
- During the meeting on 17 December 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 December 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 April 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 June 2016.
- During the PRAC meeting on 9 June 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 9 June 2016 (Annex 6).
- During the CHMP meeting on 23 June 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 August 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 1 September 2016.
- During the meeting on 15 September 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ibrance.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Breast cancer is a heterogeneous disease with subtypes having varied responses to anti-hormonal and chemotherapy treatments. Breast tumor types can be distinguished by their hormonal receptor status, with one third of tumors being ER-negative and two thirds of tumors being ER-positive. Berry, et al[1] have shown in a meta-analysis of node-positive patients in the adjuvant setting that while patients with ER-positive tumors who receive adjuvant hormonal therapy have better disease-free and overall survival than their counterparts with ER-negative tumors, advances in chemotherapy in the ER-negative setting have lessened the survival differences between these 2 groups. In this way, ER status is a strong predictive factor in identifying patients who may benefit from endocrine therapy.

ER-positive tumors make up 65% of tumors in women aged 35 to 65 years and 82% of tumors in women older than 65 years. These cancers are largely estrogen driven in postmenopausal women where the main source of the tumor's estrogen is from conversion of androgens to estrogens via aromatase enzyme action.

2.1.2. Epidemiology

Breast cancer is the most common cancer in women worldwide, with nearly 1.7 million new cases diagnosed in 2012. This cancer represents about 12% of all new cancer cases and 25% of all cancers in women[2]. In Europe, there were an estimated 464,000 new cases of breast cancer (female) in 2012 and an estimated 131,000 deaths from the disease[3].

2.1.3. Biologic features and clinical presentation

The Rb pathway in breast cancer was recently described in a publication by Witkiewicz and Knudsen. In summary it is noted that in ER-positive breast cancer, Rb pathway deregulation is generally due to aberrant Cyclin D1 expression or amplification leading to deregulation of CDK4/6, while in triple-negative disease for example, loss of the Rb gene or protein is the main mechanism (Figure xxx). It might therefore be assumed that Rb itself may not be a useful biomarker for screening of patients with ER-positive disease due to the low expected frequency of Rb loss in this population. Nevertheless, in the present pivotal study 1008 (PALOMA-2), immunohistochemical (IHC) analysis of Rb was conducted. The results in this subgroup are presented under Clinical Efficacy.

While the major activity of palbociclib is thought to be through the inhibition of the CDK4/CDK6/Cyclin D1 complex and downstream activity of Rb, the CDK4/CDK6 complex has been shown to have some Rb-independent activities (Musgrove et al, 2011) including the regulation of TSC2/mTOR pathway (Goel et al, 2016), and the regulation of FOXM1 (Castellano et al, 2016). Mechanistically, one can also hypothesize that the absence of Rb in a given tumour does not preclude the compensatory expression of other Rb family members (such as p107 and p130) (Dannenberg, 2004 and Stengel et al, 2009). Tumour cells in the absence of Rb may

[1] Berry DA, Cirrincione C, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA 2006; 295(14):1658-67.
[2] World Cancer Research Fund International. Cancer statistics; Data on specific cancers; Breast cancer. http://www.wcrf.org/cancer_statistics/data_specific_cancers/breast_cancer_statistics.php. Accessed 19 May 2014.
[3] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374-1403.

rely on an alternative pathway(s) in the CDK4/6 signalling process, for example, CDK4/SMAD3 may play a role in cell proliferation as well (Matsuura et al 2004).

2.1.4. Management

Recommendations from the American Society of Clinical Oncology Clinical Practice Guidelines, the European School of Oncology-European Society for Medical Oncology (ESO-ESMO) 2nd International Consensus Guidelines for Advanced Breast Cancer (ABC2), and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommend endocrine therapy as the preferred first-line treatment option for hormone receptor-positive, HER2-negative advanced breast cancer (except for immediately life-threatening disease or when concerns exist regarding endocrine resistance)[4,5,6]. The choice between endocrine therapies for the initial treatment is often driven by prior adjuvant endocrine therapy, potential side effects, time to progression on prior therapy, as well as the patient's menopausal status.

Currently, first-line treatment in the ER-positive, HER2-negative advanced breast cancer postmenopausal population typically includes endocrine therapies, such as letrozole, anastrozole, exemestane, fulvestrant, and tamoxifen[6] with time to progression and prolongation of PFS ranging from 5 to 15 months.[6,7,8]

Modification of oestrogen activity or synthesis represents the treatment of choice for postmenopausal women with hormone receptor-positive advanced breast cancer, particularly for those with slowly progressive disease and limited tumour-related symptoms[9].

Presently, second and subsequent lines of therapy in the hormone receptor-positive advanced breast cancer population typically include endocrine therapies, such as tamoxifen, fulvestrant, steroidal or nonsteroidal AIs, progestins, and androgens[6]. In the pivotal studies for the present application, letrozole and fulvestrant were used as endocrine backbone therapy and comparators.

Letrozole (Femara) is an oral nonsteroidal aromatase inhibitor (AI) approved worldwide for the first-line treatment of postmenopausal women with hormone receptor-positive advanced breast cancer.

Fulvestrant (Faslodex) is a potent anti-oestrogen drug that is currently indicated for the treatment of postmenopausal women with metastatic hormone receptor-positive breast cancer following the failure of anti-oestrogen therapy.

In addition, postmenopausal women with hormone receptor-positive, HER2-negative breast cancer that have progressed after treatment with letrozole or anastrozole may also receive everolimus (Afinitor) in combination with exemestane.

Chemotherapy should be reserved for cases of rapidly progressive disease or proven endocrine resistance[6].

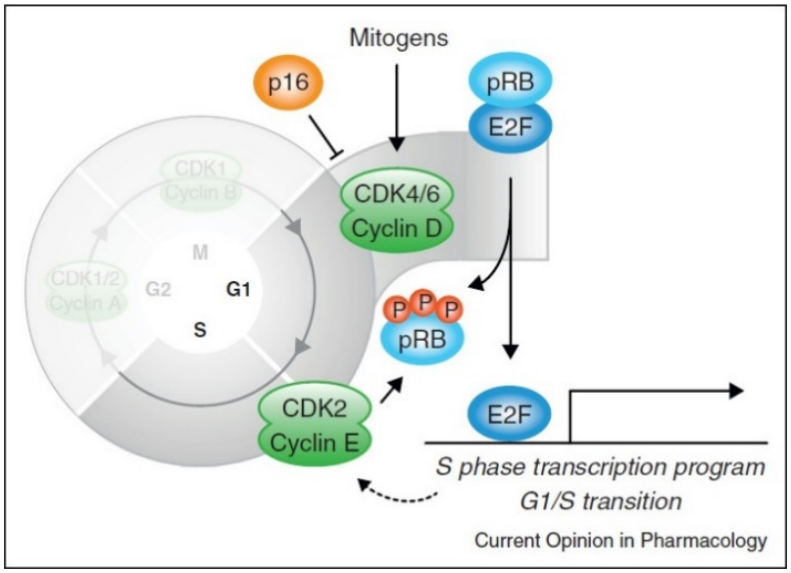
[4] Partridge AH, Rumble RB, Carey LA, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Practice Guideline. J Clin Oncol 2014; 32(29):3307-29.
[5] Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Ann Oncol 2014; 25(10):1871-88.
[6] National Comprehensive Cancer Network (NCCN) Breast Cancer Version 2.2015.
[7] Bergh J, Jonsson PE, Lidbrink EK, et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. J Clin Oncol 2012; 30(16):1919-25.
[8] Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. N Engl J Med 2012; 367(5):435-44.
[9] Burstein HJ, Harris JR, Morrow M. Malignant tumors of the breast. In: De Vita VT Jr, Lawrence TS, Rosenberg SA, editors. Cancer, Principle and Practice of Oncology, 9th Edition, Lippincott Williams and Wilkins; 2011; 1401-46.

About the product

Palbociclib (also referred to as PD-0332991 and PF-00080665) is an oral, selective and reversible inhibitor of cyclin-dependent kinase 4 and 6 (CDK4 and CDK6). Palbociclib has the molecular formula of C24H29N7O2 and a molecular weight of 447.54 Daltons.

During cell proliferation, the G1 to S transition of the cell cycle is under the control of CDKs which are activated through specific complex formation with regulatory cyclins. CDK 4 and CDK 6 are activated by binding to Cyclin D in early G1 phase. Phosphorylation of pRb and other members of the pocket protein family (p107 and p130) by active cyclin-CDK complexes leads to release of E2F and DP transcription factors and transcription of S-phase genes. This leads to subsequent cell cycle G1/S transition for initiation of cell proliferation[10]. Inhibition of CDK 4/cyclin D1 (CCND1) kinase activity as well as CDK 6/cyclin D1 kinase would prevent DNA synthesis and thus inhibits cell division.

Figure 1 - CDK4/6 Cell Cycle Pathway



Greater than 90% of human tumours subvert these control mechanisms through a variety of genetic and biochemical adaptations including up-regulation of CDK4/CDK6, amplification of the D-type cyclins, or down-regulation of p16INK4A, an endogenous inhibitor of CDK4/CDK6. Thus, tumours that depend on the activity of CDK4 for proliferation and survival may be highly sensitive to inhibition of this pathway.

There is a strong link between the action of oestradiol and cellular proliferation. Anti-oestrogen-induced growth arrest of ER+ breast cancer cells is accompanied by decreased cyclinD1. In ER+ cancer cell lines, combination treatment with palbociclib and anti-oestrogen agents led to increased inhibition of DNA synthesis and cell proliferation, and also enhanced the induction of senescence[11]. Mechanistically, the combination benefit may arise from the convergent inhibition of Rb phosphorylation via two routes – direct repression of CDK4/CDK6

[10] Weinberg RA. The retinoblastoma protein and cell cycle control. Cell 1995; 81:323-30.
[11] Hui R, Cornish AL, McClelland RA, et al. Cyclin D1 and estrogen receptor messenger RNA levels are positively correlated in primary breast cancer. Clin Cancer Res 1996; 2:923-8.

activity by palbociclib, and indirect inhibition of CDK4/CDK6 following reduction of cyclinD1 levels by anti-oestrogen agents.[12]

The combination of palbociclib with tamoxifen has also been tested in vitro in ER-positive human breast cancer cell lines indicating a synergistic interaction[11].Taken together, this evidence provided a biologic rationale for evaluating the combination of palbociclib with antihormonal therapy in patients with ER-positive, HER-2 negative breast cancer.

- *Claimed indication and recommendation for use and posology.*

The initially applied indication was:

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

- with letrozole as initial endocrine-based therapy in postmenopausal women
- with fulvestrant in women who have received prior therapy

The revised and approved indication is:

Ibrance is indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer:

- in combination with an aromatase inhibitor;
- in combination with fulvestrant in women who have received prior endocrine therapy.

In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

The recommended dose and schedule is 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment with food.

Letrozole or fulvestrant should be administered according to the respective approved dose schedules, as reported in the label.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 75 mg, 100 mg or 125 mg of palbociclib as active substance.

Other ingredients are:

Capsule content
Microcrystalline cellulose
Lactose monohydrate
Sodium starch glycolate type A
Colloidal anhydrous silica
Magnesium stearate

[12] Finn RS, Dering J, Conklin D, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res 2009; 11(5):R77.

Capsule shell
Gelatin
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)

Printing ink
Shellac
Titanium dioxide (E171)
Ammonium hydroxide (28% solution)
Propylene glycol
Simeticone

The product is available in PVC/PCTFE/PVC/Al blisters or HDPE bottles with a polypropylene (PP) closure as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of palbociclib is 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one corresponding to the molecular formula $C_{24}H_{29}N_7O_2$. It has a relative molecular weight of 447.54 Daltons and the following structure:

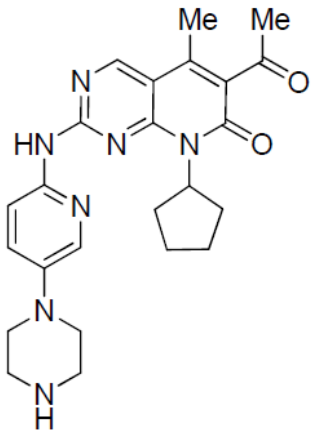


Figure 2. Chemical structure of palbociclib.

Palbociclib is an achiral molecule. The molecular structure of palbociclib has been confirmed by a combination of spectroscopic data. Evidence of key functional groups was provided by infrared (IR) spectroscopy. Mass spectrometry (ESI- MS and ESI-MS/MS) was used for the determination of the mass for the molecular ion and assignment of ions in the mass spectrum. The proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectroscopy were used to assign protons to each corresponding carbon, proton to proton assignments, and distinguish between the CH and CH_2 signals. The molecular structure of palbociclib was independently confirmed using single crystal X-ray diffraction. The UV/Vis spectrum is consistent with the compound structure.

The active substance is a non-hygroscopic yellow to orange crystalline powder that is classified as BCS Class II compound based on the Biopharmaceutical Classification System. It is slightly soluble in dimethyl sulfoxide and dimethylformamide, very slightly soluble in methanol and water.

Palbociclib isethionate was prepared and used for toxicology and clinical studies through Phase 2. However, its physical properties were deemed unsuitable for commercial development. Therefore, the free base of palbociclib, which was found to have excellent physical and chemical stability, was selected for commercial use.

Palbociclib exhibits polymorphism. The crystalline anhydrous Form A of palbociclib free base is the thermodynamically more stable form within the temperature ranges that are relevant to manufacturing and storage conditions and was the form selected for development and commercialisation.

Manufacture, characterisation and process controls

Palbociclib is synthesized in six main steps using well defined starting materials with acceptable specifications. The starting materials were redefined during the evaluation upon request from the CHMP. Their redefinition was requested on the basis that the originally proposed starting materials were the result of a custom made synthesis and the limited steps carried out under GMP hindered the regulatory oversight to ensure the quality of the active substance throughout the product lifecycle. These are now considered intermediates.

The control strategy for non-critical steps includes a list of non-critical parameters and their respective acceptable ranges. Design spaces have not been claimed as an element of control strategy in non-critical steps. The control strategy for critical steps includes a design space that is represented by the acceptable ranges of the process parameters.

In-process controls (IPC) have been described together with specifications for isolated intermediates.

An enhanced development program in line with ICH Q8 and ICH Q11 was conducted for the development of palbociclib. A structured quality risk management approach was employed, to identify potentially critical material attributes and critical process parameters and assess their impact on drug substance quality based on knowledge gained through development of palbociclib and scientific literature. The active substance critical quality attributes (CQAs) were identified based on the understanding of the drug product quality target product profile (QTPP).

The critical process parameters were also identified.Although the applicant proposed proven acceptable ranges (PAR) for the critical process steps in the original submission, during the review the applicant agreed to register the process parameter ranges in these critical steps as design spaces. This was supported by univariate and multivariate studies.

No design space was claimed for the chemical steps from the newly defined starting materials as these steps are considered non-critical.

The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. A discussion on potential impurities that may arise from starting materials, side-reaction or degradation has been provided. This also included a detailed explanation of the origin, fate, purge and control of these impurities, including genotoxic impurities. In this regard, a structure-based assessment was performed on all starting materials, intermediates and impurities in the palbociclib commercial manufacturing process. The structures were evaluated to identify potentially genotoxic impurities. Based on this assessment, there are no genotoxicity safety concerns for any impurities of the active pharmaceutical

ingredient. In addition, since palbociclib is intended to treat patients with advanced breast cancer, ICH M7 does not apply. The limits for each specified impurity are in line with ICH Q3A or suitably justified.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. Palbociclib isethionate was prepared and used for toxicology and clinical studies through Phase 2. However, its physical properties were deemed unsuitable for commercial development. Therefore, the free base of palbociclib, which was found to have adequate physical and chemical stability, was selected for commercial use. The active substance is packaged in two sealed, low density polyethylene (LDPE) antistatic liners. The bagged material is then inserted in a high density polyethylene (HDPE) drum. The LDPE liner is suitable for pharmaceutical or "in contact with food" use. It complies with Regulation 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, particle size (laser light diffraction), identification (IR, HPLC), assay (HPLC), water content (KF), residual solvents (GC, HPLC), inorganic impurities: residue on ignition (Ph Eur), palladium content (ICP-OES) and heavy metals (Ph Eur), and organic impurities (RP-HPLC).

The active substance specification was established based on understanding of the finished product Quality Target Product Profile (QTPP) (see pharmaceutical development section) and the active substance critical quality attributes (CQA). The CQA identified are: identification, assay, impurities, residual solvents, palladium, heavy metals, residue on ignition, water and particle size.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The omission of a test for polymorphism was justified based on the fact that Form A is the thermodynamically favoured form under relevant manufacturing and storage conditions, the supportive batch analysis data and primary stability studies which showed no changes after 18 months of storage at 25 °C/60% RH.

The omission of tests for certain residual solvents has been justified based on batch analysis data from the commercial process or the previous process.

The omission of microbiological testing has also been justified. Palbociclib is a non-sterile active substance. The manufacturing process includes multiple steps which are able to reduce most microorganisms. Omission of microbiological testing is also supported by batch data for release of clinical and registration lots.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis data on several batches palbociclib manufactured according to a previous process (which differed from the one proposed for commercial use, but is considered equivalent to the commercial process) and several batches from the commercial process at pilot and commercial scale were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three primary stability pilot scale batches of active substance from the proposed manufacturer, produced according to a previous process (equivalent to the proposed commercial process) and stored in the

intended commercial package for 18 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Supportive stability data were also provided from two pilot scale batches synthesized using two previous processes and a pilot scale batch manufactured using the commercial process stored for up to 24 months at 25 ºC / 60% RH and for up to 6 months at 40 ºC / 75% RH, respectively.

The following parameters were tested: appearance, assay, impurities, water content and solid form (PXRD). The analytical methods used were the same as for release, with the addition of PXRD, and were stability indicating.

No significant changes or trends were observed in any of the parameters tested through 18 months and 6 months of storage at 25 °C/60% RH and 40 °C/75% RH, respectively, compared to the initial values.

Results under stress conditions were also provided on batches manufactured according to different synthetic routes used during development exposed to high temperature and high humidity. One of those batches was also subjected to high temperature and low humidity. No significant change in appearance, assay, or purity was observed.

Photostability testing following the ICH guideline Q1B was performed on one batch. Samples were tested for appearance, identification, assay and impurities. All parameters remained unchanged versus the dark control confirming that palbociclib is not light sensitive.

Samples of palbociclib were also evaluated under forced degradation conditions to identify the primary degradation products and to evaluate the suitability of the assay and purity methods. Individual samples of the solid drug substance or solutions of active substance were exposed to acid, base, oxidation, heat, and simulated sunlight. Samples were tested for assay and impurities. Degradation was only observed in the hydrogen peroxide and AAPH studies. No significant degradation was observed for acidic or basic conditions. In the solid state, no significant degradation was observed under elevated temperatures or light exposure. The assay and purity method for palbociclib drug substance was shown to be specific, selective and stability-indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months without any storage precaution packaged and sealed in LDPE anti-static liners within a HDPE drum.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Palbociclib is provided as immediate release hard gelatin capsules using a common blend in dosage strengths of: 75 mg (Size #2, light orange body/ light orange cap) in which the body is printed with “PBC 75” and the cap printed with “Pfizer” in white; 100 mg (Size #1, light orange body/caramel cap) in which the body is printed with “PBC 100” and the cap printed with “Pfizer” in white; and 125 mg (Size # 0, caramel body/caramel cap) in which the body is printed with “PBC 125” and the cap printed with “Pfizer” in white.

The drug product is packaged in polychlorotrifluoroethylene (PCTFE) /aluminum foil blister system or in high density polyethylene bottles.

An enhanced development approach was used for the design and development of palbociclib drug product. A combination of risk based assessments, laboratory studies, and manufacturing experience across a range of scales and equipment types has been used using QbD principles to gain a comprehensive understanding of the formulation and process conditions and their impact on the quality attributes of the palbociclib drug product.

The quality target product profile (QTPP) was defined as immediate release capsules for once a day oral administration containing 75 mg, 100 mg and 125 mg of palbociclib, that meet compendial and other relevant quality standards, have a minimum shelf life of 24 months and are packaged in polychlorotrifluoroethylene (PCTFE)/aluminium foil unit dose blisters or HDPE bottles. The strengths should be differentiated by capsule shell size, colour and printing.

As mentioned above, palbociclib is a BCS Class II compound (low solubility and high permeability). The maximum dose of 125 mg does not fully dissolve in 250 mL of media over the range of pH 1 to pH 6.8, but can be fully dissolved at pH values below 4.3.

As indicated in the active substance section of this report, crystalline anhydrous Form A of palbociclib free base was selected for development as it was the thermodynamically most stable form at room temperature. All Phase III clinical supplies and registration stability batches used crystalline anhydrous Form A of the free base.

The active substance particle size is controlled in the active substance specification. Dissolution and pharmacokinetic studies were conducted to examine the impact of particle size of palbociclib free base on the dissolution and relative bioavailability of the capsules. It was concluded that the active substance particle size does not impact finished product relative bioavailability, dissolution and stability within the proposed commercial active substance particle size specification.

An excipient compatibility screening study with conventional immediate release formulation excipients was completed under accelerated stability conditions using binary mixtures of the active substance and excipient formed into compacts. All excipients selected for the commercial formulation are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. Namely, microcrystalline cellulose and spray dried lactose monohydrate are used as diluents; sodium starch glycolate as disintegrant; magnesium stearate as lubricant; and colloidal silicon dioxide as glidant.

Supporting development data and registration stability studies demonstrated the suitability of the selected excipients.

The history of the formulations used in the clinical program was also described. The differences between those clinical formulations were explained (salt vs free base, minor changes in manufacturing process, development sites versus commercial site).

Early clinical trials (pivotal study 1003) used capsules containing the palbociclib isethionate salt active substance (manufactured at the development sites).

To support Phase 3 clinical studies, formulated capsules containing the free base drug substance form were developed. With the exception of capsule shell printing, the final Phase 3 free base capsule formulation is qualitatively and quantitatively equivalent to the registration stability and proposed commercial product. Bioequivalence between the isethionate capsule taken under fasted condition and the proposed commercial free base capsule taken under fed condition was demonstrated in pivotal bioavailability Study 1036. Bioequivalence in the fasted state was demonstrated between initial Phase 3 free base and final Phase 3 free base in Study 1020. Based on the data submitted, provided commercial formulation is taken with food, as recommended in the SmPC 4.2. Method of administration) bioequivalence is considered demonstrated between the different formulations (for details on bioequivalence studies and discussion on food effect, see clinical section of this report).

Overall, a satisfactory justification has been presented with regards to the choice of the dissolution media and parameters. Dissolution profiles for commercial batches of the three strengths (registration stability batches)

using the proposed quality control dissolution method have been provided. All profiles are similar and meet the proposed specification.

For each unit operation a risk assessment was conducted to determine potential relationships between related process parameters and quality attributes of the finished product. The critical process parameters have been adequately identified. Apost-approval change management protocol (PACMP) to qualify an alternative drug product encapsulator for the production of palbociclib capsules 75, 100 and 125 mg at the proposed manufacturing site has been submitted and is considered acceptable.

The scale up strategy has been adequately described.

The primary packaging is polyvinyl chloride (PVC)/polychlorotrifluoroethylene (PCTFE)/PVC blisters with aluminum foil backing and high density polyethylene (HDPE) bottles with polypropylene (PP) closures. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Palbociclib immediate release 75 mg, 100 mg, and 125 mg capsules are manufactured using a standard manufacturing processwhich includes blending, milling, dry granulation, encapsulation and packaging using equipment commonly available in the pharmaceutical industry. All strengths are manufactured from a common blend.

The manufacturing process has been described with sufficient detail in terms of equipment and process parameters (critical and non-critical process parameters). The proposed ranges for process parameters have been established in a multivariate manner. Although the applicant initially did not claim a design space, during the review it was agreed that they represented a design space. Data provided in pharmaceutical development are sufficient to support the proposed ranges. In view of the fact that DoEs have been conducted at industrial scale (40 – 100% of the commercial scale) supported by satisfactory scale up discussion, no design space verification was deemed necessary. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Since palbociclib capsules are manufactured by a standard manufacturing process, no formal process validation data has been included in the dossier. A process validation scheme has been presented in 3.2.R.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (LC-retention time, LC-UV Spectra), assay (LC), degradation products (LC), dissolution, uniformity of dosage units (Ph Eur), water content (Ph Eur), microbial limits (Total Aerobic Microbial Count, Total Yeasts and *Escherichia coli*) (Ph Eur).

This specification is also applicable to stability testing for the following stability indicating tests: appearance, assay, degradation products, dissolution, and microbial limits.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis results are provided for several batches palbociclib capsules manufactured at different stages of development confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three batches of palbociclib capsules from each strength manufactured at the proposed manufacturing site, stored for 18 months under long term (25 ºC / 60% RH) and intermediate (30°C/75% RH) conditions at and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. All batches have identical drug product composition, were manufactured using the commercial process described and were stored in container closure systems representative of the commercial packaging (HDPE bottles and PCTFE/Aluminium foil blister).

Samples were tested for appearance, assay by HPLC, degradation products by HPLC, dissolution, water content and microbiological quality. Tests for water content and microbial enumeration were performed for information only. The analytical procedures used are stability indicating.

The stability data show there is no significant effect on the physical and chemical characteristics of capsules stored in HDPE bottles or in blister at the studied conditions. The level of the main degradant increases slightly at intermediate and accelerated conditions after 18 months. Nevertheless, the values found remained well within the specification limits under all conditions at all points.

Water content, which was monitored for information only, also increased on storage, but remained below the release specification. No consistent trends were observed for other attributes.

Supportive stress studies were performed on palbociclib 100 mg capsules stored in an open glass container included thermal, thermal and humidity, and photolysis exposure. These studies confirm that the assay and purity method is selective and stability indicating. Mass balance after treatment was close to 100% recovery for all samples.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples were tested for appearance, assay, degradation products, dissolution and water content. No significant changes were observed in any of the parameters tested for photostability study. Two degradation products observed under the strong light conditions used in the degradation study were not observed in the registration photostability study. Therefore, the drug product is considered as photo-stable and no precautionary packaging or labeling is required.

An in-use open bottle study was carried out on one batch of each strength in HDPE bottles. The bottles were opened, with the cap and seal removed and stored at 30 °C/75% RH for 30 days. Samples were tested for appearance, assay, degradation products, dissolution, and water content. No significant changes in chemical or physical stability were observed except for water content that but remained within the specifications. No in-use restriction is required as all the results met the acceptance criteria.

A bulk holding time study is being conducted to establish a period of time in which the bulk capsules can be held without additional retesting conducted prior to packaging. The data do not show any negative impact and support the proposed holding time of 18 months.

Based on available stability data, the proposed shelf-life of 24 months and with no special storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The proposed redefined starting materials for the synthesis of palbociclib are considered acceptable. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. Design spaces have been proposed for several steps in the manufacture of the active substance and finished product. A combination of risk assessments, laboratory studies, and manufacturing experience across a range of scales and equipment types has resulted in a comprehensive understanding of the formulation and process conditions and their impact on the quality attributes of the finished product. A PACMP to qualify an alternative drug product encapsulator for the production of palbociclib capsules at the proposed manufacturing site has been submitted.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

Palbociclib nonclinical pharmacology, safety pharmacology, pharmacokinetics and toxicology were studied. The applicant indicated that pivotal safety studies were executed under GLP.

The applicant has received several CHMP advices. Two of these involve non-clinical questions. In the advice given in 2012 the applicant requested the committee's view on the non-clinical program in relation to the intended indication. At this time the CHMP agreed that the completed and planned non-clinical studies would be sufficient for an MAA.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro

Biochemical characterization

The binding and inhibition data show that palbociclib is a selective inhibitor of the CDK4 and CDK6 with a 50% inhibitory concentration of between 0.011 and 0.015 μM for CDK4/6 and their ligands.

In a broader panel of kinase also binding to other, off-target, kinases was observed with CLK1 showing the highest inhibition at the lowest concentration (clinically relevant).

Cell line characterization

Palbociclib was tested *in vitro* on molecularly characterized human breast cancer cell lines. Results from these experiments indicated that those cell lines that are more sensitive to palbociclib anti-proliferative effects have low levels of CDKN2A and high levels of pRb and CCND1, while resistant cell lines showed the opposite characteristics. Sensitive cell lines in this panel represented mostly the luminal ER-positive subtype[13].

From a functional point of view, palbociclib arrests the cell cycle at G1, inhibits cell proliferation and induces senescence in a broad panel of Rb+ cancer cell lines.

The data shows that palbociclib increases the percentage of cell in G1 with increased exposure. However, in cell lines which lack a functional Rb no effect were observed.

When combined with fulvestrant an additive effect was observed compared with either drug alone. Also, the data suggests that the additive effects is due to the direct repression of CDK4/6 by palbociclib and the reduction of cyclinD1 (ligand to CDK4/6) by the anti-oestrogen drugs. Combination studies also show that cultures released from drugs for four days retained a significant inhibition of DNA synthesis in comparison to single-drug cultures.

In vivo

Anti-tumour activity was registered by tumour growth delays in tumour bearing mice. The data also shows that palbociclib exhibit no activity in Rb-negative tumours, reinforcing the *in vitro* observations that intact Rb is critical for palbociclib activity. This is also substantiated by data showing correlation between phospho-Rb inhibition, drug steady state PK and anti-tumour activity.

When combined with letrozole palbociclib led to near-tumour stasis in a transplanted human tumour murine model. The data also shows that combination treatment enhances the modification of Rb in comparison to single agent treatment. The PK data from this study also suggests no evidence of drug:drug interaction, confirming that the potentiation observed from this combination is not due to increased drug exposure.

Secondary pharmacodynamic studies

Secondary PD shows that palbociclib is able to bind a number of unrelated receptors.

PF-05089326, metabolite M17, showed binding to a wide range of receptors.

[13] Finn RS, Dering J, Conklin D, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res 2009; 11(5):R77

Safety pharmacology programme

The potential for palbociclib to cause neurofunctional effects was evaluated in Sprague-Dawley rats following administration of a single oral dose. Decreased exploratory behaviour during the open-field assessment was considered palbociclib-related at 300 mg/kg. Consistent with decreased exploratory behavior and hypoactivity, a decrease in activity (although not statistically significant) was observed at 300 mg/kg. Mean total distance and number of vertical movements were 19% and 18% less than controls, respectively. Palbociclib had no effect on neurofunction in rats at 30 or 300 mg/kg, but a decrease in locomotor activity was identified at 300 mg/kg.

The potential effect of palbociclib on pulmonary function was assessed following administration of a single intravenous dose to anesthetized Beagle dogs. Two of 4 animals administered palbociclib at 5 mg/kg stopped breathing less than 2 minutes after initiation of drug infusion. Significant increases in minute volume and respiratory rate (0.6- to 4.6-times relative to the controls) were also observed at 4 to 8 minutes postdose and at 18 to 26 minutes postdose at 5 mg/kg. Altogether, a single IV dose of palbociclib in anesthetized dogs at 5 mg/kg caused significant effects on pulmonary parameters, including increases in minute volume and respiratory rate, and decreases in compliance, peak expiratory flow, and tidal volume. The effects were transient, appeared related to peak-plasma concentrations of drug (≥2040 ng/mL; ≥843 ng/mL unbound, based on fu 0.413 in the dog, and were consistent with respiratory depression.

The potential for palbociclib to cause cardiovascular effects following administration of a single dose was evaluated in conscious Beagle dogs. The data show that single doses of palbociclib were associated with QTc interval prolongation in dogs at ≥3 mg/kg where plasma concentrations were ≥162 ng/mL (67 ng/mL unbound based on fu of 0.413 in dogs, 4 times clinical C_{max}[17 ng/mL]). Palbociclib also caused increases in QT interval, decreases in HR with a corresponding increase in RR interval, and a modest increase in systolic blood pressure at ≥10 mg/kg (mean C_{max} at 10 mg/kg was 140 ng/mL unbound).

The findings in telemetered dog were addressed in the clinic by ECG recordings performed during the Phase1/2 study 1001, 1002, 1003 and 1010. A PK/PD analysis of the relationship between palbociclib exposure and ECG data was conducted using pooled data from Studies 1001, 1002, and 1003. A positive correlation was observed between QTc and palbociclib concentration. These data are further assessed in the clinical section.

Pharmacodynamic drug interactions

Pharmacological interaction between palbociclib and anti-estrogen agents such as fulvestrant and letrozole has been described above. No additional pharmacodynamic drug interaction studies have been conducted (see non-clinical discussion).

2.3.3. Pharmacokinetics

Absorption

The single-dose pharmacokinetics of palbociclib after oral or IV routes of administration were characterized in male S-D rats and Beagle dogs (toxicology species), and in male cynomolgus monkeys. Palbociclib was administered orally as the isethionate salt, while the dose was expressed as the free base equivalents.

Table 8 - Pharmacokinetic Parameters of Palbociclib in Male Rats, Dogs, and Monkeys After Single IV or Oral Administration

Species (Strain)	Dose (mg/kg)	Route	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	CL (mL/min/kg)	V_{ss} (L/kg)	AUC_{inf} (ng·h/mL)	F[c] (%)
Rat (S-D)	1	IV[a]	--	--	2.2 (0.34)	38.0 (3.79)	5.65 (0.736)	442 (46.7)	--
	5	IV[a]	--	--	2.6 (0.19)	37.4 (1.58)	7.07 (0.317)	2230 (103)	--
	5	Oral[b]	178 (47.4)	3.5 (1.9)	2.1 (0.12)	--	--	1200 (393)	56.1
	20	Oral[b]	1110 (61.8)	5.0 (1.2)	2.8 (0.36)	--	--	10800 (651)	--
	50	Oral[b]	1660 (245)	4.5 (1.9)	4.9 (1.4)	--	--	23000 (6740)	--
	200	Oral[b]	2240 (166)	30 (0)	--	--	--	76800[d] (8900)	--
Dog (Beagle)	1	IV[a]	--	--	11 (0.29)	7.22 (0.853)	6.22 (0.789)	2330 (258)	--
	20	Oral[b]	664 (24.7)	8.7 (3.1)	21 (5.7)	--	--	17400[d] (6900)	36.9 (12.4)
Monkey (Cynomolgus)	0.5	IV[a]	--	--	4.7 (1.4)	13.4 (0.896)	5.05 (1.01)	624 (42.8)	--
	2.66	Oral[b]	86.2 (31.0)	2.7 (1.2)	5.3 (0.89)	--	--	768 (150)	23.1 (3.6)

Note: Data are mean (standard deviation); n = 3.
-- = Data not applicable or available; AUC_{inf} = Area under concentration-time curve from time zero to infinity postdose; AUC_t = Area under concentration-time curve from time zero to 24 hours postdose for intravenous dose and 48 hours postdose for oral dose; CL = Systemic plasma clearance; C_{max} = Peak plasma concentration; D5W = 5% dextrose in water; DMA = Dimethylacetamide; F = Bioavailability; IV = Intravenous; n = Number of animals; SD = Standard deviation; S-D = Sprague-Dawley; $t_{½}$ = Apparent terminal elimination half-life; T_{max} = Time to reach C_{max}; V_{ss} = Apparent volume of distribution at steady state.
a. IV vehicle/formulation solution = 5% DMA/25% PEG/70% D5W.
b. Oral vehicle/formulation = 95%, 0.5% methylcellulose/5%, PEG 200 as a suspension for rat and monkey studies and as a capsule for the dog study.
c. F (%) = ([AUC_{inf} (Oral) × Dose (IV)] / [AUC_{inf} (IV) × Dose (Oral)]) × 100.
d. Value represents AUC_t.

Distribution

Radioequivalents were widely distributed into tissues and fluids, particularly in uvea, meninges, bile, harderian gland, preputial gland, liver, lacrimal gland, lung, thyroid, and spleen, with levels consistently greater than those observed in blood. These findings were consistent with the large V_{ss} that exceeded total body water in rats.

The extent of in vitro binding of palbociclib to mouse, rat, rabbit, dog, and human plasma proteins, human serum albumin (HSA), and α1-acid glycoprotein (AAG) was determined using equilibrium dialysis. Protein binding of palbociclib was moderate to low in the evaluated species, with the overall mean fraction unbound (fu) of 0.159, 0.125, 0.0733, 0.413, 0.147, 0.622, and 0.646 in mouse, rat, rabbit, dog, human plasma, HSA, and AAG, respectively.

In vitro, blood-to-plasma ratios of palbociclib in mouse, rat, dog, monkey, and human were 1.13, 0.97, 1.0, 1.04, and 1.63, respectively, indicating a modest preferential distribution of palbociclib to blood cells over plasma in human. In contrast, similar distribution of palbociclib between blood cells and plasma was observed in mouse, rat, dog, and monkey whole blood.

Metabolism

The major circulating metabolite for palbociclib in humans was M22, accounting for 14.8% of circulating radioactivity, this metabolite was not detected in rat or dog plasma. It was however detected after incubation with rat hepatocytes and in rat urine <2%. However, since M22 is a glucuronide conjugate of palbociclib it is of low toxicological concern. The other identified metabolites observed in human plasma (M11, M12, M16, M17, M24, M25, and M26), individually, showed an abundance ranging from 1.0% to 4.7%, which were less than 10% of circulating radioactivity and were considered as minor metabolites. In general, the human plasma recovery is poor with a large portion of radioactivity being uncounted for. This could be a potential concern, however the present indication falls under the S9 guide line and in such cases separate testing of metabolites is generally not warranted, especially if positive in embryo foetal toxicity testing (assessed below). However, if palbociclib is to be used in other indications, not falling under the S9 guide line, additional testing might be warranted.

Excretion

In rat, recovery of radioactivity was essentially complete (92.6% in males and 94.3% in females, respectively) by 168 hours after dosing, with 84% and 93.6% of the dose recovered in feces. The high fecal recovery was primarily via biliary excretion of the radioactivity, as evidenced by a recovery of 50.1% (male) and 81.3% (female) of dose in bile of BDC rats over 48 hours postdose. Feces recovery was similar in dog. In healthy humans, feces were also the major route of excretion accounting for 74.1% of the dose, with urine accounting for 17.5% of the dose.

2.3.4. Toxicology

The rat and dog were the selected rodent and non-rodent species, respectively, for general toxicity studies based on their suitable pharmacokinetic profiles and representation of the major metabolism pathways in humans.

Single dose toxicity

Single doses up to 500 mg/kg were tolerated in the rat. Body weight loss, foecal changes, hypoactivity, dyspnoea, and mortality were observed at ≥1000 mg/kg in the rat. In dog, emesis, decreased body weight and food consumption, foecal changes, and haematology changes (decreases in red blood cell [RBC] parameters, leukocytes, and platelets) that correlated with decreased bone marrow cellularity were observed in animals that received single doses of ≥30 mg/kg.

Repeat dose toxicity

Morbidity and mortality

In rat mortality was observed at doses ≥100 mg/kg/day. The cause of the moribund condition was attributed to degeneration and/or inflammation in one or more of the feet; microscopic findings included myxomatous degeneration, vacuolated macrophage infiltrates, and neutrophilic inflammation. There was no palbociclib-related morbidity in the dog studies.

Non Clinical observations

In rat, dose-depended at ≥50 mg/kg/day clinical signs of toxicity included chromodacryorrhoea, dyspnoea, hypoactivity, decreased skin turgor, pallor, rales, salivation, swelling of the forepaws and urogenital area, rough pelage, thin, red and urine staining, fecal staining small testes; swollen legs, abdomen, penis, or perioral area; lateral recumbence; nonformed faeces; clear or red oral discharge; pale eyes, feet, ears, or oral mucosa; cold skin (hind feet); discoloured (red) skin and haircoat, and foecal changes (absent, reduced, discoloured, and/or soft). The clinical signs were more pronounced in males. Body weights were decreased by 5% to 38% (relative to control) in males at ≥10 mg/kg/day body weights were only slightly decreased in females. Similar decreases were observed in food consumption. Clinical signs, body weight, and food consumption changes were reversible. Cataracts, consisting of anterior cortical, incomplete, or complete cataracts were identified from slit lamp biomicroscopy in male rats only at ≥30 mg/kg/day.

In dog, emesis occurred periodically during the dosing period in males in all palbociclib-treated groups. A slight increase in the incidence of soft stools and red/swollen pinna(e) was noted at 2.0 mg/kg/day relative to controls. Slight decreases in body weight gain were also noted. Weight gain was reversible.

Haematology

Minimal to marked decreases included leukocytes (neutrophils, monocytes, eosinophils, and/or lymphocytes), red blood cell parameters, and platelets, and were observed with dose-related severity in studies of ≥2 weeks duration in both rats and dogs. Also, increased corpuscular haemoglobin, corpuscular volume, red cell distribution and platelet count were observed. Flow cytometric analysis of bone marrow also showed decreased total nucleated cells in both myeloid and erythroid lineages. Not all parameters were fully reversible after recovery.

Clinical chemistry

At high-doses in rat (100 mg/kg/day, 15-week) and dog (≥3 mg/kg/day, 39-weeks) several parameters were effected including increased aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, albumin concentrations, A/G ratio, insulin values, glucose, urea nitrogen and aspartate.

Histopathology

Male reproductive organ effects included degeneration of seminiferous tubules, hypospermia and increased intratubular cellular debris of the epididymis, decreased secretion in seminal vesicles, and atrophy, decreased content, and/or degeneration/necrosis (moribund animal only) in the prostate. The effects on male reproductive organs were seen in the rat and/or dog (prostate and seminal vesicle changes in the rat only) with dose-related severity (minimal to severe) in studies of ≥3 weeks duration. These findings are regarded as only partly reversible.

Hyperglycemia and glucosuria (up to +4 [≥1000 mg/dL]) correlated with pancreatic islet cell vacuolation and secondary effects in the kidney (tubule vacuolation) following 15 weeks of intermittent dosing in rats, and after 27 weeks of intermittent dosing the effects on glucose homeostasis and the pancreas were associated with secondary effects in the eye (cataracts/lens degeneration), incisor teeth (ameloblast degeneration), kidney (tubule vacuolation), and adipose tissue (atrophy) of rats. The vacuolation in the pancreas was shown to be due to the loss of beta cells, and correlated with a decrease in serum insulin and C-peptide. These toxicities were observed at clinically relevant exposures and the damage related to glucose metabolism persisted after recovery.

Additional findings considered to be of less adverse nature included; gastrointestinal changes, cellular vacuolation in multiple tissues (liver, adrenal and respiratory), decreased mucous in glands of the glandular stomach (mild) and non-glandular stomach, phospholipidosis vacuolation (lung, lymphnode and bone marrow) and adrenal cortical cell hypertrophy.

Genotoxicity

The data shows that palbociclib caused micronuclei formation in an in vitro micronucleus assay in CHO-WBL cells that kinetochore analysis identified as due to an aneugenic mechanism. Also, significant increases in micronucleated polychromatic erythrocytes were observed in male rats at doses ≥100 mg/kg/day in a micronucleus assay.

Carcinogenicity

In accordance with ICH S9, carcinogenicity studies with palbociclib have not been conducted given the intended treatment of patients with advanced cancer.

Reproduction Toxicity

Data from repeat-dose toxicity studies show macroscopic and microscopic impact on male reproductive organs, this was also observed in the dedicated male fertility study. However, the toxicity in the male reproductive organs did not influence mating and fertility of the treated males, ovarian and uterine parameters of the untreated females, or embryonic survival at any dose level. In the pivotal embryo-foetal developmental studies both maternal and foetal toxicity was observed in both species. Maternal toxicity generally consisted of decreased body weight gain and decreased food consumption. Thus, it can be concluded that sufficiently high doses were tested, as maternal toxicity was observed and the exposure in rat at the higher doses corresponds to 4 times the human exposure while, in rabbit, the exposure at the higher dose was 9 times the human exposure. In the offspring, in both species, skeletal variations were observed (increased foetal incidence of cervical ribs in rat and a low incidence of small phalanges on the forepaws in rabbit).

Toxicokinetic data

The NOAELs for palbociclib following 27 weeks of intermittent dosing were at <10 (males) and <50 (females) mg/kg/day in the rat and after 39 weeks of intermittent dosing in the dog were at <0.2 (males) and 3 (females) mg/kg/day. At these exposures the data show a very low exposure margin in animals in comparison to human (0.1-3 times clinical exposure).

Local Tolerance

In rabbit, palbociclib did not induce toxicity at the injection sites following in or perivascular administration.

Other toxicity studies

Phototoxicity

In 3T3 cells palbociclib is regarded as non-phototoxic and according to the present guidelines, additional *in vivo* phototoxicity testing is therefore not warranted.

Haemolysis and Bone Marrow toxicity

Palbociclib did not induce haemolysis. Treatment of hBMNCs with palbociclib caused a concentration-dependent increase of cells in G1 phase, and decrease in S and G2/M phases, consistent with G1 cell cycle arrest, and was characterized by a fully reversible, concentration-dependent inhibition of proliferation without apoptosis, cellular senescence, or DNA damage. The hBMNC response to palbociclib did not change when combined with fulvestrant.

Impurities

The applicant proposed specification limits for two impurities, PF-00710042 and PF-00447880, at 0.4% and 0.5% respectively. In addition, the applicant has performed extended studies on PF-06694807, a degradant of palbociclib.

In general, the lots used for the overall safety testing holds lower levels of the impurities than the levels suggested by the applicant (except for PF-00447880 used in bacterial mutagenicity testing). To extend the specification and since PF-00447880 exceed the 1 mg/day qualification threshold the applicant has performed additional genotoxicity studies. The data showed that PF-00447880 and PF-00710042 was negative for mutagenicity in bacterial revers mutation assay. In the case of PF-00447880 the data show that it causes micronuclei formation in the in vitro micronucleus assay performed in TK6 cells, which kinetochore analysis by fluorescent in situ hybridization (FISH) identified as due to an aneugenic mechanism. PF-00447880 was present in the lot used for *in vivo* micronucleus assessment and the applicant concluded based of the NOAEL in that study (50 mg/kg/day) that PF-00447880 is safe to for use up to 0.47 mg/kg/day (0.5 mg/kg/day*0.94%).

2.3.5. Ecotoxicity / environmental risk assessment

PBT screening

Palbociclib does not meet the criteria for classification as a PBT compound.

The PEC_{sw} value is greater than the 0.01 µg/L action limit.

Environmental Fate Summary

Palbociclib is expected to rapidly dissipate from the water to the sediment.

Aquatic Effects

Palbociclib is unlikely to represent a risk to the aquatic environment (surface and ground water) nor a risk to wastewater micro-organisms nor a risk to sediment organisms.

Table 9 - Summary of main study results

Substance (INN / Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	LogD<4.5 at relevant pH pH5 – 0.228 pH7 – 1.11 pH9 – 2.26	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B

Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined	0.409	µg/L			> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = **Sludge** Cambridge - 7586 Denton – 6026 **Soil** Silt – 575440 Sandy – 134896 **Sediment** Sandy Loam – 85114 Sandy – 10964787 Average - 590796			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 1.5 – 2.2 days $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = 1.3 – 1.9 days % shifting to sediment = 22-57%			Not required if readily biodegradable
Sludge Die Away – 28 day sludge biodegradation	OECD 314B	Ultimate biodegradation (CO2 evolution) 2.0% in 28 days 26.4% remaining with solids at Day 28 Loss of parent DT_{50} is 4.8 days			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	0.091 (biomass) 0.90 (growth rate	mg a.i./ L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.27	mg a.i./ L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	0.13	mg a.i./ L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>1400	mg a.i./ L	
Determination of effects in sediment on emergence of the midge	OECD 218	NOEC LOEC	513 946	mg/ kg	*Chironomus riparius*

2.3.6. Discussion on non-clinical aspects

The pharmacology, pharmacokinetics, safety pharmacology and toxicology programs were considered sufficient for the appropriate non-clinical assessment of palbociclib. No major objections for the safety evaluation have been identified; some other concerns regarding GLP were identified and solved during the assessment.

In general the non-clinical program holds data/studies which are expected for an anti-cancer drug.

The binding and inhibition data show that palbociclib is a selective inhibitor of the CDK4 and CDK6 with a 50% inhibitory concentration of between 0.011 and 0.015 μM for CDK4/6 and their ligands. The data show that palbociclib increases the percentage of cell in G1 with increased exposure. However, in cell lines which lack a functional Rb no effect were observed.

However, the data also show that Palbociclib has binding to a wider range of off-target kinases. The IC_{50} concentration for such off-target binding is higher than clinical $C_{max.}$ However, biological consequences of binding below IC_{50} cannot be ruled out and thus some toxicity might be caused by off-target kinase binding.

Palbociclib is a potent and selective reversible inhibitor of CDK4 and CDK6, the inhibition of which in turn inhibits the phosphorylation of the Rb protein, which results in G1-phase cell cycle arrest and inhibition of DNA synthesis. Expression of cyclin D1 (CCND1), which activates CDKs, in breast tumours correlates with ER-positive status. ER-positive breast cancer was therefore chosen for drug development. The combination of palbociclib with anti-hormonal agents in vitro in ER-positive human breast cancer cell lines indicated a synergistic effect on growth arrest accompanied by increased cell senescence. According to pre-clinical data, palbociclib lacks functional efficacy in Rb-negative cancer cell lines indicating the importance of intact Rb function for the efficacy of palbociclib. Alternative mechanisms of action and complementary pathways may be hypothesised, and confounding of preclinical experiments related to the immortalisation of cell lines that affect Rb-status has been suggested, but cannot be used to dismiss the actual preclinical findings. It is somewhat unclear in what way the dependence on functional Rb is covered by the intended indication. This matter was raised as clinical other concern and resulted in a preclinical post-authorisation commitment. The applicant committed to submit a preclinical study to address this uncertainty (see non-clinical conclusion). This is also further addressed in the Clinical Efficacy and benefit-risk sections.

When combined with letrozole, palbociclib led to near-tumour stasis in a transplanted human tumour murine model.

Secondary PD shows that palbociclib is able to bind a number of unrelated receptors. However, due to the low binding affinity against these receptors in relation to the steady state level in plasma it is unlikely that this binding contribute to the effect observed.

PF-05089326, metabolite M17, showed binding to a wide range of receptors. However, considering the level of this metabolite in circulation, its protein binding and the intended indication, additional data on this binding was not considered necessary.

The potential for palbociclib to cause cardiovascular effects following administration of a single dose was evaluated in conscious Beagle dogs. The data show that single doses of palbociclib were associated with QTc interval prolongation in dogs at ≥3 mg/kg where plasma concentrations were ≥162 ng/mL (67 ng/mL unbound based on fu of 0.413 in dogs, 4 times clinical Cmax[17 ng/mL]). The findings in telemetered dog were addressed in the clinic by ECG recordings performed during the Phase1/2 studies.

The issue of QTcS increase and palbociclib treatment has been evaluated in non-clinical safety pharmacology studies and the signal has been addressed in four clinical studies. In addition, the signal has been added to the

RMP and SmPC (section 5.2 and 5.3). From a non-clinical point of view additional studies or risk evaluation were not considered necessary at this time and future risk management is to be performed in the clinic.

Consistent with the pharmacologic activity of palbociclib (cell cycle inhibition, CDK4/6 inhibition), the primary target organ findings included hematolymphopoietic and male reproductive organ effects in rats and dogs and altered glucose metabolism that was accompanied by effects on the pancreas and secondary changes in the eye, teeth, kidney, and adipose tissue (rats only). This information has been included in the SmPC in section 5.3.

Gastrointestinal effects would be anticipated from a cell cycle inhibitor and while effects were observed in rats and dogs following single- and repeat-dose studies up to 3 weeks in duration (emesis, fecal changes, and microscopic changes in stomach and intestines), the effects were of limited severity at clinically relevant doses.

Toxicokinetics data from the repeat-dose toxicity studies showed no or low exposure margins to the clinical exposure. Such low margins of exposure are not unexpected considering the mode-of-action of palbociclib.

Palbociclib has genotoxic potential, which is not unexpected considering the mode of action. A warning was included in section 4.6 of the SmPC stating that Ibrance is not recommended during pregnancy and in women of childbearing potential not using contraception. Also in section 5.3 it is stated that Ibrance may cause foetal harm if used during pregnancy.

Data from embryofetal developmental studies show that palbociclib induces maternal toxicity and an increase in skeletal variations in the offspring. In the pivotal embryo-foetal developmental studies both maternal and foetal toxicity was observed in both species. Maternal toxicity generally consisted of decreased body weight gain and decreased food consumption. In the offspring, in both species, skeletal variations were observed (increased foetal incidence of cervical ribs in rat and a low incidence of small phalanges on the forepaws in rabbit). However, no malformations were observed and it is possible that the detected foetal variation is due to maternal toxicity rather than a direct toxic effect. In addition, considering the mode of action, the positive genotoxicity and the lack of placenta transfer data it is difficult to draw a firm conclusion as to the foetal toxicity induced by palbociclib. Nevertheless, the data available is accurately reflected in section 4.6 and 5.3 of the SmPC.

However, no malformations were observed and it is possible that the detected foetal variation is due to maternal toxicity rather than a direct toxic effect. In addition, considering the mode of action, the positive genotoxicity and the lack of placenta transfer data it is difficult to draw a firm conclusion as to the foetal toxicity induced by palbociclib. The pharmacodynamic properties of palbociclib and the lack of foetal exposure data is reflected in section 5.3 and as a consequence the potential risk of reproductive and developmental toxicity needs to be kept in the RMP.

The findings in male reproductive organs have been accounted for in SmPC sections 4.6 and 5.3 in which male patients are recommended to preserve sperm before initiation of treatment.

The applicant proposed specification limits for two impurities, PF-00710042 and PF-00447880. Data showed that PF-00447880 causes micronuclei formation. PF-00447880 was present in the lot used for *in vivo* micronucleus assessment and the applicant concluded based of the NOAEL in that study (50 mg/kg/day) that PF-00447880 is safe to use up to 0.47 mg/kg/day (0.5 mg/kg/day0.94%). Based on the indication, dose and set specification limit it is agreed and accompanied risk for clastogenicity/carcinogenicity, is acceptable. However, this could potentially change if palbociclib is to be used in indications which do not fall under the S9 guide line.

The data presented by the applicant so far show that palbociclib do not present an environmental risk following patient use. In addition, the applicant has agreed to rerun the OECD 308 study and to extend the analysis of palbociclib transformation, transformation products, half-life and potential persistence. This study is to be submitted no later than the 31st of January 2017.

2.3.7. Conclusion on the non-clinical aspects

The data submitted to support the non-clinical aspects of this application are considered acceptable. Nevertheless, the CHMP recommended the submission of a non-clinical study investigating the activity of palbociclib *in vitro*, and if possible *in vivo*, utilizing explants from human IHC Rb-positive and IHC Rb-negative fresh tumour samples by June 2019.

In addition, the applicant committed to rerun the OECD 308 study and to extend the analysis of palbociclib transformation, transformation products, half-life and potential persistence. The CHMP recommended that the results are to be submitted no later than the 31st of January 2017.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Protocol No. **Country**	**Study Design and Objective**	**Treatment Groups, No. of Subjects** (by Treatment Group)	**Demographics** (by Treatment Group)	**Duration of Treatment**	**Study Start, End/Status (Available results)**
A5481003 /PALOMA-1 ***"Study 1003"*** Phase 1: US; 3 centres. Phase 2: 12 countries, Canada, France, Germany, Hungary, Ireland, Italy, Russia, South Africa, South Korea, Spain, Ukraine,	Open label, randomized, Phase 1/2 clinical study to assess the efficacy, safety, and pharmacokinetics of palbociclib (isethionate capsule formulation) in combination with letrozole and letrozole alone for the **first-line treatment of ER positive, HER2- negative advanced breast cancer (i.e. locally advanced and metastatic disease) in postmenopausal wome**n.	Phase 1: N = 12 Cycle 1: 125-mg palbociclib QD on Schedule 2/1 Cycle 2 and beyond: 125-mg palbociclib QD on Schedule 3/1+2.5-mg letrozole QD continuously.	Sex: 12 F Median Age: 60.5 years (range: 43-74 years) Race: W/B/O: 11/0/1.	Median days on treatment (min/max): Palbociclib: 373.5 (63.0, 1682.0) Letrozole: 353.0 (55.0, 1661.0)	Study start date: 15 September 2008 Status: Completed Primary completion date for the final analysis 29 November 2013 Cut-off date for Phase 1 and Phase 2 (CSR available)
		Phase 2: Palbociclib + letrozole N = 84 125-mg palbociclib QD on Schedule 3/1 + 2.5-mg letrozole QD continuously.	Sex: 84 F (randomized) Median Age: 62.5 years (range: 41-89 years) Race: W/B/O: 76/1/7.	Median days on treatment (min-max) palbociclib: 420.0 (7.0-1242) letrozole: 428.0 (7.0-1242)	

and the US; 50 centres.		Phase 2: Letrozole, N = 81 2.5-mg letrozole QD continuously	Sex: 81 F (randomized) Median Age: 64.0 years (range: 38-84 years) Race: W/B/O: 72/1/8	Median days on treatment (min-max): letrozole: 231.0 (28.0-1194.0)	
A5481008 /PALOMA-2 ***"Study 1008"*** Phase 3 US, Canada, Belgium, France, Germany, Hungary, Ireland, Italy, Poland, Russian Federation, Spain; Ukraine, UK, Australia, Japan, Korea, and Taiwan (186 centres).	An international, multicentre, randomized, double-blind, placebo controlled, parallel group, Phase 3 clinical trial comparing the efficacy and safety of palbociclib in combination with letrozole versus placebo in combination with letrozole to demonstrate that the combination of palbociclib with letrozole is superior to placebo plus letrozole in prolonging PFS in **postmenopausal women with ER-positive, HER2-negative advanced breast cancer who have not received any prior systemic anti-cancer therapies for their advanced/ metastatic disease**.	N=666 2:1 randomization. Arm A (Investigational arm): palbociclib + letrozole (route: oral); Dose Regimen: 125-mg palbociclib (initial Phase 3 free base capsule, final Phase 3/ commercial free base capsule) QD on Schedule 3/1 + 2.5-mg letrozole orally QD continuously. Arm B (Comparator arm): placebo + letrozole (route: oral); Dose regimen: placebo QD, on Schedule 3/1 + 2.5-mg letrozole orally QD continuously	Sex: 666 F/0 M Mean Age : 61.3 (range: 28-89) years Race: W/B/O: 516/11/139	Ongoing Median days on treatment not yet reported (**Q**)	Status: **Ongoing** Top-line summary submitted during assessment (Day 121) Data cut-off date: 26 February 2016
A5481023 /PALOMA-3 ***"Study 1023"*** Phase 3 Canada, US, Belgium, Germany, Ireland, Italy, Netherlands, Portugal, Romania, Russian Federation, Turkey, Ukraine, UK, Australia, Japan, Republic of Korea, and Taiwan (144 centres).	An international, multicentre, randomized, double-blind, placebo controlled, parallel group, Phase 3 clinical trial comparing the efficacy and safety of palbociclib in combination with fulvestrant (with or without goserelin) versus placebo in combination with fulvestrant (with or without goserelin) in women with **HR-positive, HER2-negative metastatic breast cancer whose disease has progressed on prior endocrine therap**y. The primary objective is to demonstrate the superiority of palbociclib in *combination* with	N=521 2:1 randomization Arm A (Investigational arm): Palbociclib 125-mg/day (Initial Phase 3 free base capsule, Final Phase 3/ commercial free base capsule) orally QD on Schedule 3/1 plus fulvestrant 500-mg intramuscularly on Days 1 and 15 of Cycle 1, and then on Day 1 of each subsequent 28-day cycle. Arm B (Comparator arm): Placebo orally QD on	Sex: 521 F/0 M Mean Age : 56.9 (range: 29-88) years Race: W/B/O: 385/20/116	Median days on treatment: Arm A palbociclib 144, fulvestrant 148. Arm B Placebo 120, fulvestrant 128	Study start date: 26 Sep 2013 Status: Completed Primary completion date for the final analysis: 05 Dec 2014 (Full CSR submitted during assessment, 1 month after start of procedure) In addition, a PFS update has

	fulvestrant (with or without goserelin) over fulvestrant (with or without goserelin) alone in prolonging investigator assessed PFS.	Schedule 3/1 plus fulvestrant 500-mg intramuscularly on Days 1 and 15 of Cycle 1, and then on Day 1 of each subsequent 28-day cycle.			been submitted with data cut-off: 16 March 2015
A5481001 ***"Study 1001"*** Dose-finding Phase 1 US; 3 centres.	Open label, non-comparative, dose-finding, Phase 1 study of 2 dose schedules to establish the safety profile of palbociclib (isethionate capsule) by identifying DLTs, MAD, MTD, and RP2D for 2 dosing schedules: 3 weeks on treatment/1 week off treatment (Schedule 3/1) and 2 weeks on treatment/1 week off treatment (Schedule 2/1) in patients with **advanced cancer**.	Schedule 3/1: (N = 41) 25 mg QD, 50 mg QD, 75 mg QD, 100 mg QD, 125 mg QD, 150 mg QD, of palbociclib orally (isethionate capsule). Schedule 2/1: (N=33) (100 mg QD, 150 mg QD, 200 mg QD, and 225mg QD of palbociclib orally [isethionate capsule]).	Schedule 3/1: Sex: 20 M/21 F Median Age: 55 years (range: 22-77 years) Race: W/B/O: 39/1/1 Schedule 2/1: Sex: 16 M/17 F Median Age: 63 years (range: 35-78 years) Race: W/B/O: 30/2/1	Schedule 3/1: Median days on treatment (min/max): 55.0 (1.00/1245) Schedule 2/1: Median days on treatment (min/max): 42.0 (4.0/730)	Study start date: 02 September 2004 Status: Completed Study completion date: 12 June 2008 (CSR available)
A5481010 ***"Study 1010"*** Phase 1/2 [as of 02 January 2014 data cut-off date]: Japan, 15 centres.	Phase 1/2 study: Phase 1, non-randomized, open label single country study conducted in 2 parts. Part 1: dose escalation for palbociclib (isethionate capsule) administered *alone* in **Japanese patients with advanced solid tumours** in order to estimate the MTD. Part 2: a cohort to assess the overall safety and tolerability of the *combination* of palbociclib (isethionate capsule) at the MTD identified in Part 1 and letrozole as the **first-line treatment of postmenopausal Japanese patients with ER-positive, HER2-negative advanced breast cancer**. Phase 2: Non-randomized, open label, single country, single cohort study of palbociclib (free base) in combination with letrozole for the **first-line treatment of**	Phase 1: Part 1: palbociclib (isethionate capsule), orally QD, Schedule 3/1, investigated in sequential cohorts of patients at 2 dose levels Dose Level 1: 100 mg QD (N=6) Dose Level 2: 125 mg QD (N=6) Part 2: (N=6) palbociclib (isethionate capsule), orally QD, Schedule 3/1, one dose level (125 mg of palbociclib + 2.5 mg of letrozole). Phase 2: (N=32) palbociclib (free base capsule), orally QD, Schedule 3/1; 125 mg of palbociclib + 2.5 mg of letrozole	Phase 1: Part 1: Dose Level 1: Sex: 5 F/1 M Mean Age: 56.8 years (range: 44-65 years) Race: W/B/O: 0/0/6 (Asian) Dose Level 2: Sex: 2 F/4 M Mean Age: 45.3 years (range: 24-69 years) Race: W/B/O: 0/0/6 (Asian) Part 2: Sex: 6 F/0 M Mean Age: 66.0 years (range: 59-76 years) Race: W/B/O: 0/0/6 (Asian) Phase 2: Sex: 32 F/0 M Mean Age: 61.2 years (range: 43-84 years) Race: W/B/O: 0/0/32 (Asian)	Ongoing	Study start date: October 2012 Status: **Ongoing** (Interim PK report available)

	postmenopausal Japanese patients with ER-positive HER-2-negative advanced breast cancer. To evaluate the efficacy of palbociclib in combination with letrozole as measured by PFS probability at 12 months (1-year PFS probability).				
A5481034 ***"Study 1034"*** Expanded Access US (12 centres)	Open-label, single arm, multicentre expanded access study designed to provide access to palbociclib in the United States (Cohort 1) and Canada (Cohort 2) to **post-menopausal patients with HR+, HER2- advanced breast cancer** who are deemed appropriate for letrozole therapy. For Cohort 2, patients must have **not received prior antihormonal therapy for their advanced disease**.	N=93 Single arm: Palbociclib (125-mg QD on Schedule 3/1) + Letrozole (2.5-mg letrozole QD continuously)	Sex: 93 F/0 M Mean Age : 61.8 (range: 29-89 years) Race: W/B/O: 80/5/8	Ongoing	Status: **Ongoing** (SAEs and deaths available)

2.4.2. Pharmacokinetics

Absorption

Seven (7) biopharmaceutic 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), and food effect (Study 1021). In addition, 2 clinical pharmacology studies were conducted to assess the antacid effect (Studies 1018 and 1038).

Table 10 - Overview of Palbociclib Biopharmaceutic and Antacid Studies

Study Number Study Start/ Study End	Study Design and Objective	Dose	Treatment: Dosage Forms/Formulations Studied	Number of Subjects	Demographics
A5481009 24May2012/ 02Nov2012	OL, single-dose, 4-period, 4-sequence, crossover Relative BA	Treatment A: 125 mg Treatment B: 125 mg Treatment C: 125 mg Treatment D: 50 mg	A: Isethionate capsule B: Hand-filled initial Phase 3 free base capsule, 4-μm drug substance particle size C: Hand-filled initial Phase 3 free base capsule, 17-μm drug substance particle size D: Oral solution (all after overnight fast)	24 HV	24 M/ 0 F Mean age (Std Dev): 38.7 (9.5) yr Range: 24 to 55 yr Race: 10W/13B/1O
A5481015 14May2013/ 24Jun2013	OL, single-dose, 2-period, fixed-sequence, crossover Absolute BA	Treatment A: 125 mg Treatment B: 50 mg	A: Initial Phase 3 free base capsule (after overnight fast) B: IV solution	14 HV	14 M/ 0 F Mean age (Std Dev): 38.1 (10.2) yr Range: 18 to 53 yr Race: 11W/2B/1O
A5481018 04Sep2013/ 06Dec2013	OL, 2-period, fixed-sequence crossover PPI DDI	Palbociclib: 125 mg Rabeprazole: 40 mg QD for 7 days	Final Phase 3/commercial free base capsule (after overnight fast)	26 HV	15 M/ 11 F Mean age (Std Dev): 45.4 (8.1) yr Range: 24 to 55 yr Race: 25W/1B
A5481020 03Sep2013/ 03Jan2014	OL, single-dose, 3-period, 6-sequence, crossover BE	Palbociclib: 125 mg	A (Ref 1): Isethionate capsule B (Ref 2): Initial Phase 3 free base capsule C (Test): Final Phase 3/commercial free base capsule (all after overnight fast)	73 HV	71M/ 2 F Mean age (Std Dev): 34.5 (10.0) yr Range: 19 to 54 yr Race: 28W/42B/1A/2O
A5481021 22Jul2013/ 20Oct2013	OL, single-dose, 4-period, 4-sequence, crossover Food Effect	Palbociclib: 125 mg	Final Phase 3/commercial free base capsule A: After overnight fast B: Fed (high-fat, high-calorie meal) C: Fed (low-fat, low-calorie meal) D: Between 2 separate moderate-fat meals	28 HV	28 M/ 0 F Mean age (Std Dev): 37.8 (9.4) yr Range: 22 to 54 yr Race: 7W/16B/1A/4O

Study Number Study Start/ Study End	Study Design and Objective	Dose	Treatment: Dosage Forms/Formulations Studied	Number of Subjects	Demographics
A5481022 03Jun2013/ 22Aug2013	OL, single-dose, 4-period, 4-sequence, crossover Relative BA	Palbociclib: 125 mg	Final Phase 3/commercial free base capsule A: Particle size (D[4,3]=16 μm) and dissolution Level 1;[a] B: Particle size (D[4,3]=41 μm) and dissolution Level 1;[a] C: Particle size (D[4,3]=16 μm) and dissolution Level 2;[a] D: Particle size (D[4,3]=16 μm) and dissolution Level 3[a] (all after overnight fast)	24 HV	24 M/ 0 F Mean age (Std Dev): 39.6 (10.1) yr Range: 21 to 55 yr Race: 9W/11B/4O
A5481036 15Jan2014/ 11Mar2014	OL, single-dose, 3-period, 6-sequence, crossover Relative BA (and food effect)	Palbociclib: 125 mg	A: Isethionate capsules, after overnight fast B: Isethionate capsules, 1 hr after and 2 hr before 2 separate moderate-fat meals C: Final Phase 3/commercial free base capsule, after moderate-fat meal	36 HV	36 M/ 0 F Mean age (Std Dev): 37.5 (9.7) yr Range: 21 to 55 yr Race: 10W/20B/1A/5O

Study Number Study Start/ Study End	Study Design and Objective	Dose	Treatment: Dosage Forms/Formulations Studied	Number of Subjects	Demographics
A5481038 03Apr2014/ 04Jun2014	OL, 2-Cohort, 3-period, fixed-sequence PPI, H2-receptor antagonist, and local antacid DDI	Palbociclib: 125 mg Famotidine: 20 mg Rabeprazole: 40 mg QD for 7 days Mi-Acid Maximum Strength: 30 mL	Final Phase 3/commercial free base capsule A: Single dose palbociclib 125 mg B: Single dose palbociclib 125 mg, plus single dose of famotidine 20 mg 10 hours prior to and 2 hours after palbociclib administration C: Single dose palbociclib 125 mg, plus single dose of rabeprazole (PPI) 40 mg QD from Day -5 to Day 0 and 4 hours before palbociclib administration D: Single dose palbociclib 125 mg, plus Mi-Acid Maximum Strength Liquid 30 mL 2 hours before palbociclib administration E: Single dose palbociclib 125 mg, plus Mi-Acid Maximum Strength Liquid 30 mL 2 hours after palbociclib administration (fed conditions - moderate-fat meal)	27 HV	27 M/ 0 F Mean age (Std Dev): 34.9 (7.4) yr Range: 24 to 54 yr Race: 3W/15B/9O
A5481040 18Mar2014/ 08May2014	OL, single dose, 3-period, 6-sequence, crossover Relative BA	Palbociclib: 125 mg	Final Phase 3/commercial free base capsule A: Particle size (D[4,3]=16 µm) and dissolution Level 1;[a] B: Particle size (D[4,3]=41 µm) and dissolution Level 1;[a] C: Particle size (D[4,3]=16 µm) and dissolution Level 2;[a] (fed conditions - moderate-fat meal)	30 HV	30 M/ 0 F Mean age (Std Dev): 38.5 (9.1) yr Range: 23 to 55 yr Race: 5W/18B/1A/6O

Source: Study 1009 CSR; Study 1015 CSR; Study 1018 CSR; Study 1020 CSR; Study 1021 CSR; Study 1022 CSR; Study 1036 CSR; Study 1038 CSR; and Study 1040 CSR.
Abbreviations: A=Asian; B=Black; BA=bioavailability; BE=bioequivalence; DDI=drug-drug interaction; F=female; hr=hour; HV=healthy volunteers; IV=intravenous; M=male; O=other; OL=open-label; PPI=proton pump inhibitor; QD=once daily; Std Dev=standard deviation; W=White; yr=year.
a. Formulations with different dissolution levels used in Study 1022 and Study 1040 are described in Section 2.7.1.1.1.1.7.

- *Bioavailability*

The absolute oral bioavailability (BA) of palbociclib from the 125-mg initial Phase 3 free base capsule was 46%. Based on CL, Cp/Cb ratio, fe and Q_H, the fraction absorbed is ca 70%. The rate and extent of palbociclib free base capsule dissolution is strongly pH dependent and decrease at higher pH (see section on drug interaction). The rate of absorption moderate with median Tmax in the range 6-8 hours after a single dose. Palbociclib is a substrate of the intestinal transporters MDR1 and BCRP in vitro. These transporters may affect the rate and extent of absorption of palbociclib.

- *Bioequivalence*

The commercial formulation of palbociclib is an *immediate-release free base capsule* at three palbociclib dosage strengths of 75 mg, 100 mg, and 125 mg. When submitting this application, phase II data was available with an initial formulation, the isotretionate capsule. During the clinical development program, early clinical trials including Study 1003 (phase 1/2-study), the isethionate capsule was administered under *"minimal fasting conditions"* ie fasting 1 hour before to 2 hours after dosing.

Another formulation, the "free base capsule formulation" has been used in the phase III study which was submitted during the assessment period (1023) and is administered under *fed* conditions. This formulation is intended for marketing.

Administration with food was recommended in the Phase 3 studies submitted and this is reflected in the SmPC (see section 4.2). Bioequivalence has been established between the final Phase 3/commercial free base capsule given with food and the isethionate capsules given under fasting conditions supporting the bridge to Study 1003. Two (2) fasting conditions: an overnight fast and a "minimal fasting conditions" with 2 separate moderate-fat meals on each end represent the 2 extreme scenarios for compliant palbociclib dosing with regard to surrounding moderate meal intake in Study 1003 in which patients were instructed to fast from 1 hour before until 2 hours after palbociclib dosing. The bridge to the commercial formulation taken with food is considered

well supported as BE was shown between these treatments. Equivalence was also shown between Final Phase 3/commercial free base capsule formulation vs the isethionate capsule and the initial Phase 3 free base capsule under fasting conditions with respect to AUC, while Cmax was slightly lower for the isotretionate capsule.

The effect of a high-fat, low-fat, and "minimal fasting conditions" surrounded by moderate-fat meals was investigated on the phase 3/commercial free base capsule formulation. There was a moderate increase in exposure which was considered to lack clinical relevance. However, there were three so called low-liers (see below) when the capsules were taken in fasting conditions. This was not the case during the studied fed conditions and the variability decreased accordingly. BE was shown versus administration after an overnight fast for the data subset excluding so called low-liers.

The applicant submitted a special analysis on so called "low-liers" in the PK studies. The commercial/phase III free base capsule formulation was used in most of the clinical pharmacology and biopharmaceutic studies. 13% of all PK profiles observed after palbociclib phase III free base capsule formulations under an overnight fasted condition were associated with substantially lower palbociclib exposure. These were called "low-liers", which is defined as having a Cmax value less than or equal to 21.4 ng/mL or with a Cmax value that has a marginal studentized residual lower than –2 (based on DDI data with rabeprazol). It has been observed in clinical studies of palbociclib in healthy subjects that the low-lier incidence may or may not be consistent within an individual subject. The reason for low-lier occuring with the phase III free base formulation is thought to be the more sensitive pH-dependent dissolution profile of the free base capsules. Low-liers were not identified in studies conducted with palbociclib isothionate capsules or oral solution nor were they observed with phase III free base capsules administered with a high-fat or moderate-fat meal or in between meals (moderate-fat meal 1 hour before and 2 hours after dosing).

Figure 5- Individual Cmax observed in phase I studies with "low-liers" marked in red.

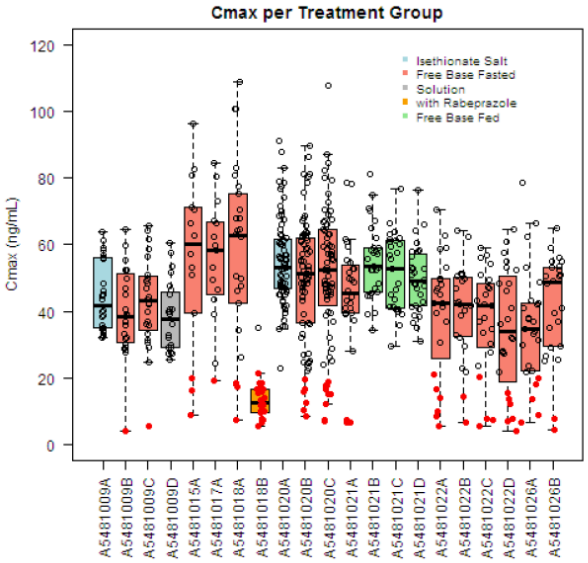
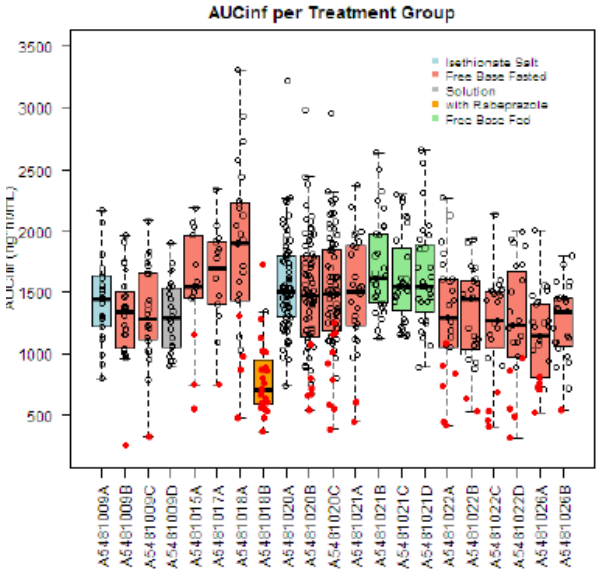


Figure 6 - Individual AUCs observed in phase I studies with "low-liers" marked in red.



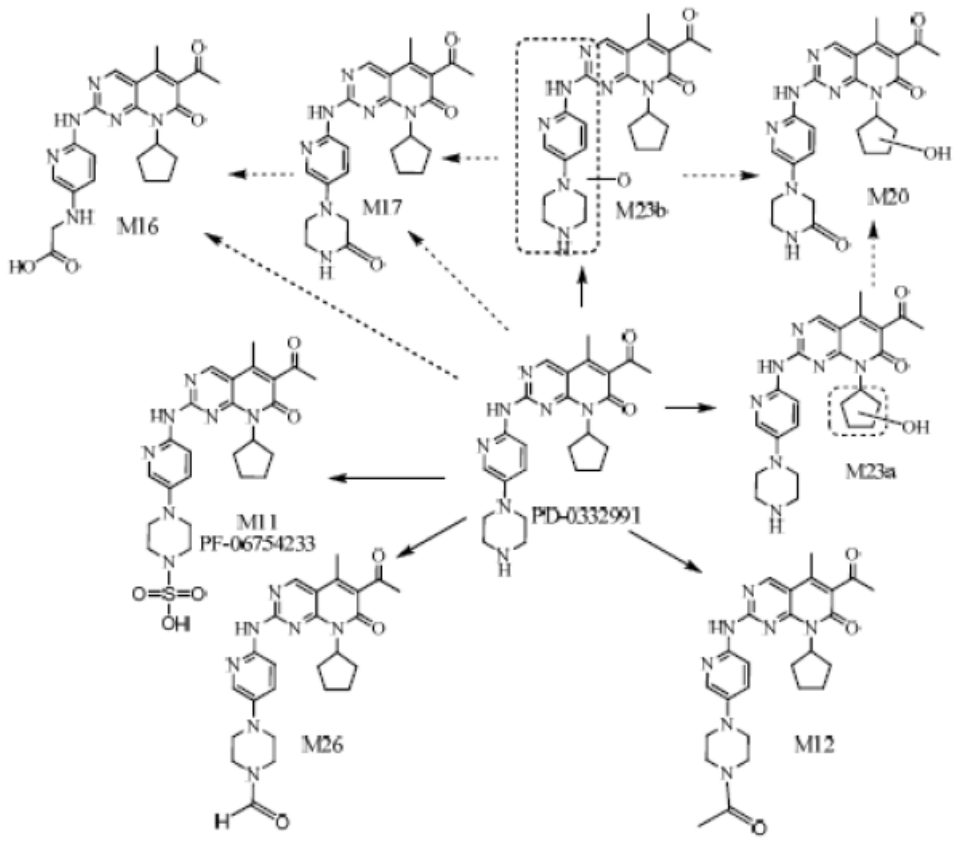
Distribution

Following IV administration, palbociclib geometric mean steady-state volume of distribution (Vss) was 1008 L. The fraction unbound in plasma, to HSA and the glucoprotein was 14%, 74%, and 63%. Other components, such as free fatty acids, may be contributing to the plasma binding. The protein binding of the palbociclib metabolite PF-05089326 was 0.05. For both substances, binding was not concentration-dependent. The human blood-to-plasma concentration ratio for palbociclib was 1.63.

Elimination

Palbociclib is mainly eliminated through metabolism. The major primary metabolic pathways were comprised of oxidation (14% of dose) and sulfonation (26% of dose), leading to metabolites M16 and M11, respectively. Metabolite M20 and metabolite 23 a/b were excreted in small amounts (5 and 4%, respectively). Glucuronidation and acylation appeared to be minor pathways. Palbociclib is not a substrate for OATP1B1 and 1B3.

Figure 7- Proposed metabolism schedule based on substances identified in faeces



Only a small fraction of the dose was recovered as unchanged drug in faeces (2%) and urine (3.5 or 7%). Thus renal and biliary excretion appears of little importance for drug clearance. An extended sampling was needed for unchanged palbociclib in urine to reach 7%. This is not understood as the half-life (24 hrs) is sufficiently short for all palbociclib to be excreted within 120 hours.

Itraconazole inhibits about half the elimination indicating that CYP3A4 is responsible for nearly half of the elimination of palbociclib. In addition, sulphate conjugates (SULT2A1 responsible for metabolism) is found in excreta contributing to 26% of the administrated dose (30-40% contribution to palbociclib elimination based on the fraction absorbed). Renal excretion has a minor contribution to palbociclib elimination. In conclusion, CYP3A4 and SULT2A1 are the main elimination pathways.

Palbociclib contributed to one fifth of the radioactivity in plasma after a radiolabelled dose. Palbociclib Cmax was generally observed 6 hours after oral dosing, while Cmax of the metabolite PF-05089326 was observed earlier, around 4 hours after dosing. Median peak concentrations for total radioactivity in plasma were observed at 4 hours after dosing (2 hours before palbociclib Cmax).

Fifty-six % of the radioactivity in plasma over the first 120 hours was identified as palbociclib and metabolites. Unchanged palbociclib was the primary drug-related material accounting for 23% of the total plasma radioactivity. M22 (the glucuronide conjugate of palbociclib also found in urine) was the most abundant metabolite, at 14.8% of circulating radioactivity. The other primary clearance metabolites, M11, M26, and M12,

were present in plasma at low levels (1.3%, 1.5%, and 1.0%, respectively). M16, the major fecal metabolite, was present in plasma at 2.6%, whereas M20 was not detected. Three additional minor metabolites were identified as the lactam of palbociclib (M17, PF-05089326), a dilactam of palbociclib (M24), and a metabolite with the pyrido-piperazine substructure cleaved (M25), at 4.7%, 4.4%, and 2.3%, respectively. In addition, a number of metabolites have been identified, each with a less <2% contribution of the radioactivity up to 120 hours.

Metabolite M17 (PF-05089326) was shown to have comparable potency with that of palbociclib for inhibiting CDK 4 and CDK 6. However the exposure was too low for it to contribute to the in vivo activity. No "major metabolites" were identified in plasma contributing to >10% other than the glucuronide M22.

Variability: C_{max} and $AUC_{(0-10)}$ values demonstrated moderate inter-individual variability after single or multiple palbociclib dose administration. The %CVs for $AUC_{(0-10)}$ across all dose levels ranged from 5% to 55% on Day 1 and 15% to 64% on Day 8. The %CV for C_{max} ranged from 3% to 63% on Day 1 and 16% to 64% on Day 8 in the dose escalation study A5481001. Inter-individual variability in CL/F, estimated in the population PK analysis, was 36.7 %CV and for V/F 30 %CV.

Population PK analysis: The population pharmacokinetics of palbociclib was described with a two-compartment model with first-order absorption (Ka) and absorption lag time (Tlag). Of the various evaluated covariates, food intake on relative bioavailability and absorption lag time, age and body weight on CL/F and body weight on V2/F were statistically significant. The analysis included PK information on palbociclib obtained in subjects included in study A5481001, A5481002 and A5481003.

Dose proportionality and time dependencies

Palbociclib exhibit dose-independent pharmacokinetics at single dose conditions. However as it is a TDI on CYP3A, it inhibits part of its own metabolism and thus, during multiple dose conditions, pharmacokinetics should be dose-dependent to some extent.

The accumulation ratio is ca 2 and the terminal half-life is ca. 22 hours. Steady state is reached on day 8 in contrast to the day 3-5 that is expected based on the half-life. This is likely due to the weak time dependent CYP3A inhibitory property of palbociclib.

Special populations

Renal impairment: No formal study of the PK of palbociclib in renal impairment has been conducted. The effect of estimated creatinine clearance (Cockroft-Gault) in the range of mild (39.6.8% of the patients CRCL ≥60 and <90 mL/min) and moderate renal impairment (15.7%, CRCL ≥60 and <90 mL/min) was evaluated in the PPK analysis.

Hepatic impairment: Subjects with moderate and severe hepatic impairment have been excluded from participation in clinical trials. 41 patients with mild hepatic impairment according to the National Cancer Institute (NCI) scale were included in the studies. Baseline liver transaminase and bilirubin levels were evaluated as covariates in the PPK analysis and within the evaluated range of the liver function markers, no statistical significant effect was observed

Weight, gender, race and age: The effect of weight, gender, race and age on the PK of palbociclib was evaluated in the population PK analysis.

Body weight (median 74 kg, range 38-123 kg) was identified as a significant covariate on CL/F and relative to the typical value of 60.2 L/h, CL/F was predicted to decrease by 13.2% at a weight of 55 kg (10^{th} percentile) and to increase by 14.2% at a weight of 97 kg (90^{th} percentile). Weight was also a significant covariate for V2/F. The quantified effects of bodyweight on exposure were not considered clinical relevant.

Age (median 61, range 37-89) years was found to have a statistically significant effect on CL/F. At an age of 74 years, CL/F was predicted to decrease by approximately 8 % compared to the value at 61 years, which was considered not being a clinical relevant effect

A study conducted in healthy Japanese subjects showed that the mean AUC_{inf} and C_{max} values were 30% and 35% higher, respectively, in Japanese subjects (n= 14) when compared with demographic-matched non-Asian subjects (n=13) after 125-mg single dose. Furthermore, across studies in patients and following 125-mg multiple QD administration, the observed PK parameters at steady-state in Japanese patients (study 1010) indicated that palbociclib geometric mean AUC and C_{max} are at least 43 and 60% respectively, higher than those observed in non-Asian patients who received the same 125-mg QD doses in separate studies 1001 (n=13) and 1003 (n=12).

Pharmacokinetic interaction studies

IVIVC cut-offs: For DDI in vivo relevance assessment, the intestinal palbociclib concentration (0.1 x dose/250 ml) is 112 uM. 50 x Cmax(u) is 1.9 uM.

Enzyme inhibition: Palbociclib is a mild time dependent inhibitor of CYP3A in vitro (KI and kinact values of 10 µM, 0.036 min-1 and 19 µM, 0.087 min-1 respectively) and this has been confirmed in vivo in a DDI study with midazolam where a 60% increase in AUC was observed. No inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 was observed in vitro. Unbound IC50 for UGT1A4, 1A9 and 2B7 is 58, 13, and 37 uM, respectively and UGT1A1 and 1A6 were not inhibited.

Transporter inhibition: Palbociclib IC50 for Pgp was 9.9 µM using digoxin and 3.8 µM using talinolol as substrate. For BCRP, the IC50 of palbociclib was 11.6 µM using digoxin and 4.2 µM using talinolol. It may not be excluded that palbociclib inhibits BCRP and Pgp in the intestine. Systemic inhibition (liver, kidney) is not expected. Palbociclib does not inhibit BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2.

Increased gastric pH: Rabeprazole gave rise to a marked (61%) reduction in palbociclib exposure during fasting conditions due to the pH dependent solubility of palbociclib. However under fed conditions (moderate-fat meal), the effect was only a 13% decrease and therefore not clinically relevant. Famotidine had no effect on the exposure of palbociclib. Antacids 2 hours before palbociclib did not have any effect on palbociclib exposure.

CYP3A inhibition: Itraconazole 200 mg qd gave rise to an 87% increase in palbociclib exposure, showing the importance of CYP3A (Pgp) in palbociclib elimination.

Enzyme induction: Rifampicin for 7 days gave rise to a 85% reduction of palbociclib exposure. The moderate inducer modafinil gave a 32% reduction in exposure.

Potential to inhibit CYP3A: Palbociclib 125 mg qd for 7 days increased the exposure of midazolam by 61%. The steady state is probably a bit higher but the classification will still be a mild inhibitor.

Antiestrogens: There was no effect of tamoxifen on the pharmacokinetics of palbociclib. There was no interaction between letrozole and palbociclib. Based on trough levels, fulvestrant does not affect the palbociclib pharmacokinetics.

Regarding the risk for interactions between aromatase inhibitors/LHRH agonists and palbociclib

Palbociclib effect on anastrozole: Palbociclib is a weak time-dependent inhibitor of CYP3A and it has been suggested that CYP3A4 is involved in the elimination of anastrozole. This may lead to a theoretical interaction risk between palbociclib and anastrozole. However, given the weak nature of palbociclib as a CYP3A inhibitor (61% exposure increase of midazolam) and the fact that anastrozole has multiple elimination pathways the risk for a clinically relevant drug interaction of palbociclib on anastrozole is considered unlikely.

Anastrozole effect on palbociclib: Palbociclib is a CYP3A4 substrate. Anastrozole is an in vitro inhibitor of CYP3A with a Ki of 10 µM (Grimm and Dyroff, 1997). The steady state Cmax of anastrozole is 0.3 µM and its plasma protein binding is 40%. Consequently, the 50×Cmax(u) of anastrozole is 6 µM and lower than the anastrozole CYP3A Ki. In addition, multiple 1 mg doses of anastrozole did not show any effect on the CYP3A4 substrate tamoxifen steady-state through concentrations in a study by The ATAC Trialists' Group, 2001. These data clearly shows that anastrozole is neither an inhibitor nor an inducer of CYP3A and therefore the risk of a clinically relevant interaction of anastrozole on palbociclib is considered low.

In addition, currently ongoing clinical studies include palbociclib and anastrozole co-administration and may inform further on a possible interaction.

Palbociclib effect on exemestane: Exemestane are metabolised by CYP3A4 and aldoketoreductase. According to the product information of exemestane, ketoconazole (a potent CYP3A4 inhibitor) did not affect the PK of exemestane. In contrast, rifampicin (a potent CYP3A inducer) reduced the exposure of exemestane by 54%. These data suggests that metabolism via CYP3A4 is a minor elimination pathway for exemestane and that the weak CYP3A4 inhibitor palbociclib would most probably not affect the PK of exemestane.

Exemestane on palbociclib: Palbociclib is metabolised by CYP3A4. Exemestane at steady-state did not affect the exposure of tamoxifen (a CYP3A4 substrate) according to an in vivo study by Hutson 2005[14]. Thus, it may be concluded that exemestane are not likely to affect the PK of palbociclib.

In addition, currently ongoing clinical studies include palbociclib and exemestane coadministration and may inform further on a possible interaction.

The effect of palbociclib on LHRH agonists: LHRH agonists are unlikely to be metabolised by microsomal enzymes in the liver but rather by hydrolytic cleavage and peptidases. Therefore, no interactions of palbociclib on LHRH agonists are awaited.

The effect of LHRH agonists on palbociclib: No clinically relevant DDI between palbociclib and goserelin when the two agents were dosed concurrently. For the other LHRH agonists no indications of an interaction potential at CYP enzymes were found neither in its product information nor in the literature. This together with the relatively limited effect of the strong CYP3A4 inhibitor itraconazole on palbociclib exposure (87% increase) supports that the risk for an effect of LHRH agonists on palbociclib PK is low.

The risk for clinically relevant drug interactions between palbociclib and anastrozole/exemestane is considered low.

[14] Hutson PR1, Love RR, Havighurst TC, Rogers E, Cleary JF. Effect of exemestane on tamoxifen pharmacokinetics in postmenopausal women treated for breast cancer. Clin Cancer Res. 2005 Dec 15;11(24 Pt 1):8722-7

2.4.3. Pharmacodynamics

Mechanism of action

The applicant did not submit studies on the mechanism of action.

Primary and Secondary pharmacology

Based upon the observation that the expression of the downstream target of palbociclib, CCND1, in breast tumour isolates correlates with ER-positive status, palbociclib was tested *in vitro* on molecularly characterized human breast cancer cell lines. Results from these experiments indicated that cell lines that were more sensitive to palbociclib (half maximal inhibitory concentration [IC50] <150 nM) had low levels of the CDK inhibitor 2A (CDKN2A; also known as 'p16INK4A'), and high levels of the retinoblastoma (RB) 1 gene, while resistant cell lines show the opposite characteristics. Sensitive cell lines in this panel represented mostly the luminal ER-positive subtype.

The combination of palbociclib with tamoxifen has also been tested *in vitro* in ER-positive (ER+) human breast cancer cell lines indicating a synergistic interaction, and recently, the combination of palbociclib with letrozole has also shown a synergistic effect.

Exposure-response/safety

Exposure-response analyses of palbociclib exposure on progression free survival (PFS) were conducted using data obtained from study 1003. The analyses indicate a trend for better PFS with increasing exposure. However, due to limited data (n=81) with a fixed dose of 125 mg in study 1003, a quantification of the relationship could not be obtained with high confidence.

PK-safety response relationship for neutropenia and thrombocytopenia relationships were characterized by a semi-mechanistic population longitudinal PK/PD model. A larger exposure was associated with a larger reduction in absolute neutrophil count and absolute thrombocyte count.

2.4.4. Discussion on clinical pharmacology

In general, the bioanalysis methods used were well described and both pre-study and within-study validation was acceptable.

The bridging between formulations and associated food recommendations is considered well supported. 13% of all PK profiles obtained with the phase II/commercial free base tablet in fasting conditions were identified as "low-liers". Low-liers were not identified in fed conditions (high-fat or moderate-fat meal or in between meals (moderate-fat meal 1 hour before and 2 hours after dosing). This, together with the fact that palbociclib was dosed with food in phase III, palbociclib should be taken with food, preferably a meal (see SmPC sections 4.2 and 5.2).

Palbociclib is mainly eliminated through metabolism. Only a small fraction of the dose was recovered as unchanged drug in faeces (2%) and urine (3.5 or 7%).Renal and biliary excretion of palbociclib appears of limited importance for drug clearance. CYP3A4 and SULT2A1 are the enzymes responsible for the majority of elimination of palbociclib.

Palbociclib exhibit dose-independent pharmacokinetics at single dose conditions. However as it is a TDI on CYP3A4, it inhibits part of its own metabolism and thus, during multiple dose conditions, pharmacokinetics should be dose-dependent to some extent. Steady state is reached on day 8 in contrast to the day 3-5 that is

expected based on the half-life. This is likely due to the weak time dependent CYP3A inhibitory property of palbociclib. Inter-individual variability in CL/F is moderate.

Palbociclib contributed to one fifth of the radioactivity in plasma after a radiolabelled dose. Palbociclib Cmax was generally observed 6 hours after oral dosing, while Cmax of the metabolite PF-05089326 was observed earlier, around 4 hours after dosing. Median peak concentrations for total radioactivity in plasma were observed at 4 hours after dosing (2 hours before palbociclib Cmax) but this could not be explained by the metabolite PF-05089326 due to too low exposure. The higher exposure for radioactivity may be due to the presence of metabolite(s) with high exposure in plasma. In line with this, the mean t½ for total radioactivity (77 hours) was more than 3-fold longer than that for palbociclib or PF-05089326 (~21 hours).

No formal study of the PK of palbociclib in renal impairment has been submitted. The effect of mild and moderate renal impairment was evaluated in the PPK analysis. Since renal elimination appears to be a minor route of elimination for palbociclib, no initial dose adjustment is needed in subjects with mild and moderate renal impairment. No data is available in severe renal impairment or ESRD which is acceptable (see SmPC sections 4.2, 4.4 and 5.2). A study (1014) in renal impairment is ongoing and planned to be submitted in June 2017.

There is an ongoing study in hepatic impairment which should be submitted as a post-approval commitment. Mild hepatic impairment was evaluated with PPK and no initial dose adjustment is needed in mild hepatic impairment (see SmPC sections 4.2, 4.4 and 5.2). A study (1013) in hepatic impairment is ongoing and planned to be submitted in December 2017.

The applicant has not discussed whether the pharmacokinetics of palbociclib can be subject to genetic differences. CYP3A has some genetic component. SULT2A1 is subject to copy number polymorphism expressed. However, due to the apparent multiple pathways, CHMP decided to not pursue this issue further.

Weight, gender, race and age were considered having no clinically relevant effect on palbociclib exposure.

No statistically significant effects of gender (72.2 % female) on the PK parameters as found. Considering the intended patient population (women with breast cancer) the conclusion is of less importance.

No initial dose adjustment in elderly was proposed which considered the available data was considered acceptable.

No studies have been conducted to investigate the pharmacokinetics of palbociclib paediatric patients, which is acceptable since a class waiver for paediatric patients < 18 years of age apply.

.Inhibition *in vivo* at a “systemic level” is unlikely. Inhibition in the intestine of UGT1A4, 1A9 and 2B7 cannot be excluded but is considered of negligible clinical relevance.

The proposed Ibrance indication is treatment in combination with aromatase inhibitors and LHRH agonists. Thus, the risk for interactions between palbociclib and aromatase inhibitors and LHRH agonists was assessed and shown to be low. Consequently, the combination of palbociclib and aromatase inhibitors/LHRH agonists is considered acceptable from a pharmacokinetic perspective.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of palbociclib has in general been well characterised and considered acceptable to support this application.

2.5. Clinical efficacy

2.5.1. Dose response studies

Two dose-response studies were mentioned, Study 1001 and Study 1010. Only the former was completed and available for assessment.

Study 1001 – Dose finding

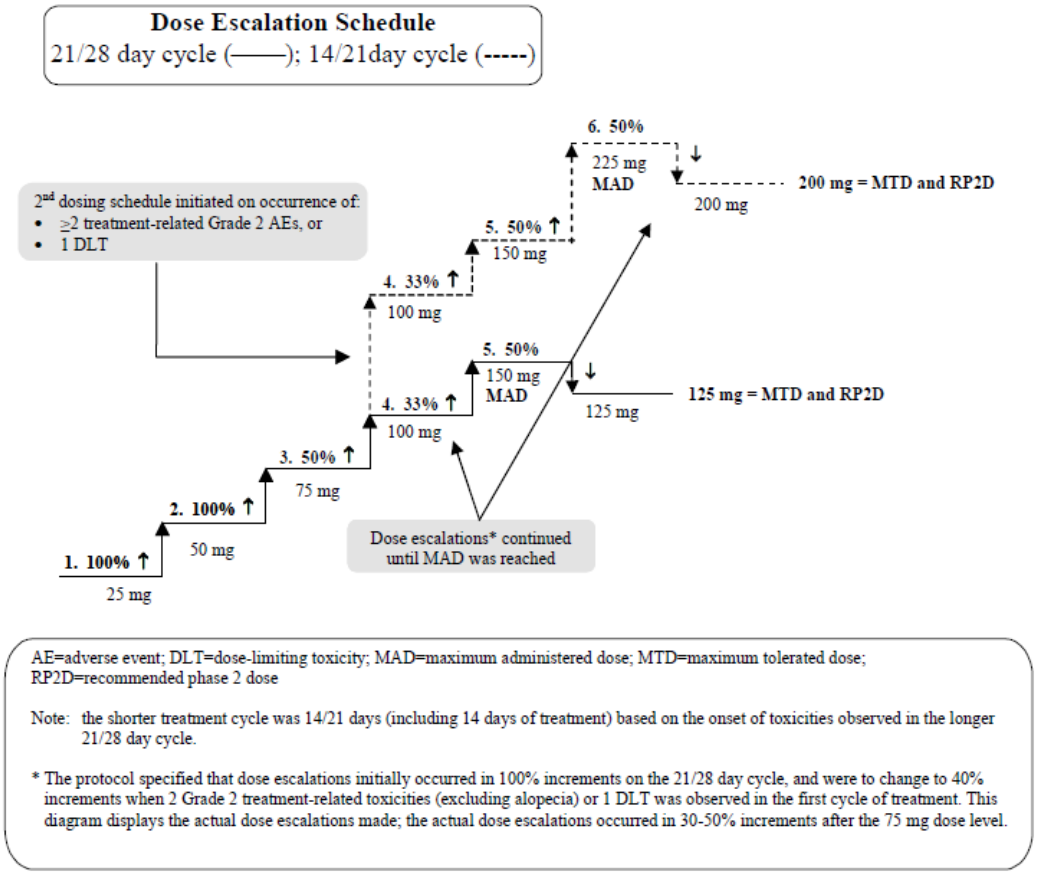
A Phase 1 Clinical, Pharmacokinetic, and Pharmacodynamic Evaluation of 2 Schedules of Oral PD 0332991, a Cyclin-Dependent Kinase Inhibitor, in Patients With Advanced Cancer

Study 1001 evaluated 2 different dosing schedules of palbociclib in patients with advanced cancer: a 4-week schedule consisting of 21 days of treatment followed by 7 days without treatment (Schedule 3/1) and a 3-week schedule consisting of 14 days of treatment followed by 7 days without treatment (Schedule 2/1). The palbociclib treatment schedules were selected based in part on (1) anticipated toxicities and (2) plans to test palbociclib both as a single agent and in combination with cytotoxic chemotherapy. The predicted toxicity of reversible myelosuppression observed non-clinically in rats and dogs prompted the inclusion in each schedule of a 1-week treatment interruption in each cycle to allow recovery of haematologic parameters.

The maximum tolerated dose (MTD) was defined as the highest dose level studied for which the incidence of first-cycle DLT was less than 33%, i.e. as commonly done with cytotoxic compounds.

The recommended Phase 2 doses, and MTDs, were determined to be 125 mg QD on Schedule 3/1 and 200 mg on Schedule 2/1. (Figure 8)

Figure 8 - Study 1001 - Dose Escalation and Schedule Summary



AE=adverse event; DLT=dose-limiting toxicity; MAD=maximum administered dose; MTD=maximum tolerated dose; RP2D=recommended phase 2 dose

Note: the shorter treatment cycle was 14/21 days (including 14 days of treatment) based on the onset of toxicities observed in the longer 21/28 day cycle.

* The protocol specified that dose escalations initially occurred in 100% increments on the 21/28 day cycle, and were to change to 40% increments when 2 Grade 2 treatment-related toxicities (excluding alopecia) or 1 DLT was observed in the first cycle of treatment. This diagram displays the actual dose escalations made; the actual dose escalations occurred in 30-50% increments after the 75 mg dose level.

Dose-limiting toxicities (DLTs)

DLTs were defined as: Grade 4 haematologic toxicity, Grade 3 neutropenia associated with a documented infection or fever ≥38.5°C, Grade≥ 3 non-haematologic treatment-related toxicity, except those that had not been maximally treated (e.g., nausea, vomiting, diarrhoea) or that the patient considered tolerable (such as skin rash), inability to receive the next dose of palbociclib within 1 week (±1 day) of the last dose due to lack of haematologic recovery (platelets <50,000/µL, ANC <1,000/µL, and haemoglobin <8.0 g/dL) or due to prolonged non-haematologic toxicities of ≥Grade 3 severity.

Table 11 - Summary of Safety Outcomes Used to Determine Dose Escalation and MTD (Study 1001, Full Analysis Set Population)

Dose regimen (mg)		Number of Patients	No. of patients with a Cycle 1 DLT
25 mg QD	21/28 days	3	0
50 mg QD	21/28 days	3	0
75 mg QD	21/28 days	7	2*
100 mg QD	21/28 days	3	0
125 mg QD	21/28 days	22	1
150 mg QD	21/28 days	3	2
100 mg QD	14/21 days	3	0
150 mg QD	14/21 days	4	0
200 mg QD	14/21 days	20	4
225 mg QD	14/21 days	6	2

* Although 2 DLTs were documented in this cohort, dose escalation continued because the investigators did not consider them to be 'significant' DLTs due to the low dose being inconsistent with pre-clinical data and the small number of patients.

All observed DLTs were haematological, mostly neutropenia. The overall incidence of TEAEs was higher in Cycle 1 compared with subsequent treatment cycles (93% vs 77%) and consistently lower frequencies were seen for almost all SOCs, with the main exception of Musculoskeletal and connective tissue disorders which did not reach the 5% frequency cut-off in Cycle 1, but occurred in 27% (4% related) of patients across regimens and doses in subsequent cycles.

Efficacy

One patient (who had testicular cancer and was on the 14/21 day dosing schedule) had a confirmed partial response (PR) during the study. Thirty-five percent of patients on the 21/28 day schedule and 29% of patients on the 14/21 day schedule had stable disease (SD) for two or more cycles of treatment; 27% of patients on the 21/28 day schedule and 19% of patients on the 14/21 day schedule had SD for 4 or more cycles; and 16% of patients on the 21/28 day schedule and 10% of patients on the 14/21 day schedule had SD for 10 or more cycles.

The conclusion was that the safety profiles of Schedule 2/1 and Schedule 3/1 were generally comparable; however, a greater proportion of patients on Schedule 2/1 had treatment-related adverse events than on Schedule 3/1. The safety profiles, along with the suggestion of greater long-term anti-tumour activity observed on Schedule 3/1, led to the selection of this treatment schedule for the advanced breast cancer study.

2.5.2. Main studies

The Phase 1/2 study 1003 (PALOMA-1) was initially submitted as the pivotal study, but in view of issues identified in this study, and with the submission during review of the Marketing Authorisation Application (MAA) of data from 2 phase 3 studies, Study 1003 was no longer considered pivotal for the marketing application. As such, it is discussed in the section for Supportive studies below.

Study 1023 (PALOMA-3)

Multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial of fulvestrant (Faslodex) with or without PD-0332991 (palbociclib) ± goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy.

This study was submitted in order to support the indication for palbociclib in combination with fulvestrant.

Methods

Study Participants

Inclusion Criteria

Patients must have met all of the following criteria for inclusion in the study:

1. Women 18 years of age or older, who were either:

Postmenopausal, as defined by at least one of the following criteria:

- Age ≥60 years;
- Age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and serum estradiol and follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females;
- Documented bilateral oophorectomy;
- Medically confirmed ovarian failure

or

Pre/ perimenopausal, ie, not meeting the criteria for being postmenopausal.

- Pre/perimenopausal women could have been enrolled if amenable to be treated with the LHRH agonist goserelin. Patients were to have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to randomization. But, if patients had received an alternative LHRH agonist prior to study entry, they were to switch to goserelin for the duration of the study.

2. Histologically or cytologically proven diagnosis of breast cancer with evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent.

3. Documentation of ER-positive and/or PR-positive tumour (≥1% positive stained cells) based on most recent tumour biopsy (unless bone-only disease, see below) utilizing an assay consistent with local standards.

4. Documented HER2-negative tumour based on local testing on most recent tumour biopsy:

HER2-negative tumour was determined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH [fluorescent in situ hybridization]/CISH [chromogenic in situ hybridization]/SISH [silver fluorescent in situ hybridization]/DISH [dual fluorescent in situ hybridization]) defined as a human epidermal growth factor receptor 2/centromeric probe for chromosome 17 (HER2/CEP17) ratio <2 or for single probe assessment a HER2 copy number <4.

5. Patients were to satisfy the following criteria for prior therapy:

- Progressed during treatment or within 12 months of completion of adjuvant therapy with an aromatase inhibitor if postmenopausal, or tamoxifen if pre- or perimenopausal.

or

- Progressed while on or within 1 month after the end of prior aromatase inhibitor therapy for advanced/metastatic breast cancer if postmenopausal, or prior endocrine treatment for advanced/metastatic breast cancer if pre- or perimenopausal.

- One previous line of chemotherapy for advanced/metastatic disease was allowed in addition to endocrine therapy.

6. Except where prohibited by local regulations, all patients were to agree to provide and had available a formalin-fixed paraffin embedded (FFPE) tissue biopsy sample taken at the time of presentation with recurrent or metastatic disease. A de novo biopsy was required if no archived tissue taken at the time of presentation with recurrent/metastatic disease was available. The sole exceptions were those patients with bone-only disease for whom provision of previous archival tissue only was acceptable. Patients who had surgery within the last 3 years (but without neoadjuvant chemotherapy prior to surgery) and relapsed while receiving adjuvant therapy may provide a tumour specimen from that surgery.

7. Measurable disease as defined by RECIST version 1.1, or bone-only disease. Patients with bone-only metastatic cancer were to have a lytic or mixed lytic-blastic lesion that could be accurately assessed by computed tomography (CT) or magnetic resonance imaging (MRI). Patients with bone-only disease and blastic-only metastasis were not eligible. Tumour lesions previously irradiated or subjected to other loco-regional therapy were only deemed measurable if progression at the treated site after completion of therapy was clearly documented.

8. Eastern Cooperative Oncology Group (ECOG) performance status 0-1.

9. Adequate organ and marrow function defined as follows:

Absolute neutrophil count (ANC) ≥1,500/mm3 (1.5 x 109/L);

Platelets ≥100,000/mm3 (100 x 109/L);

Haemoglobin ≥9 g/dL (90 g/L);

Serum creatinine ≤1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution;

Total serum bilirubin ≤1.5 x ULN (<3ULN if Gilbert's disease);

Aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT) ≤3 x ULN (≤5.0 x ULN if liver metastases present);

Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN if bone or liver metastases present).

10. Resolution of all acute toxic effects of prior therapy or surgical procedures to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤1 (except alopecia).

11. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study.

12. Patients who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion Criteria

Patients who met any of the following exclusion criteria were not included in the study:

1. Prior treatment with any CDK inhibitor, or fulvestrant, or with everolimus, or any agent whose mechanism of action is to inhibit the PI3K-mTOR pathway.

2. Patients with advanced/metastatic, symptomatic, visceral spread, that were at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement).

3. Known active uncontrolled or symptomatic Central Nervous System (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral oedema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they had been definitively treated (eg, radiotherapy, stereotactic surgery) and were clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.

4. Current use of food or drugs known to be potent CYP3A4 inhibitors, drugs known to be potent CYP3A4 inducers (for examples, see the Prohibited Medications Section 9.4.8.2.1), and drugs that are known to prolong the QT interval.

5. Major surgery, chemotherapy, radiotherapy, or other anti-cancer therapy within 2 weeks before randomization. Patients who received prior radiotherapy to ≥25% of bone marrow were not eligible independent of when it had been received.

6. Any other malignancy within 3 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.

7. QTc interval >480 ms (based on the mean value of the triplicate electrocardiogram [ECGs]), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation or Torsade de Pointes.

8. Any of the following within 6 months of randomization: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.

9. Impairment of gastrointestinal (GI) function or GI disease that might have significantly altered the absorption of palbociclib, such as history of GI surgery with might have resulted in intestinal blind loops and patients with clinically significant gastroparesis, short bowel syndrome, unresolved nausea, vomiting, active inflammatory bowel disease or diarrhoea of CTCAE Grade >1.

10. Prior hematopoietic stem cell or bone marrow transplantation.

11. Known abnormalities in coagulation such as bleeding diathesis, or treatment with anticoagulants precluding intramuscular injections of fulvestrant or goserelin (if applicable).

12. Known or possible hypersensitivity to fulvestrant, goserelin, any of their excipients or to any palbociclib/placebo excipients.

13. Known human immunodeficiency virus infection.

14. Other severe acute or chronic medical or psychiatric condition, including recent or active suicidal ideation or behaviour, or laboratory abnormality that might have increased the risk associated with study participation or

investigational product administration or might have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the patient inappropriate for entry into this study.

15. Patients who were investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

16. Participation in other studies involving investigational drugs (Phases 1-4) within 4 weeks before randomization in the current study.

Treatments

Arm A: palbociclib 125 mg administered orally once daily for 21 days followed by 7 days off treatment for each 28-day cycle (Schedule 3/1) plus fulvestrant (Faslodex) 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and every 28 days (+/-7 days) thereafter starting from Day 1 of Cycle 1.

Arm B: placebo administered orally once daily for 21 days followed by 7 days off treatment for each 28-day cycle (Schedule 3/1) plus fulvestrant (Faslodex) 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and every 28 days (+/-7 days) thereafter starting from Day 1 of Cycle 1.

Palbociclib doses could be reduced to 100 mg daily and 75 mg daily on 3/1 schedule, respectively, or to 75 mg on a 2-week on/2-week off (2/2) schedule.

Objectives and endpoints

The primary endpoint of the study was PFS as determined by the investigators' assessment. The secondary endpoints included an assessment of secondary measures of efficacy and the safety and tolerability of palbociclib administered in combination with fulvestrant as well as of placebo plus fulvestrant.

Secondary efficacy endpoints included OS, objective response, duration of response, clinical benefit response, and patient reported outcomes (PROs).

Primary objective:

To demonstrate the superiority of palbociclib in combination with fulvestrant (with or without goserelin) over fulvestrant (with or without goserelin) plus placebo in prolonging investigator-assessed progression-free survival (PFS) in women with hormonal receptor positive (HR-positive)/human epidermal growth factor negative (HER2-negative) metastatic breast cancer whose disease had progressed on prior endocrine therapy.

Secondary objectives:

• To compare measures of tumour control, including objective response (OR), duration of response (DR), clinical benefit response (CBR = CR or PR or stable disease [SD] ≥24 weeks) and overall survival (OS) between the treatment arms.

• To compare safety and tolerability between the treatment arms.

• To evaluate trough concentrations of palbociclib when given in combination with fulvestrant or fulvestrant plus goserelin compared to historical palbociclib data.

• PK: To compare fulvestrant and goserelin trough concentrations when given in combination with palbociclib to those when given without palbociclib.

• PK: To explore correlations between palbociclib exposures and efficacy/safety findings in this patient population.

• To compare Patient Reported Outcomes (PROs) measures between treatment arms. PRO endpoints such as global Quality of Life (QOL), functioning, breast symptoms, time to deterioration (TTD) in pain, EQ-5D index and general health status.

• To characterize alterations in genes, proteins, and ribonucleic acids (RNAs) relevant to the cell cycle, drug targets, tumour sensitivity and/or resistance.

• To conduct subgroup analysis for primary and secondary endpoints in stratified groups.

Tumour assessments

Post-baseline tumour assessments were performed every 8 weeks (±7 days) for the first year, then after 1 year every 12 weeks (±7 days) (calculated from randomization) until radiographically and/or clinically (i.e., for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation, initiation of new anticancer therapy, or discontinuation of patient from overall study participation (e.g., death, patient's request, lost to follow-up)

Sample size

The sample size for this study was determined based on the results of a randomized Phase 2 trial assessing fulvestrant with or without dasatinib in postmenopausal patients with HR positive metastatic breast cancer previously treated with an AI. The median PFS for the fulvestrant alone arm was 5.3 months and the median PFS for the combination arm was 6.0 months. Based upon these results, the median PFS for the comparator arm in this study was assumed to be 6.0 months.

An improvement of 56% to a median PFS of 9.38 months (corresponding to a HR=0.64) was to be considered clinically meaningful. A total of 238 PFS events were required in the two treatment arms for the study to have a 90% power to detect a hazard ratio of 0.64 (representing a 56% improvement in median PFS [6.00 months vs 9.38 months]) with a 1-sided significance level of alpha=0.025.

Assuming a non-uniform accrual accomplished over a period of about 14 months, data follow-up for approximately 20 months from the start of study randomization for final PFS analysis, and a non-uniform dropout with dropout rate of 25% at 18 months for PFS, a total sample size of approximately 417 patients (278 in the fulvestrant plus palbociclib arm and 139 in the placebo plus fulvestrant arm) was required.

The sample size described above also allowed the assessment of differences in the secondary endpoint of OS. The median OS for women with advanced or metastatic breast cancer treated with AI and fulvestrant monotherapy was assumed to be 24 months. With an overall one-sided α of 0.025 and one interim analysis of OS, the study had approximately 80% power to detect a HR of 0.65 (representing a 54% increase in median OS from 24 months to37 months) when 198 deaths had occurred.

A sample-size re-estimation was allowed by protocol at the interim analysis (see below), using the inferential procedure described by Cui et al (1999)[15] to preserve the type I error.

[15] Cui L1, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics. 1999 Sep;55(3):853-7

Randomisation

Randomization was stratified by documented sensitivity to prior hormonal therapy (Yes versus No), by menopausal status at study entry (pre-/peri- versus postmenopausal), and by the presence of visceral metastases (Yes versus No). 'Visceral' referred to lung, liver, brain, pleural and peritoneal involvement. Sensitivity to prior hormonal therapy was defined as either: documented clinical benefit (CR, PR, SD ☐24 weeks) to at least one prior hormonal therapy in the metastatic setting, or at least 24 months of adjuvant hormonal therapy prior to recurrence.

Blinding (masking)

This was a double-blind trial.

Statistical methods

PFS data were censored on the date of the last tumor assessment on study for patients who did not have objective tumor progression and who did not die while on study. Patients lacking an evaluation of tumor response after randomization had their PFS time censored on the date of randomization with the duration of one day. Additionally, patients who started a new anticancer therapy prior to documented PD were censored at the date of the last tumor assessment prior to the start of the new therapy. Patients with documentation of PD or death after an unacceptably long interval (ie, 2 or more incomplete or non-evaluable assessments) since the last tumor assessment were censored at the time of last objective assessment that did not show PD.

Time-to-event endpoints between the 2 treatment arms will be compared with a 1-sided stratified log-rank test adjusting for presence of visceral metastases and sensitivity to prior hormonal therapy (two of the baseline stratification factors). PFS time associated with each treatment arm will be summarized for the ITT population using the Kaplan-Meier method and displayed graphically where appropriate. Hazard ratios and 2-sided 95% confidence intervals (subject to the multiplicity adjustment at the final analysis for PFS and OS) will be estimated using Cox proportional hazards regression.

Cox proportional hazard models will also be used to explore the potential influences of the baseline stratification factors on time-to-event endpoints.

The study is designed to have one interim analysis and the final analysis at 238 events based on the primary PFS endpoint with the investigator assessment. The interim analysis will be conducted to allow for early stopping of the study due to efficacy or to potentially re-estimate the sample size of the trial based upon the primary endpoint of PFS. The safety of the combination will also be assessed at the interim analysis. The Haybittle-Peto boundary will be used (alpha=0.00135 was to be spent at interim analysis) in developing the efficacy boundary of the interim analysis of PFS. The analysis will be performed after approximately 143 investigator-assessed PFS events (documented progressive disease or death; approximately 60% of the total events expected). The information fraction for the interim analysis may be adjusted if needed.

Only one interim analysis of OS is planned. Although the first possible time for OS interim analysis could be at the time of the PFS IA, it is anticipated that the number of deaths could be low at PFS IA and yield non-robust analysis results. Therefore, the OS interim analysis will be planned at approximately 97 deaths (at the estimated time for planned PFS final analysis). For the interim analysis of OS, O'Brien-Fleming boundary will be used and the overall significance level for the efficacy analysis of OS will be preserved at 0.025 (one-sided test).

Results

Participant flow

Table 12 - Patient's Disposition (Study 1023)

Number (%) of Patients	Palbociclib plus Fulvestrant	Placebo plus Fulvestrant	Total
Randomized to study treatment	347	174	521
Randomized and not treated	2 (0.6)	2 (1.1)	4 (0.8)
Randomized and treated	345 (99.4)	172 (98.9)	517 (99.2)
Completed [1]	0	0	0
Discontinued [2]	107 (30.8)	97 (55.7)	204 (39.2)
Ongoing at data cutoff date	238 (68.6)	75 (43.1)	313 (60.1)
Reason for discontinuation [1]			
AE (reason for palbociclib/placebo discontinuation) [2]	9 (2.6)	3 (1.7)	12 (2.3)
AE (reason for fulvestrant discontinuation)	7 (2.0)	3 (1.7)	10 (1.9)
Global deterioration of health status	8 (2.3)	3 (1.7)	11 (2.1)
Lost to Follow-Up	0	0	0
Medication error without associated AE	0	0	0
Objective progression or relapse plus progressive disease	85 (24.5)	87 (50.0)	172 (33.0)
Protocol violation	0	0	0
Study terminated by the sponsor	0	0	0
Patient died	0	1 (0.6)	1 (0.2)
Patient refused to continue treatment for reason other than AE	1 (0.3)	1 (0.6)	2 (0.4)
Patient started new treatment for disease under study	0	0	0
Withdrew consent	4 (1.2)	2 (1.1)	6 (1.2)
Other	0	0	0

Abbreviation: AE: adverse event, CRF: Case Report Form, N: number of patients, n: number of patients affected
[1] Includes patients who discontinued treatment for progression or any other reason. Discontinued is as per the Conclusion of Treatment page of the CRF.
[2] The patients 11241001 and 11241006 completed the End of Treatment CRF page for palbociclib/placebo only.
Percentages are calculated using N as a denominator.
0 mg doses have not been excluded from the algorithm determining patient status.

Recruitment

Between 26 Sept 2013 and 26 Aug 2014, a total of 521 pre- /peri- and postmenopausal women were randomized (2:1) to the study at 144 sites in 17 countries: Australia (11 sites), Belgium (11 sites), Canada (11 sites), Germany (2 sites), Ireland (1 site), Italy (9 sites), Japan (8 sites), the Netherlands (6 sites), Portugal (2 sites), Romania (4 sites), the Russian Federation (5 sites), the Republic of South Korea (5 sites), Taiwan (2 sites), Turkey (1 sites), the Ukraine (6 sites), the United Kingdom (4 sites), and the United States (56 sites).

Three hundred forty-seven (347) patients were randomized to the palbociclib plus fulvestrant arm, and 174 patients were randomized to the placebo plus fulvestrant arm, of which 99 pre- /perimenopausal patients additionally received goserelin across both treatment arms.

Conduct of the study

The frequencies of different types of protocol deviations were similar across study arms. The majority of the inclusion/exclusion criteria violations in both arms pertained to exclusion criteria 5, which states that all anti-cancer treatments should have been stopped at least 2 weeks prior to randomization. Secondly, violations with regard to providing tumour samples for central lab analysis were frequent.

There were 2 protocol amendments and 1 SAP amendment during study.

The protocol was amended to revise the study drug administration instructions from administration in a fasted state to administration with food and to prohibit the concomitant use of proton-pump inhibitors. Prospective ophthalmic examinations, and prospective monitoring of haemoglobin A1c were added to characterize whether or not palbociclib affected glucose metabolism. SAP amendments included eg changes due to that biomarker analyses were not performed.

Baseline data

Table 13 - Demographic Characteristics (Study 1023, ITT)

Number(%) of Patients	Palbociclib plus Fulvestrant N=347	Placebo plus Fulvestrant N=174	Total N=521
Age (years) n (%)			
<65	261 (75.2)	131 (75.3)	392 (75.2)
≥65	86 (24.8)	43 (24.7)	129 (24.8)
Mean (SD)	56.9 (11.7)	56.8 (10.4)	56.9 (11.3)
Median (range)	57.0 (30-88)	56.0 (29-80)	57.0 (29-88)
Race n (%)			
White	252 (72.6)	133 (76.4)	385 (73.9)
Black	12 (3.5)	8 (4.6)	20 (3.8)
Asian	74 (21.3)	31 (17.8)	105 (20.2)
Other	8 (2.3)	1 (0.6)	9 (1.7)
Unspecified	1 (0.3)	1 (0.6)	2 (0.4)
Ethnicity n (%)			
Hispanic/Latino	17 (4.9)	11 (6.3)	28 (5.4)
Not Hispanic/Latino	329 (94.8)	161 (92.5)	490 (94.0)
Unspecified	1 (0.3)	2 (1.1)	3 (0.6)
Weight (kg)			
n (%)	347 (100)	171 (98.3)	518 (99.4)
Mean (SD)	70.4 (17.5)	72.0 (17.6)	70.9 (17.6)
Median (range)	67.2 (35.6-142.0)	69.8 (35.1-126.8)	68.5 (35.1-142.0)
Height (cm)			
n (%)	347 (100)	174 (100)	521 (100)
Mean (SD)	161.1 (7.0)	(161.3 (7.6)	161.2 (7.2)
Median (range)	161.5 (139.8-182.9)	162.0 (121.9-180.3)	162.0 (121.9-182.9)

Abbreviations: N: number of patients, n: number of patients affected, SD: standard deviation.

The demographic characteristics were well balanced across arms.

Table 14 - Baseline Disease Characteristics (Study 1023, ITT)

	Palbociclib plus Fulvestrant N=347 n (%)	Placebo plus Fulvestrant N=174 n (%)	Total N=521 n (%)
Measurable disease present [1]			
Yes	268 (77.2)	138 (79.3)	406 (77.9)
No	79 (22.8)	36 (20.7)	115 (22.1)
Adequate baseline assessment [2]			
Yes	346 (99.7)	174 (100)	520 (99.8)
No	1 (0.3)	0	1 (0.2)
ER status [3]			
Positive	339 (97.7)	167 (96.0)	506 (97.1)
Negative	1 (0.3)	2 (1.1)	3 (0.6)
Missing	7 (2.0)	5 (2.9)	12 (2.3)
PR status [3]			
Positive	243 (70.0)	117 (67.2)	360 (69.1)
Negative	91 (26.2)	48 (27.6)	139 (26.7)
Missing	13 (3.7)	9 (5.2)	22 (4.2)
HER2 status [3]			
Positive	2 (0.6)	2 (1.1)	4 (0.8)
Negative	341 (98.3)	171 (98.3)	512 (98.3)
Equivocal	3 (0.9)	1 (0.6)	4 (0.8)
Missing	1 (0.3)	0	1 (0.2)
Histopathological classification			
Diffuse adenocarcinoma	2 (0.6)	0	2 (0.4)
Mixed adenocarcinoma	3 (0.9)	3 (1.7)	6 (1.2)
Adenocarcinoma	33 (9.5)	11 (6.3)	44 (8.4)
Ductal carcinoma	233 (67.1)	106 (60.9)	339 (65.1)
Lobular carcinoma	40 (11.5)	22 (12.6)	62 (11.9)
Other	34 (9.8)	25 (14.4)	59 (11.3)
Unknown	2 (0.6)	7 (4.0)	9 (1.7)
Histopathological grade			
Grade 1	22 (6.3)	16 (9.2)	38 (7.3)
Grade 2	162 (46.7)	79 (45.4)	241 (46.3)
Grade 3	93 (26.8)	40 (23.0)	133 (25.5)
Grade 4	3 (0.9)	0	3 (0.6)
Not done	9 (2.6)	9 (5.2)	18 (3.5)
Unknown	58 (16.7)	29 (16.7)	87 (16.7)
Missing	0	1 (0.6)	1 (0.2)

Recurrence type			
Locoregional recurrence	16 (4.6)	10 (5.7)	26 (5.0)
Local recurrence	18 (5.2)	8 (4.6)	26 (5.0)
Regional recurrence	15 (4.3)	7 (4.0)	22 (4.2)
Distant recurrence	229 (66.0)	121 (69.5)	350 (67.2)
Newly diagnosed	67 (19.3)	25 (14.4)	92 (17.7)
Unknown	2 (0.6)	2 (1.1)	4 (0.8)
Missing	0	1 (0.6)	1 (0.2)
Involved disease sites [4]			
Bone	263 (75.8)	129 (74.1)	392 (75.2)
Breast	61 (17.6)	19 (10.9)	80 (15.4)
Liver	127 (36.6)	81 (46.6)	208 (39.9)
Lung	103 (29.7)	44 (25.3)	147 (28.2)
Lymph node	138 (39.8)	63 (36.2)	201 (38.6)
Other	109 (31.4)	46 (26.4)	155 (29.8)
Number of involved disease sites [4]			
1	111 (32.0)	60 (34.5)	171 (32.8)
2	99 (28.5)	50 (28.7)	149 (28.6)
3	73 (21.0)	36 (20.7)	109 (20.9)
4	45 (13.0)	18 (10.3)	63 (12.1)
>4	17 (4.9)	8 (4.6)	25 (4.8)
Not reported	2 (0.6)	2 (1.1)	4 (0.8)
ECOG performance status			
0	207 (59.7)	115 (66.1)	322 (61.8)
1	140 (40.3)	59 (33.9)	199 (38.2)

Abbreviations: CT: computed tomography, ECOG: Eastern Cooperative Oncology Group, ER: Eastern Cooperative Oncology Group, ER: estrogen receptor, HER: human epidermal growth factor receptor, N: number of patients, n: number of patients affected, PR: progesterone receptor

1. At least 1 target lesion ≥20 mm by conventional techniques or at least 1 target lesion >10 mm for spiral CT. Source data for [1] is Table 16.2.6.2.1.
2. Patient either had a Measurable Disease or bone only disease. Patients with target lesions: All target lesions have measurable measurement(s).
   Patients with bone lesions only: All bone lesions have non-missing assessments(s) and at least 1 of the bone lesions assessed as non-indeterminate. Assessments conducted within 84 days for Bone and 42 days for Breast from randomization considered to be in Adequate Baseline Window.
3. For ER and PR results of IHC method: 0 and Negative are classified as 'Negative'; 1+, 2+, 3+ and Positive are classified as 'Positive'.
   For HER2 results of IHC method: 0, 1+ and Negative are classified as 'Negative'; 2+ as 'Equivocal'; 3+ and Positive as 'Positive'.
   For 4 patients Positive result of HER2 was reported due to mistake. For 4 patients Equivocal result of HER2 was confirmed Negative by confirmatory test.
   Patients with discrepant biomarker qualitative results are not included in this analysis (treated as missing).
   Source data for [3] is Table 16.2.6.4.1.
4. Involved sites include both target and non-target sites. Sites with multiple lesions are counted once.

Table 15 - Patient by Stratification Factors (Study 1023)

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

Abbreviations: CRF: case report form, N: number of patients, n: number of patients affected.

Table 16 - Prior Therapies (Study 1023, ITT)

	Palbociclib plus Fulvestrant N=347 n (%)	Placebo plus Fulvestrant N=174 n (%)	Total N=521 n (%)
Prior surgeries			
No	62 (17.9)	25 (14.4)	87 (16.7)
Yes	285 (82.1)	148 (85.1)	433 (83.1)
Not reported	0	1 (<1.0)	1 (<1.0)
Prior radiation therapies			
No	107 (30.8)	43 (24.7)	150 (28.8)
Yes	238 (68.6)	130 (74.7)	368 (70.6)
Not reported	2 (<1.0)	1 (<1.0)	3 (<1.0)
Prior systemic therapies			
No	0	0	0
Yes	347 (100)	174 (100)	521 (100)
Number of regimens			
1	71 (20.5)	39 (22.4)	110 (21.1)
2	106 (30.5)	56 (32.2)	162 (31.1)
3	98 (28.2)	35 (20.1)	133 (25.5)
>3	72 (20.7)	44 (25.3)	116 (22.3)
Not reported	0	0	0
Previous chemo regimen for primary diagnosis [1]			
No	96 (27.7)	36 (20.7)	132 (25.3)
Yes	251 (72.3)	138 (79.3)	389 (74.7)
Oncology treatment types			
Neoadjuvant	69 (19.9)	33 (19.0)	102 (19.6)
Adjuvant	151 (43.5)	91 (52.3)	242 (46.4)
Advanced/metastatic	107 (30.8)	63 (36.2)	170 (32.6)
Missing	1 (<1.0)	0	1 (<1.0)
Previous hormonal regimen for primary diagnosis			
1	133 (38.3)	77 (44.3)	210 (40.3)
>1	214 (61.7)	97 (55.7)	311 (59.7)
Prior tamoxifen [2]	211 (60.8)	104 (59.8)	315 (60.5)
Prior aromatase inhibitors	296 (85.3)	151 (86.8)	447 (85.5)

Abbreviations: ITT: intent-to-treat, N: number of patients, n: number of patients affected, WHO: World Health Organization

1. The site confirmed that TAC, at variance of what reported by WHO Drug classification, is the acronym of the combination of the following chemotherapeutic agents: Docetaxel, Doxorubicin and Cyclophosphamide. TAC was classified as Chemotherapy.
   Chemotherapies reported as 'PALLIATIVE' oncology treatment type are classified as 'ADVANCED/METASTATIC'.
2. Includes Tamoxifen and Tamoxifen citrate.

Prior therapies were balanced across study arms.

In conclusion, no major imbalances in baseline characteristics were seen study across arms.

Numbers analysed

All efficacy analyses were based on intent-to-treat (ITT) population. Some efficacy sensitivity analyses were also performed on AT populations.

The intent-to-treat (ITT) population or full analysis set will include all patients who are randomized, with study drug assignment designated according to initial randomization, regardless of whether patients receive study drug or receive a different drug from that to which they were randomized. The ITT population will be the primary population for evaluating all efficacy endpoints and patient characteristics.

The as-treated (AT) population or safety analysis set will include all patients who receive at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received. The AT population will be the primary population for evaluating treatment administration/compliance and safety. Efficacy and clinical benefit endpoints may be assessed in this population as well.

Table 17 - Analysis populations, Study 1023

Number (%) of Patients	Palbociclib plus Fulvestrant	Placebo plus Fulvestrant	Total
ITT Analysis population	347	174	521
ITT Analysis with measurable disease at baseline population	268	138	
As treated (Safety Analysis) population	345	172	517
Analyzed for BICR	147 (42.4)	64 (36.8)	211 (40.5)
Analyzed for PRO	335 (96.5)	166 (95.4)	501 (96.2)
Analyzed for PK:	345 (99.4)	172 (98.9)	
Early Safety Review population[1]	38 (11.8)	21 (61.8)	
With goserelin	9 (12.7)	5 (55.6)	14 (17.5)
Without goserelin	29 (11.6)	16 (64.0)	45 (16.4)
Palbociclib Analysis population [2]	321 (100.0)	34 (100.0)	
With goserelin	71 (100.0)	9 (100.0)	80 (100.0)
Without goserelin	250 (100.0)	25 (100.0)	275 (100.0)

Outcomes and estimation

Primary endpoint –Progression-free survival

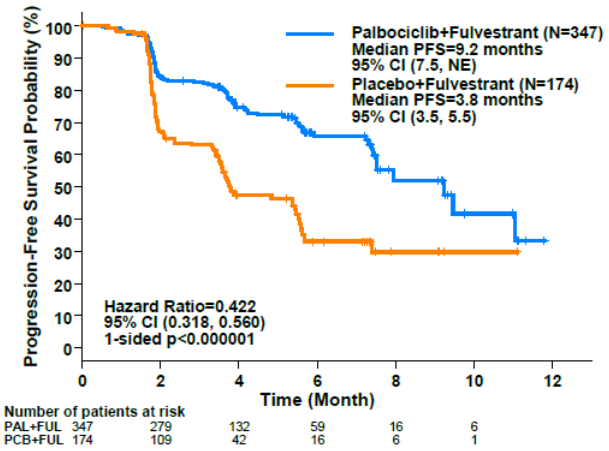
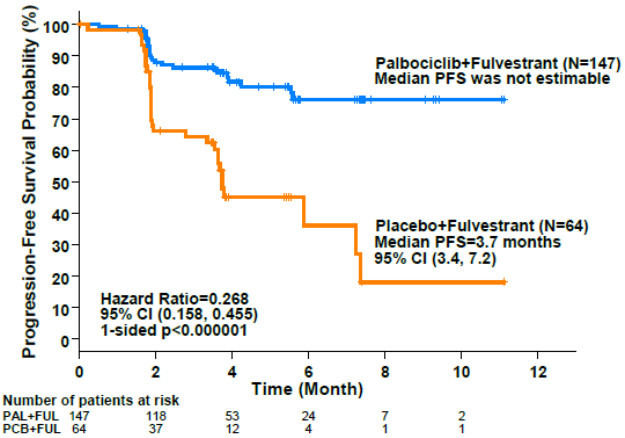
The study met its primary objective of prolonging investigator-assessed PFS at the interim analysis; the results crossed the prespecified Haybittle-Peto efficacy boundary (α=0.00135), demonstrating a statistically significant prolongation in PFS and a clinical meaningful treatment effect. The observed HR was 0.422 (95% CI: 0.318, 0.560; stratified 1-sided p-value <0.000001) in favour of palbociclib plus fulvestrant. The median PFS was 9.2 months (95% CI: 7.5, not estimable) for 347 patients randomized to palbociclib plus fulvestrant and 3.8 months (95% CI: 3.5, 5.5) for 174 patients randomized to placebo plus fulvestrant.

At the primary data cutoff date, the most common type of PFS event was disease progression, for 100 (28.8%) patients in the palbociclib plus fulvestrant arm and 91 (52.3%) patients in the placebo plus fulvestrant arm. Two deaths were reported in each treatment arm.

A total of 245 (70.6%) patients in the palbociclib plus fulvestrant arm and 81 (46.6%) in the placebo plus fulvestrant arm were censored in the investigator-assessed PFS analysis. The majority of censored patients were still in follow-up for disease progression at the time of censoring, 227 (65.4%) patients in the palbociclib plus fulvestrant arm and 70 (40.2%) patients in the placebo plus fulvestrant arm.

Two efficacy updates have subsequently been submitted; see further below.

Figure 9 - Kaplan-Meier Plot of Progression-Free Survival (Study 1023, ITT)

Investigator Assessment	Blinded Independent Central Review (BICR subset)
	

Sensitivity analyses

The prospectively defined sensitivity analyses of PFS all showed statistically significantly longer investigator-assessed PFS for the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm.

Table 18 - Sensitivity Analyses for PFS by Treatment (Study 1023, ITT)

Analysis	Number of Patients Palbociclib plus Fulvestrant vs Placebo plus Fulvestrant	Number of Events	Hazard Ratio (95% CI) [1]	p-value[2]
Sensitivity analysis 1 AT population	345 vs 172	102 vs 93	0.422 (0.318, 0.560)	<0.000001
Sensitivity analysis 2 ITT population	347 vs 174	102 vs 93	0.417 (0.314, 0.553)	<0.000001
Sensitivity analysis 3 ITT population	347 vs 174	102 vs 93	0.395 (0.297, 0.525)	<0.000001
Sensitivity analysis 4 ITT population	347 vs 174	102 vs 93	0.426 (0.321, 0.565)	<0.000001
Sensitivity analysis 5 ITT population	347 vs 174	102 vs 93	0.422 (0.318, 0.560)	<0.000001
Sensitivity analysis 6.1 ITT population	347 vs 174	102 vs 93	0.422 (0.318, 0.560)	<0.000001
Sensitivity analysis 6.2 ITT population	347 vs 174	104 vs 93	0.432 (0.326, 0.573)	<0.000001
Sensitivity analysis 6.3 ITT population (bone-only patients excluded)	263 vs 137	83 vs 77	0.411 (0.300, 0.563)	<0.000001
Sensitivity analysis 7 ITT population	347 vs 174	114 vs 101	0.438 (0.335, 0.574)	<0.000001
Sensitivity analysis 8 ITT population	347 vs 174	103 vs 103	0.378 (0.287, 0.498)	<0.000001

Abbreviations: AE: adverse event, AT: as treated, BICR: Blinded Independent Central Review, CI: confidence interval, ECOG: Eastern Cooperative Oncology Group, HR: hazard ratio, IND: indeterminate, ITT: intent-to-treat, vs: versus, PD: progressive disease, PFS: progression-free survival.
Sensitivity analysis 1: Influence of analysis population; based on AT population
Sensitivity analysis 2: A 1-sided unstratified log-rank test was used to compare treatments and the HR was based on an unstratified Cox proportional hazards model.
Sensitivity analysis 3: To investigate whether the stratification factors and important covariates influenced the outcome of the primary endpoint PFS. Final explanatory variables for the multivariate model were selected using a backward selection process with the significance level of 0.1 for retaining the effects in the model. Baseline factors that entered the model selection included age (≥65 vs <65), race (White, Black, Asian, Other), baseline ECOG status (1 vs 0), disease site (Non-Visceral vs Visceral), sensitivity to prior hormonal therapy (Yes vs No), menopausal status at study entry (Pre/Peri vs Post), ethnic origin (Hispanic vs Not-Hispanic), and geographical region (North America, Europe, Asia Pacific).
Assessor's note: Baseline ECOG status (1 vs. 0), and disease site (non-visceral vs. visceral) met the criteria and were the two baseline factors included in the model to yield the HR 0.395.
Sensitivity analysis 4: Influence of disease assessment scheduling. If disease progression was documented between 2 scheduled tumour assessments, then the date of progression was assigned to the earlier scheduled tumour assessment. In the event of death, the date of the endpoint was not adjusted.
Sensitivity analysis 5: Influence of deviations in tumour lesion assessment. If a lesion was classified as "indeterminate" (IND) at time point "X" and was adequately evaluated as PD at the next time point "X+1", then PD was assigned to the time point "X" or earlier (the first date of the consecutive INDs) instead of the date of the next time point "X+1" as the primary analysis.
Sensitivity analysis 6.1: Influence of bone-only disease patients. Patients with bone-only disease with fracture, radiation therapy, surgery, ECOG at least 2 point increase from baseline or change of therapy were censored at the date of prior tumour assessment with no PD.
Sensitivity analysis 6.2: Influence of bone-only disease patients: Patients with bone-only disease with fracture, radiation therapy, surgery, ECOG at least 2 point increase from baseline or change of therapy were considered as events.
Sensitivity analysis 6.3: Influence of bone-only disease patients: Bone-only disease patients were excluded from the analysis.
Sensitivity analysis 7: Influence of Missing Data: The following missing PFS data that might have resulted in the censored PFS data in the primary analysis were considered PFS events in addition to the documented PD and death: new anti-cancer treatment, lost to follow-up, consent withdrawal, medication error without associated AE.
Sensitivity analysis 8: Influence of potential investigator bias. Random sample BICR data and investigator assessed PFS (event) data were combined. For events identified by both BICR and investigator, BICR data were used to determine event time. For patients who were censored by both BICR and investigator, BICR (when applicable) data were used to determine the censoring time.
1) For sensitivity analyses 1 and 4 to 8, stratified hazard ratios are presented, for sensitivity analyses 2 and 3 unstratified hazard ratio ratios.

2) 1-sided p-values are reported except for sensitivity analysis 3 (2-sided p-value)

PFS updates

16 March 2015

An updated analysis of the PFS endpoint was performed after 259 patients had documented PD or death based on investigator assessment. The median duration of follow-up across the trial as of the 16 March 2015 data cutoff was 8.9 months. No data from blinded independent review were provided in the efficacy updates.

At an overall event rate of 50% (42 vs. 65%) the PFS HR was 0.46 (0.36-0-59), slightly higher but in line with the results in the interim analysis. Median PFS was 9.5 vs. 4.6 months, i.e. a difference of 4.9 months.

23 October 2015

A later update with data cut-off date 23 Oct 2015 was subsequently submitted based on an overall event rate of 64% (333 events in 521 patients) and a median follow-up of over 15 months in both arms. Again the PFS HR is slightly higher, at 0.497, but in line with the results in the interim analysis.

In the second update, the difference between arms in median PFS has increased to 6.6 months (11.2 vs 4.6 months, respectively). A summary is given in table 19, details in table 20 and figure 10.

Table 19 - PFS summary (Study 1023, investigator assessments, ITT, 23 October 2015)

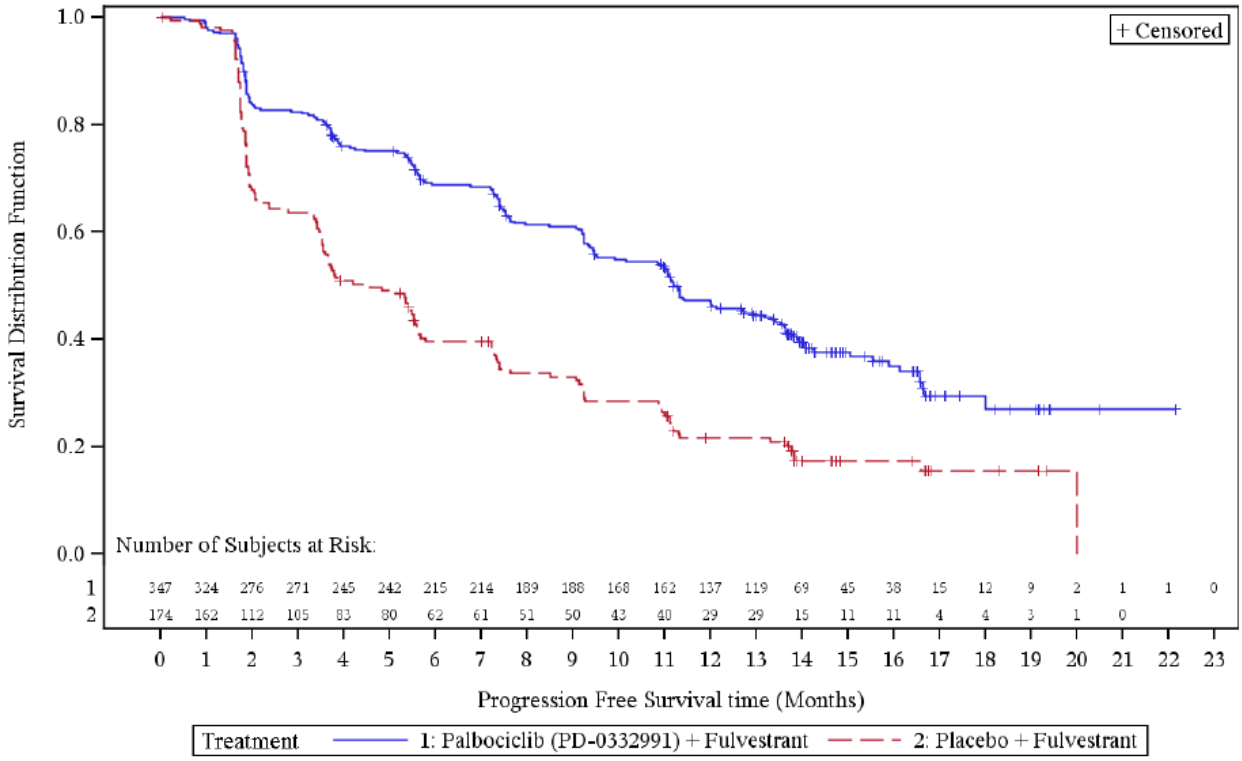
	IBRANCE plus fulvestrant (N=347)	**Placebo plus fulvestrant (N=174)**
Progression-free survival (PFS)		
Number of PFS events (%)	200 (57.6%)	133 (76.4%)
Median [months (95% CI)]	11.2 (9.5, 12.9)	4.6 (3.5, 5.6)
Hazard ratio (95% CI) and p-value	0.497 (0.398, 0.620), p<0.000001	

Table 20 - Progression-Free Survival - Investigator Assessment (Study 1023, ITT, 23 October 2015)

Category	Palbociclib + Fulvestrant (N=347)	Placebo + Fulvestrant (N=174)
Number of patients with event, n (%)	200 (57.6)	133 (76.4)
Type of event		
Objective progression	198 (57.1)	130 (74.7)
Death without objective progression	2 (<1.0)	3 (1.7)
Number censored, n (%)	147 (42.4)	41 (23.6)
Reason for censorship, n (%)		
No adequate baseline assessments	4 (1.2)	2 (1.1)
No on-study disease assessments	13 (3.7)	7 (4.0)
Given new anticancer treatment[a] prior to disease progression and after last dose of study treatment	15 (4.3)	5 (2.9)
Discontinued study without disease progression or death	5 (1.4)	2 (1.1)
Withdrew consent for follow-up	3 (<1.0)	2 (1.1)
Lost to follow-up	0 (0)	0 (0)
Other	2 (<1.0)	0 (0)
Unacceptable gap (>20 weeks) between PD or death and the most recent prior adequate assessment	1 (<1.0)	0 (0)
In follow-up for progression	109 (31.4)	25 (14.4)
Probability of being event free at Month 6[b] (95% CI)[c]	68.7 (63.4-73.5)	39.6 (32.1-47.0)
Probability of being event free at Month 12[b] (95% CI)[c]	46.5 (40.9-51.9)	21.5 (15.4-28.3)
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI)[d]		
25%	5.2 (3.6-5.7)	1.9 (1.8-1.9)
50%	11.2 (9.5-12.9)	4.6 (3.5-5.6)
75%	NE (16.6-NE)	11.1 (9.1-13.8)
Stratified analysis		
Hazard ratio[e]	0.497	
95% CI of hazard ratio	0.398-0.620	
p-value[f]	<0.0001	
Unstratified analysis[g]		
Hazard ratio[e]	0.501	
95% CI of hazard ratio	0.401-0.624	
p-value	<0.0001	

CI=confidence interval; PD=progressive disease; N=total number of patients in population; n=number of patients meeting prespecified criteria; NE=not estimable. a. Anticancer treatment includes surgery containing a lesion removal or subsequent anticancer systemic therapies. b. Estimated from Kaplan-Meier curve. c. Calculated using the product-limit method. d. Based on the Brookmeyer and Crowley Method. e. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favour of palbociclib + fulvestrant. f. 1-Sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior hormonal therapy per randomization. g. Sensitivity Analysis 2: used a 1-sided unstratified log-rank test and an unstratified Cox proportional hazards model

Figure 10 - Kaplan-Meier plot of progression-free survival (Study 1023, ITT, investigator assessment, 23 October 2015)



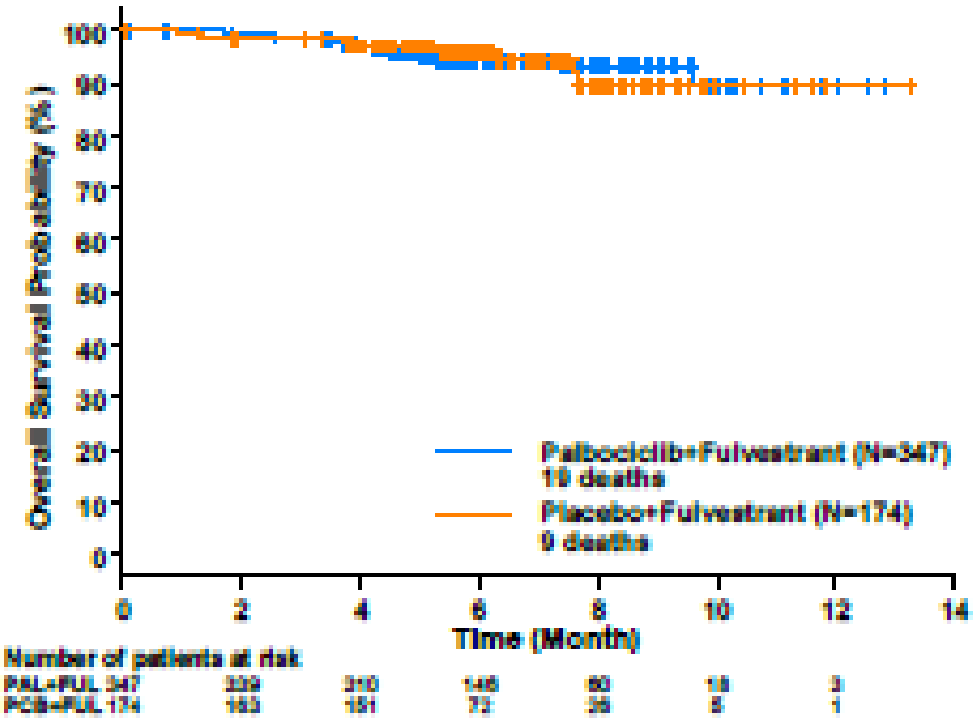
Data cut-off: 23 October 2015

Secondary endpoints

Overall survival

At the 05 December 2014 data cut-off date for the primary PFS analysis, there were 28 deaths from 521 patients, 19 (5.5%) patients had died in the palbociclib plus fulvestrant arm and 9 (5.2%) patients had died in the placebo plus fulvestrant arm. The median OS was not reached in either treatment arm. The median follow-up time was 5.6 months for both treatments arms. The corresponding Kaplan-Meier plot of OS is presented in figure 11.

Figure 11 – Kaplan-Meier Plot of Overall Survival – Intent-to-Treat Population



At the data cut-off date of 16 March 2015 for the updated analysis, there were an additional 29 deaths resulting in a total of 57 deaths, 36 in the palbociclib arm and 21 in the control arm.

A pre-specified Interim OS Analysis was undertaken with a data cut-off date of 23 Oct 2015. At this time, there were a total of 112 death events [71 (20.5%) vs 41(23.6%) on the palbociclib plus fulvestrant arm and placebo plus fulvestrant arm, respectively, representing 21.5% of the 521 total patients. The detailed summary of the deaths as of the data cut-off date of 23 Oct 2015 are presented in Table 21.

Table 21 - Summary of Deaths, 23 October 2015 update (Study 1023, ITT)

	Palbociclib (PD-0332991) + Fulvestrant (N=347)		Placebo + Fulvestrant (N=174)	
	n	(%)	n	(%)
Number of deaths	71	(20.5)	41	(23.6)
Cause of death				
Disease Under Study	64	(18.4)	38	(21.8)
Study Treatment Toxicity	0		1	(<1.0)
Unknown	4	(1.2)	0	
Other	3	(<1.0)	2	(1.1)
Number censored	276	(79.5)	133	(76.4)
Reason for censorship				
Subject Remains In Follow-up	264	(76.1)	121	(69.5)
Subject No Longer Being Followed For Survival	12	(3.5)	12	(6.9)

Objective Response, Clinical Benefit Response and Duration of Response

A summary of results are given in table 22. Results are based on the most recent efficacy update, based on the data cut-off of 23 October 2015.

Table 22 - Summary of Objective Response, Clinical Benefit Response, and Duration of Response (Study 1023, ITT, updated)

Secondary Endpoint	Palbociclib + Fulvestrant (N=347) (95% CI)	Placebo + Fulvestrant (N=174) (95% CI)	Odds Ratio (95% CI)	1-Sided P-Value[a]
OR (%)	21.0 (16.9-25.7)[b]	8.6 (4.9-13.8)[b]	2.78 (1.56-5.60)	0.0001
OR in patients with measurable disease at baseline (%)	27.3 (22.1-33.1)[b]	10.9 (6.2-17.3)[b]	3.03 (1.64-5.99)	<0.0001
CBR (%)[c]	66.3 (61.0-71.2)[b]	39.7 (32.3-47.3)[b]	3.02 (2.05-4.57)	<0.0001
DOR (months [median])	10.4 (8.3-NE)[d]	9.0 (5.6-NE)[d]	NA	NA

*Response endpoints based on confirmed responses.

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

Patient-Reported Outcomes

The PRO evaluable population was defined as a subset of ITT patients, who had completed a baseline and at least one post–baseline PRO assessment prior to end of study treatment. No update was provided for PROs.

Patient–reported outcomes were investigated using the instruments, EORTC QLQ-C30, QLQC30 and EQ-5D. These are considered standard. However, no primary objective and no strategy to protect the type-1 error rational are put forward in the study protocol or SAP. Furthermore, the results indicated emotional functioning as a driver for the overall health related QoL, why the plausibility of results may also be questioned. Unblinding due to the effects of palbociclib on the bone marrow may clearly be present and the results potentially associated with hopes with regard to the benefit of the experimental compound. The claims concerning Global Health Status/QoL were therefore not accepted.

Time to Deterioration in Pain

A time to event analysis was prespecified for pain. Time to Deterioration (TTD) in pain was defined as time from baseline to first occurrence of an increase of at least 10 points in pain on study. This is an established cut-off in QLQ-C30.

Table 23 - QLQ-C30 Time to Deterioration - Symptom Scale of Pain Increase of ≥10 Points (Study 1023, PRO Analysis Population)

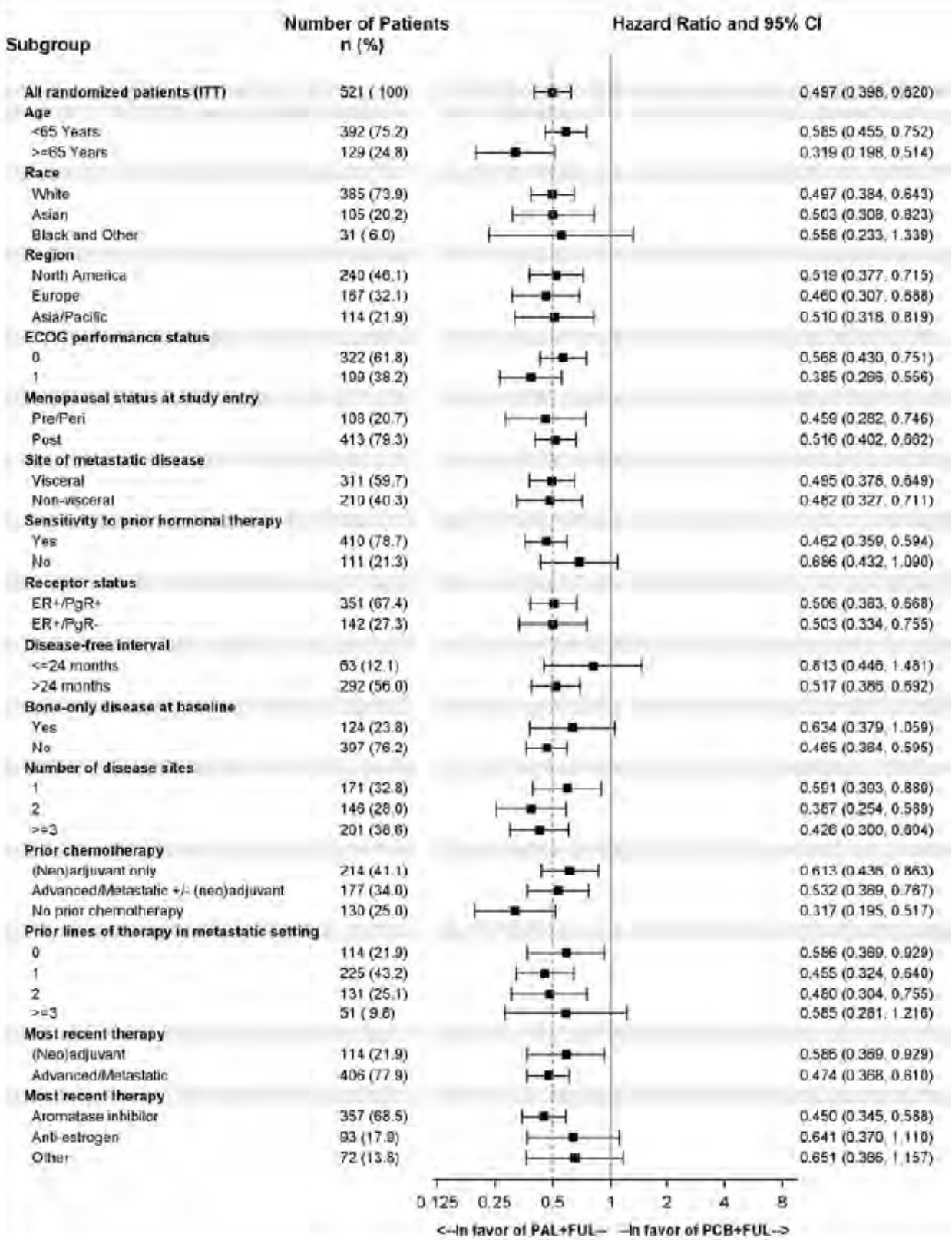
	Palbociclib plus Fulvestrant N=335	Placebo plus Fulvestrant N=166
	n (%)	n (%)
Patient had symptom scale of pain increase of ≥10 points while on study [n (%)]	131 (39.1)	83 (50.0)
Patient did not have symptom scale of pain increase of ≥10 points while on study [n (%)]	204 (60.9)	83 (50.0)
Kaplan-Meier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

Source: Section 14.2, Table 14.5.1.1.3
Abbreviations: CI: confidence interval, EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, N: number of patients, n: number of patients affected, NE: not estimable, PRO: patient-reported outcome

1 Based on the Brookmeyer and Crowley Method.
2 Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of the palbociclib plus fulvestrant arm.
3 Used a 1-sided unstratified log-rank test and an unstratified Cox proportional hazards model.

PFS subgroups analyses (updated)

Figure 12 - PFS Subgroup analyses (Study 1023, ITT, updated)



Notes: 1) Sensitivity to prior hormonal therapy is defined as either: a) documented clinical benefit (ie, complete response, partial response, or stable disease ≥24 weeks) to at least 1 prior hormonal therapy in the metastatic setting or b) at least 24 months of adjuvant hormonal therapy prior to recurrence. 2) Disease-free interval is time from diagnosis of primary breast cancer to first relapse in patients who received adjuvant therapy. 3) Aromatase inhibitor=anastrozole, letrozole, or exemestane; anti-estrogen=tamoxifen, tamoxifen citrate, toremifene, or toremifene citrate; other=neither an aromatase inhibitor nor an anti-estrogen. 4) Race=Black and Other data derived from Table 1023.560.11. 5) Menopausal status at study entry, Site of metastatic disease, and Sensitivity to prior hormonal therapy data were derived based on the IMPALA.
CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptor; FUL=fulvestrant; ITT=intent-to-treat; n=number of patients meeting prespecified criteria; PAL=palbociclib; PCB=placebo; PgR=progesterone receptor.

Study 1008 (PALOMA-2)

A Randomized, Multicenter, Double-Blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women With ER-positive, HER2-negative Breast Cancer Who Have Not Received Any Prior Systemic Anticancer Treatment for Advanced Disease

This study has been submitted in order to support the indication for palbociclib in combination with an aromatase inhibitor.

Methods

Study Participants

Inclusion Criteria

1. Adult women (≥ 18 years of age) with proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease not amenable to resection or radiation therapy with curative intent and for whom chemotherapy is not clinically indicated.

2. Documentation of histologically or cytologically confirmed diagnosis of oestrogen-receptor positive (ER+) breast cancer based on local laboratory results.

3. Previously untreated with any systemic anti-cancer therapy for their locoregionally recurrent or metastatic ER+ disease.

4. Postmenopausal women defined as women with:

- Prior bilateral surgical oophorectomy, **or**
- Medically confirmed post-menopausal status defined as spontaneous cessation of regular menses for at least 12 consecutive months or follicle-stimulating hormone (FSH) and estradiol blood levels in their respective postmenopausal ranges with no alternative pathological or physiological cause.

5. Measurable disease as defined per RECIST v.1.1 or bone-only disease (with bone lesions confirmed by CT, MRI or bone X-ray). Tumour lesions previously irradiated or subjected to other locoregional therapy will only be deemed measurable if disease progression at the treated site after completion of therapy is clearly documented.

6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2.

7. Adequate organ and marrow function defined as follows:

- ANC ≥ 1,500/mm3 (1.5 x 109 /L);
- Platelets ≥ 100,000/mm3 (100 x 109 /L);

● Hemoglobin ≥ 9 g/dL (90 g/L);

● Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution;

● Total serum bilirubin ≤ 1.5 x ULN (≤ 3.0 x ULN if Gilbert's disease);

● AST and/or ALT ≤ 3 x ULN (≤ 5.0 x ULN if liver metastases present);

● Alkaline phosphatase ≤ 2.5 x ULN (≤ 5.0 x ULN if bone or liver metastases present).

8. Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCI CTCAE version 4.0 Grade ≤ 1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).

9. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

10. All patients must agree to provide tumour tissues for centralized retrospective confirmation of ER status and to evaluate correlation between genes, proteins, and RNAs relevant to the cell cycle pathways and sensitivity/resistance to the investigational agents. Freshly biopsied, recurrent/metastatic tumour samples must be provided whenever possible. If such a biopsy is not feasible or cannot be safely performed, then an archived tumour sample may be accepted. In either case a formalin fixed, paraffin embedded (FFPE) block or 12 unstained FFPE slides are required for patient participation.

11. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study before any study-specific activity is performed.

Exclusion Criteria

1. HER2-positive tumour as defined by documentation of erbB-2 gene amplification by FISH (as defined by a HER2/CEP17 ratio ≥ 2) or chromogenic in situ hybridization (CISH, as defined by the manufacturer's kit instruction) or INFORM HER2 dual ISH (as defined by manufacturer's kit instruction) or documentation of HER2-overexpression by IHC (defined as IHC3+, or IHC2+ with FISH or CISH confirmation) based on local laboratory results utilizing one of the sponsor-approved assays (see Appendix 2). If HER2 status is unavailable or was determined using a test other than a sponsor-approved assay, then testing must be performed/repeated using one of these assays prior to randomization. If tissue sample from both primary and recurrent/metastatic tumours are available, HER2 assessment from the most recent sample (i.e., recurrent/metastatic sample) should be used to define eligibility whenever feasible.

2. Patients with advanced, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement).

3. Known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral oedema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated with local therapy (eg, radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.

4. Prior neoadjuvant or adjuvant treatment with a non-steroidal aromatase inhibitor (ie, anastrozole or letrozole) with disease recurrence while on or within 12 months of completing treatment.

5. Prior treatment with any CDK4/6 inhibitor.

6. Patients treated within the last 7 days prior to randomization with:

- Food or drugs that are known to be CYP3A4 inhibitors (i.e., amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit or grapefruit juice);

- Drugs that are known to be CYP3A4 inducers (ie, carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort).

- Drugs that are known to prolong the QT interval

7. Major surgery, chemotherapy, radiotherapy, any investigational agents, or other anti-cancer therapy within 2 weeks before randomization. Patients who received prior radiotherapy to ≥ 25% of bone marrow are not eligible independent of when it was received (see Appendix 4).

8. Diagnosis of any other malignancy within 3 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.

9. QTc >480 msec (based on the mean value of the triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes (TdP).

10. Uncontrolled electrolyte disorders that can compound the effects of a QTc-prolonging drug (e.g., hypocalcaemia, hypokalaemia, hypomagnesaemia).

11. Any of the following within 6 months of randomization: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE version 4.0 Grade ≥ 2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.

12. Active inflammatory bowel disease or chronic diarrhoea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection.

13. Known hypersensitivity to letrozole, or any of its excipients, or to any PD-0332991/placebo excipients.

14. Known human immunodeficiency virus infection.

15. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

16. Patients who are investigational site staff members or relatives of those site staff members or patients who are Pfizer employees directly involved in the conduct of the trial.

17. Participation in other studies involving investigational drug (s) (Phases 1-4) within 2 weeks before randomization and/or during participation in the active treatment phase of the trial.

18. Recent or active suicidal ideation or behaviour.

Treatments

Patients received palbociclib 125 mg once daily (QD) or placebo QD orally for 3 weeks followed by 1 week off treatment and letrozole 2.5 mg QD orally continuously.

Objectives and endpoints

The primary endpoint is investigator-assessed PFS. Secondary objectives include the comparison of OS, objective response, duration of response, disease control, biomarkers, health-related quality of life, and the safety and tolerability between the treatment arms.

Primary objective:

The primary objective of the study was to evaluate if palbociclib in combination with letrozole would be superior to placebo plus letrozole in prolonging investigator-assessed progression-free survival (PFS) in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received any prior systemic anticancer therapies for their advanced/metastatic disease.

Secondary objectives:

- To compare measures of tumour control duration and overall survival between the treatment arms;
- To compare safety and tolerability between the treatment arms;
- To compare health related quality of life between the treatment arms;
- To characterize the effects of palbociclib at therapeutic doses in combination with letrozole on QTc interval in this patient population;
- To determine trough palbociclib plasma concentration in this patient population and explore the correlations between exposure and response and/or safety findings;
- To characterize alterations in genes, proteins, and RNAs relevant to the cell cycle (e.g., CCND1 amplification, CDKN2A deletion), drug targets (eg, CDK 4/6), and tumour sensitivity and/or resistance (e.g., Ki67, pRb) in tumour tissues.

Sample size

The sample size for this study was determined based on the assumptions that the median PFS for patients receiving placebo plus letrozole in the first-line treatment setting was 9 months and a risk reduction by 31% (a HR of 0.69) or an improvement by 44% to median PFS of 13 months in the palbociclib plus letrozole treatment was clinically significant. A total of 347 events were needed in the 2 arms of the study based on a 2:1 randomization to have 90% power to detect a HR ratio of 0.69 in favor of the palbociclib plus letrozole arm using a 1-sided, log-rank test at a significance level of 0.025. A total sample size of approximately 650 patients (~433 in palbociclib plus letrozole arm and ~217 in placebos plus letrozole arm) was required.

The sample size described above will also allow the assessment of differences in the secondary endpoint of overall survival (OS) with a high level of significance.

Randomisation

Randomization was stratified by site of disease (visceral versus non-visceral), disease-free interval since the end of (neo)adjuvant treatment to disease recurrence (de novo metastatic versus ≤12 months versus >12 months),

and nature of prior (neo)adjuvant anticancer therapies (prior hormonal therapy versus no prior hormonal therapy). “Visceral” refers to any lung (including pleura) and/or liver involvement. "Non-visceral" refers to absence of lung (including pleura) and/or liver involvement.

Blinding (masking)

This was a double-blind trial.

Statistical methods

The intent-to-treat (ITT) population will include all patients who are randomized, with study drug assignment designated according to initial randomization, regardless of whether patients receive study drug or receive a different drug from that to which they were randomized. The ITT population will be the primary population for evaluating all efficacy endpoints and patient characteristics.

The MITT population will include all patients who are randomized, with the Sponsor designated central laboratories confirmed ER (+) status, with study drug assignment designated according to initial randomization, regardless of whether patients receive study drug or receive a different drug from that to which they were randomized. This will be the secondary population for evaluating all efficacy endpoints as well as patient characteristics.

The as-treated (AT) population or safety analysis set will include all patients who receive at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received. The AT population will be the primary population for evaluating treatment administration/compliance and safety. Efficacy and clinical benefit endpoints may be assessed in this population as well.

Time-to-event endpoints between the 2 treatment arms will be compared with a 1-sided stratified log-rank test adjusting for Site of disease and/or a 1-sided unstratified log-rank test at the α=0.025 overall significance level. Hazard ratios and 2-sided 95% confidence intervals (subject to the multiplicity adjustment at the final analysis for PFS and OS) will be estimated using Cox proportional hazards regression.

Time-to-event endpoints between the 2 treatment arms will be compared with a 1-sided stratified log-rank test adjusting for Site of disease and/or a 1-sided unstratified log-rank test at the α=0.025 overall significance level. Hazard ratios and 2-sided 95% confidence intervals (subject to the multiplicity adjustment at the final analysis for PFS and OS) will be estimated using Cox proportional hazards regression.

The study was designed to have 1 interim analysis and the final analysis at 347 events based on the primary endpoint of PFS. The Haybittle-Peto efficacy boundary for rejecting the null hypothesis was used at the time of the interim analysis. The interim analysis of PFS was to be performed after at least 226 patients had documented progressive disease or died (approximately 65% of the total events expected). The overall significance level for the efficacy analysis of PFS was preserved at 0.025 (1-sided test). OS will be hierarchically tested for significance at its interim analysis (at the time of the interim or final PFS analyses), provided the primary endpoint, PFS, is statistically significant at the interim PFS analysis, or at the final PFS analysis.

Results

Patient disposition

Table 24 - Patient Disposition at End of Treatment – Palbociclib or Placebo (ITT, Study 1008)

	Palbociclib Plus Letrozole N = 444 n (%)	Placebo Plus Letrozole N = 222 n (%)
Palbociclib or Placebo		
Ongoing	199 (44.8)	61 (27.5)
Discontinued	245 (55.2)	161 (72.5)
Reason for discontinuation		
Objective progression or relapse	171 (38.5)	126 (56.8)
Adverse event	33 (7.4)	10 (4.5)
Global deterioration of health status	14 (3.2)	9 (4.1)
Subject refused continued treatment for reason other than AE	9 (2.0)	9 (4.1)
Other	6 (1.4)	3 (1.4)
Subject died	6 (1.4)	2 (<1.0)
Protocol violation	4 (<1.0)	2 (<1.0)
Lost to follow-up	1 (<1.0)	0
Study terminated by sponsor	1 (<1.0)	0

Discontinued and Ongoing is as per the Conclusion-of-Treatment page in the Case Report Form.
Patients may have continued on letrozole alone after stopping palbociclib or placebo treatment.
Abbreviations: AE=adverse event; N=number of patients in population; n=number of patients with parameter.

Recruitment

Between 28 February 2013 and 29 July 2014, 666 women were randomized at 186 sites in 17 countries (Australia, Belgium, Canada, France, Germany, Hungary, Ireland, Italy, Japan, Republic of Korea, Poland, Russia, Spain, Taiwan, Ukraine, United Kingdom, and United States of America). Four hundred forty-four (444) patients were randomized to the palbociclib plus letrozole arm, and 222 patients were randomized to the placebo plus letrozole arm.

Conduct of the study

Discontinuations due to protocol violations were infrequent <1% in both arms. A summary of significant protocol deviations was provided (abbreviated in table 25 below). Following assessment of the non-abbreviated version, it is considered that the observed protocol violations were unlikely to have affected the overall efficacy or safety results of the study.

Table 25 - Summary of Significant Protocol Deviations – (ITT, Study 1008)

Category **Sub Category**	**Palbociclib plus Letrozole (N=444) n (m) [%]**	**Placebo plus Letrozole (N=222) n (m) [%]**	**Total (N=666) n (m) [%]**
Inclusion/exclusion	**24 (22) [5.0]**	**19 (17) [7.7]**	**43 (39) [5.9]**
Investigational product administration/ treatment	**75 (54) [12.2]**	**13 (12) [5.4]**	**88 (66) [9.9]**
Overdoses (ie, >1 dose of either study drugs on any given day)	12 (10) [2.3]	7 (7) [3.2]	19 (17) [2.6]
Retreatment parameters following dose interruption or start of new cycle not met per protocol but treatment given	58 (40) [9.0]	3 (3) [1.4]	61 (43) [6.5]
Concomitant treatment	**152 (94) [21.2]**	**43 (27) [12.2]**	**195 (121) [18.2]**
Procedures/tests	**14 (13) [2.9]**	**8 (7) [3.2]**	**22 (20) [3.0]**
Randomization	**21 (21) [4.7]**	**3 (3) [1.4]**	**24 (24) [3.6]**
Safety reporting	**15 (14) [3.2]**	**3 (3) [1.4]**	**18 (17) [2.6]**
AE/SAE not recorded in Clinical Database	2 (2) [0.5]	0	2 (2) [0.3]
SAE Delayed or not reported to sponsor	13 (12) [2.7]	3 (3) [1.4]	16 (15) [2.3]
Discontinuation	**1 (1) [0.2]**	**0**	**1 (1) [0.2]**
Informed consent deviation	**617 (261) [58.8]**	**281 (129) [58.1]**	**898 (390) [58.6]**

Abbreviations: AE=Adverse event; CT= computed tomography; N=number of patients; 'n' Number of deviations;'m' Number of patients with deviations;% = % of N.

The current protocol version, Amendment 6 dated 07 April 2015, was provided, including a summary of, and rationale for, all changes since original protocol. Changes of importance included the following:

Based on preliminary results from two clinical pharmacology studies (A5481018 and A5481021) the drug administration instructions were amended (Amendment 2, 03 January 2014) from administration in a minimally fasted state to administration with food and also to prohibit the concomitant use of proton-pump inhibitors. Due to a concern that these effects might affect the power of the study the protocol was amended prior to the interim analysis to increase the sample size from 450 patients to 650 patients to preserve the desired statistical power (Amendment 3, 21 March 2014). The protocol was also amended to implement prospective ophthalmic assessments in all newly enrolled, lens grading patients at baseline and while on study treatment (Amendment 3), and to prospectively characterize whether or not palbociclib affects glucose metabolism, through monitoring of appropriate laboratory measurements (Amendment 4, 18 September 2014). In Amendment 5 (02 December 2014), the interim analysis was revised to ensure that the study would only be stopped at the interim analysis if the primary analysis (PFS) results are statistically significant and clinically meaningful, due to a concern that the planned minimum of about 4 months' PFS improvement might not to be considered clinically relevant. In order to assess the breast cancer specific quality of life of patients beyond progression in the follow-up period, patient reported outcomes using the FACT-B questionnaire will continue to be collected every 6 months (Amendment 6, 07 April 2015).

It is considered that the protocol amendments have not put the integrity of the study at risk.

Baseline data

Table 26 - Summary of Demographic and Baseline Characteristics by Treatment – Study 1008 (ITT)

Parameter	Palbociclib Plus Letrozole (N = 444)	Placebo Plus Letrozole (N = 222)
Age (years)		
Median (min, max)	62 (30, 89)	61 (28, 88)
<65, n (%)	263 (59.2)	141 (63.5)
≥65, n (%)	181 (40.8)	81 (36.5)
Race, n (%)		
White	344 (77.5)	172 (77.5)
Black	8 (1.8)	3 (1.4)
Asian	65 (14.6)	30 (13.5)
Other	27 (6.1)	17 (7.7)
Region		
North America	168 (37.8)	99 (44.6)
Europe	212 (47.7)	95 (42.8)
Asia/Pacific	64 (14.4)	28 (12.6)
Japan	32 (7.2)	14 (6.3)
ECOG performance status, n (%)		
0	257 (57.9)	102 (45.9)
1	178 (40.1)	117 (52.7)
2	9 (2.0)	3 (1.4)
Disease site[a], n (%)		
Visceral	217 (48.9)	111 (50.0)
Non-visceral	227 (51.1)	111 (50.0)
Measurable disease at baseline		
Yes	338 (76.1)	171 (77.0)
No	106 (23.9)	51 (23.0)
Disease free interval[a], n (%)		
>12 months since completion of prior (neo)adjuvant therapy	207 (46.6)	104 (46.8)
≤12 months since completion of prior (neo)adjuvant therapy	89 (20.0)	44 (19.8)
De novo advanced disease	148 (33.3)	74 (33.3)
Prior hormonal therapy use in (neo)adjuvant treatment[a], n (%)		
No	191 (43.0)	95 (42.8)
Yes	253 (57.0)	127 (57.2)
Prior chemotherapy for primary diagnosis in (neo)adjuvant treatment		
Yes	213 (48.0)	109 (49.1)
No	231 (52.0)	113 (50.9)
Most recent hormonal therapy		
Aromatase inhibitors	91 (36.5)	44 (34.9)
Anti-estrogens	154 (61.8)	75 (59.5)
Other	4 (1.6)	7 (5.6)
Number of involved disease sites		
1	138 (31.1)	66 (29.7)
2	117 (26.4)	52 (23.4)
3	112 (25.2)	61 (27.5)
4	52 (11.7)	29 (13.1)
>4	25 (5.6)	14 (6.3)

Abbreviations: ECOG=Eastern Cooperative Oncology Group; max=maximum; min=minimum; N=number of patients in population; n=number of patients with parameter. a. Based on the randomization.

The baseline characteristics are considered to be in overall balanced across arms. A 12% difference in ECOG performance status 0 is noted, but not considered important to the overall results. It is noted that 57% of patients in both study arms had prior hormonal therapy in the neo/adjuvant setting, and nearly half had prior chemotherapy.

Outcomes and estimation

Primary endpoint –Progression-free survival

The final PFS analysis was conducted based on the data with the cut-off date of 26 February 2016. A total of 331 patients had documented progressive disease (PD) or death in the final analysis. The secondary analysis of PFS based on BICR data is not available at this time.

Among 331 patients with disease progression or death as PFS events, 194 (43.7% of 444 patients) were from the palbociclib plus letrozole arm and 137 (61.7% of 222 patients) were from the placebo plus letrozole arm, respectively.

The estimated HR was 0.576 (95% CI: 0.463-0.718; 1-sided p<0.000001) in favour of palbociclib plus letrozole. The median PFS was 24.8 months (95% CI: 22.1-NE) for palbociclib plus letrozole and 14.5 months (95% CI: 12.9-17.1) for placebo plus letrozole (Figure 13, Table 27).

Figure 13 - Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, ITT, Study 1008/PALOMA-2)

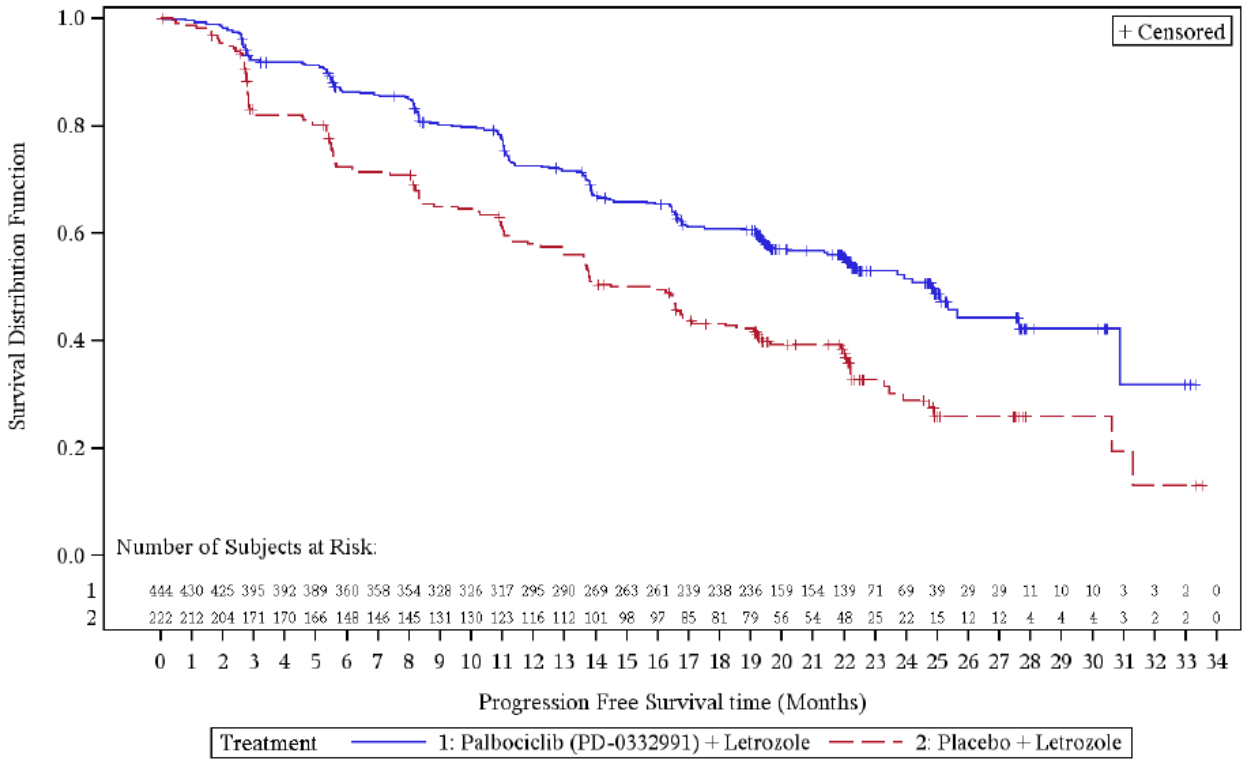


Table 27 - Primary endpoint - Progression-free survival (ITT) - Study 2008/PALOMA-2

	Palbociclib Plus Letrozole (N = 444) Median (95% CI)	Placebo Plus Letrozole (N = 222) Median (95% CI)	Hazard Ratio (95% CI)	1-Sided p-value (Log-Rank)
PFS (months)	24.8 (22.1-NE)	14.5 (12.9-17.1)	0.576 (0.463-0.718)	<0.000001

Table 28 - Summary of Progression-Free Survival Event Types and Reasons for Censorship (Investigator Assessment, Intent-to-Treat Population) – Study 1008/PALOMA-2

	Palbociclib Plus Letrozole (N = 444) n (%)	Placebo Plus Letrozole (N = 222) n (%)
Number with event	194 (43.7)	137 (61.7)
Objective progression	183 (41.2)	134 (60.4)
Death without objective progression	11 (2.5)	3 (1.4)
Number with censored observation	250 (56.3)	85 (38.3)
Reasons for censorship		
In follow-up for progression	199 (44.8)	58 (26.1)
No adequate baseline assessments	0	0
No on-study disease assessments	12 (2.7)	7 (3.2)
Given new anticancer treatment prior to disease progression and after last dose of study treatment	0	1 (<1.0)
Unacceptable gap (>30 weeks) between PD or Death to the most recent prior adequate assessment	2 (<1.0)	2 (<1.0)
Discontinued treatment without disease progression or death	37 (8.3)	17 (7.7)
Adverse event	13 (2.9)	4 (1.8)
Global deterioration of health status	8 (1.8)	4 (1.8)
Lost to follow-up	8 (1.8)	5 (2.3)
Other	8 (1.8)	4 (1.8)

Anticancer treatment included any anticancer related systemic therapies and surgeries for the disease under study. Abbreviations: N=number of patients in analysis; n=number of patients in category; PD=progressive disease.

PFS by Blinded Independent Central review (BICR)

Table 29 - Summary of Progression-Free Overall Survival by Treatment, (BICR Assessment – Intent-to-Treat Population) – Study 1008/PALOMA-2

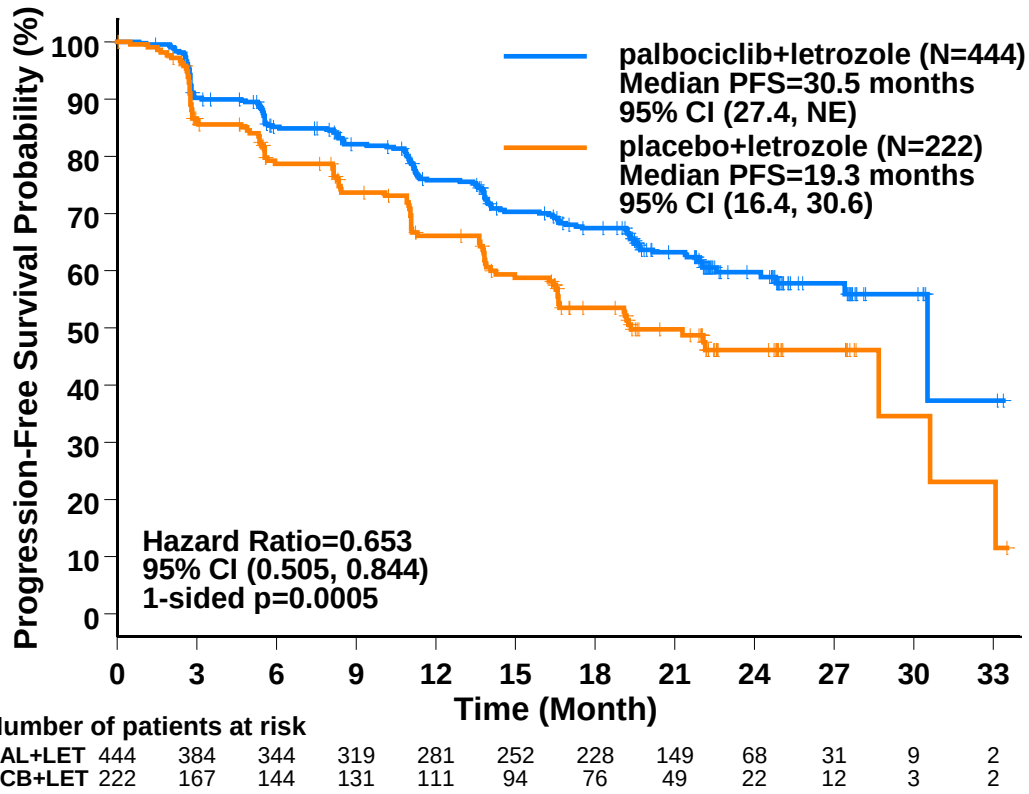
	Palbociclib plus Letrozole N = 444 n (%)	Placebo plus Letrozole N = 222 n (%)
Number with event	152 (34.2)	96 (43.2)
Objective progression	145 (32.7)	94 (42.3)
Death without objective progression	7 (1.6)	2 (<1.0)
Number with censored observation	292 (65.8)	126 (56.8)
Reasons for censorship		
In follow-up for progression	188 (42.3)	57 (25.7)
No scans/data available	10 (2.3)	7 (3.2)
No adequate baseline assessments	0	0
No on-study disease assessments	2 (<1.0)	0
Given new anticancer treatment prior to disease progression and last dose of study treatment	0	1 (<1.0)
Unacceptable gap (>30 weeks) between PD or Death to the most recent prior adequate assessment	2 (<1.0)	2 (<1.0)
Discontinued treatment without disease progression or death	90 (20.3)	59 (26.6)
Adverse event	12 (2.7)	4 (1.8)
Global deterioration of health status	8 (1.8)	3 (1.4)
Objective progression assessed by investigator	55 (12.4)	44 (19.8)
Lost to follow-up/patient refused continued treatment for reason other than AE	8 (1.8)	5 (2.3)
Other	7 (1.6)	3 (1.4)
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI) [c]		
25%	13.5 [11.0, 14.4]	8.3 [5.6, 11.1]
50%	30.5 [27.4, NE]	19.3 [16.4, 30.6]
75%	NR [30.5, NE]	30.6 [28.7, NE]
Stratified analysis		
Hazard ratio [d]	0.653	
95% Hazard ratio	0.505, 0.844	
p-value [e]	0.000532	

Abbreviations: AE=adverse event; BICR=Blinded Independent Central Review; N=number of patients in analysis; n=number of patients in category; PD=progressive disease.

Anticancer treatment included any anticancer-related systemic therapies and surgeries for the disease under study.

a. Estimated from the Kaplan-Meier curve.
b. Calculated from the product-limit method.
c. Based on the Brookmeyer and Crowley method.
d. Assuming proportional hazards, a hazard ratio of less than 1 indicates a reduction in hazard rate in favor of palbociclib plus letrozole.
e. 1-sided p-value from the log-rank test.

Figure 14 - Kaplan-Meier Plot of Progression-Free Survival (BICR Assessment, ITT, Study 1008/PALOMA-2)



Abbreviations: BICR=blinded independent central review; CI=confidence interval; LET=letrozole; N=number of patients in population; NE=not estimable; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

Secondary endpoints

Overall survival

A planned OS interim analysis was performed at the time of the final PFS analysis based on 133 deaths (34% of 390 events for final analysis) from 666 patients. Since the pre-specified level of significance was not met, the OS data will be continuously followed for the final analysis when 390 deaths have been observed. The median follow-up time for the palbociclib plus letrozole arm was 23.0 months (95% CI: 22.6-23.4) and for the placebo plus letrozole arm was 22.3 months (95% CI: 21.9-22.9). No OS conclusions can be made due to the immaturity of the data. The patients will continue to be followed for the final OS analysis.

Other secondary endpoints

Table 30 - Secondary efficacy results - (Investigator, ITT) - Study 2008/PALOMA-2

	Palbociclib Plus Letrozole (N = 444) (95% CI)	Placebo Plus Letrozole (N = 222) (95% CI)	Odds Ratio (95% CI)	1-Sided p-value (Exact)
ORR (%)	42.1 (37.5-46.9)	34.7[a] (28.4-41.3)	1.40 (0.98-2.01)	0.0310
DOR (months)	22.5 (19.8-28.0)	16.8[a] (14.2-28.5)	NA	NA
ORR (%) for patients with measurable disease at baseline	55.3 (49.9-60.7)	44.4 (36.9-52.2)	1.55 (1.05-2.28)	0.0132
DOR (months) for patients with measurable disease at baseline	22.5 (19.8-28.0)	16.8 (15.4-28.5)	NA	NA
CBRR/DCR (%)	84.9 (81.2-88.1)	70.3 (63.8-76.2)	2.39 (1.58-3.59)	<0.0001

Abbreviations: CBRR/DCR=clinical benefit response rate/disease control rate (CR+PR+SD ≥24 weeks); CI=confidence interval; CR=complete response; DOR=duration of response; N=number of patients in analysis; NA=not applicable; NE=not estimable; ORR=objective response rate; PR=partial response; SD=stable disease.

a. Included 1 patient with bone-only disease at baseline; all other patients had measurable disease at baseline.

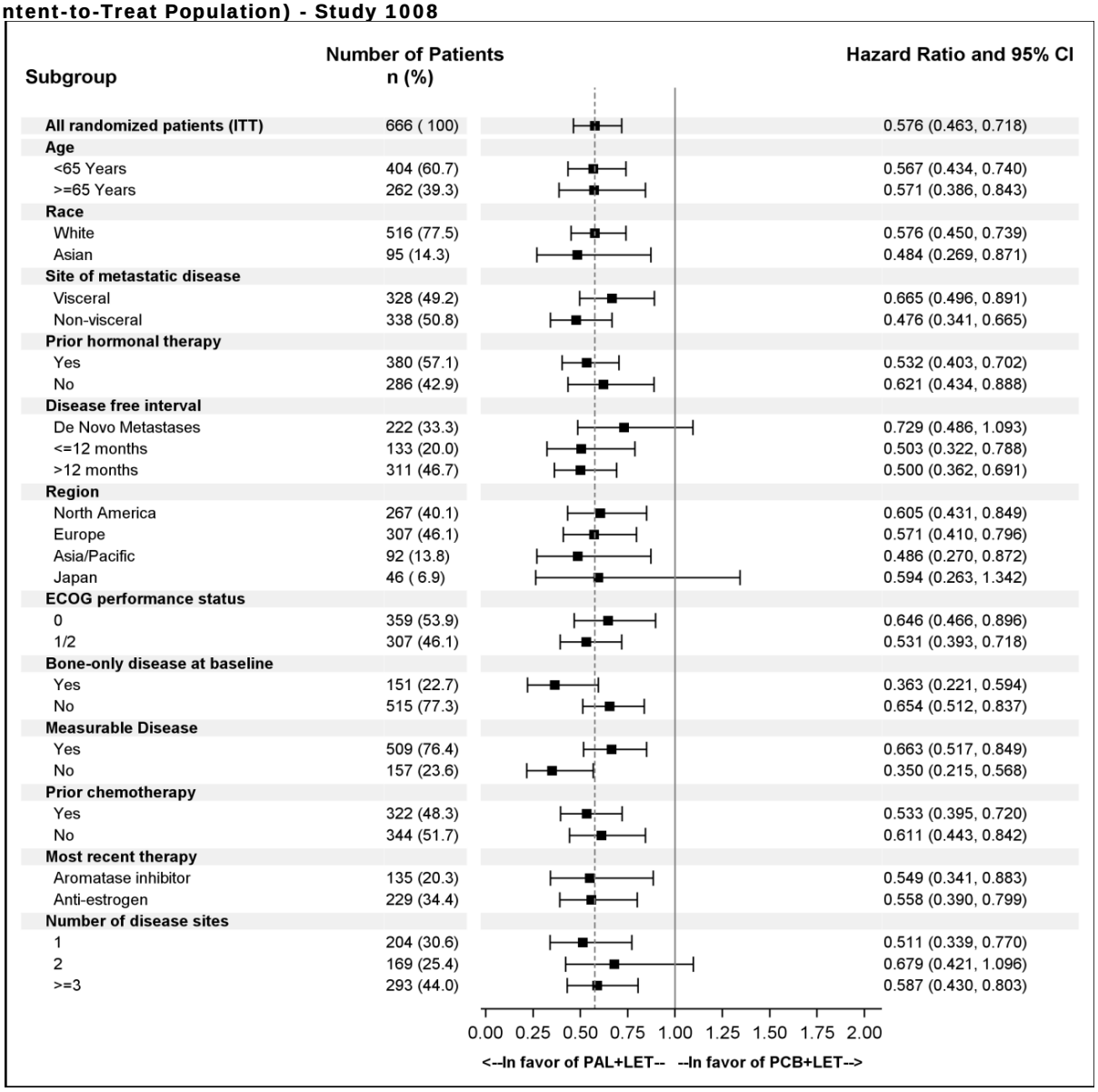
Table 31 - Summary of Clinical Benefit Response (Confirmed only) by Treatment (Investigator Assessment, ITT)- Study 1008/PALOMA-2

	Palbociclib (PD-0332991) + Letrozole (N=444)		Placebo + Letrozole (N=222)	
	n	(%)	n	(%)
Complete response	9	(2.0)	5	(2.3)
Partial response	178	(40.1)	72	(32.4)
Stable Disease >=24 weeks	190	(42.8)	79	(35.6)
Stable Disease <24 weeks	20	(4.5)	17	(7.7)
Objective progression	34	(7.7)	37	(16.7)
Indeterminate	13	(2.9)	12	(5.4)
Clinical Benefit Response (CR + PR + SD>=24 Weeks) and Rate	377	(84.9)	156	(70.3)
95% Exact CI [1]	[81.2, 88.1]		[63.8, 76.2]	
Stratified Analysis [4]:				
Odds Ratio [2]	2.385			
(95% Exact CI)	[1.584,3.589]			
P-value [3]	<.0001			
Unstratified Analysis:				
Odds Ratio [2]	2.381			
(95% Exact CI)	[1.583,3.572]			
P-value [3]	<.0001			

[1] CI was calculated using the exact (Clopper-Pearson) method based on binomial distribution.
[2] An Odds Ratio > 1 means better response in favor of Palbociclib (PD-0332991) + Letrozole group.
[3] 1-sided p-value is from exact test. [4] Stratified by disease site (visceral vs. non-visceral) per Randomization.

PFS subgroup analyses

Figure 15 - Forest Plot of Subgroup Analyses of Progression-Free Survival (Investigator Assessment, Intent-to-Treat Population) - Study 1008



The subgroup analysis showed overall consistent results in all pre-specified subgroups, indicating robustness of the PFS results.

PFS in relation to Rb expression

Tissue samples from 568 of 666 enrolled patients were suitable for all biomarker testing and had results for analysis, of which 379 (66.7%) were from patients in the palbociclib plus letrozole arm and 189 (33.3%) from patients in the placebo plus letrozole arm. Total Rb protein expression had been evaluated using a validated IHC assay at a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. Overall, 563 patients had evaluable Rb testing results.

Table 32 - Progression-Free Survival by Rb Status Across Treatment (Investigator Assessment, Biomarker Analysis Set) – Study 1008

	Palbociclib Plus Letrozole	Placebo Plus Letrozole	Hazard Ratio[b]	Log-Rank 1-sided p-value[c]
Rb Positive				
N (% of biomarker analysis population)	512 (90.9%)			
N (% of patients in study arm)	345 (92.2)	167 (88.4)		
Median PFS[a] (months)	24.2	13.7	0.531	<0.0001
95% CI	(21.4-25.7)	(11.0-16.5)	(0.416-0.680)	
Rb Negative				
N (% of biomarker analysis population)	51 (9.1%)			
N (% of patients in study arm)	29 (7.8)	22 (11.6)		
Median PFS[a] (months)	NR	18.5	0.675	0.1619
95% CI	(11.4-NR)	(2.9-NR)	(0.308-1.481)	

Only patients with Central Laboratory data are included in the analysis. Positive was defined as H-Score ≥1 and negative as H-Score <1.
H-Score was calculated as the sum of the percentage of cells at each level of staining intensity (0, 1+, 2+, and 3+) multiplied by the staining intensity value:
H-Score=(% at 0)*0+(% at 1+)*1+(% at 2+)*2+(% at 3+)*3.
H-Score values range from 0 to 300.
Abbreviations: CI=confidence interval; N=number of patients in analysis; NR=not reached; PFS=progression-free survival; Rb=retinoblastoma protein.

a. Median PFS and its 95% CI were based on the Brookmeyer and Crowley Method.
b. The hazard ratio was calculated using an unstratified Cox proportional hazards model.
c. The log-rank p-value was calculated using a 1-sided unstratified log-rank test

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 33 - Summary of efficacy for Study 1023 (PALOMA-3), primary and updated analyses

Title: Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial of fulvestrant (Faslodex®) with or without PD-0332991 (palbociclib) ± goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy.		
Study identifier	A5481023	
Design	International, multicentre, 2:1 randomised, double-blind, placebo-controlled, parallel-group, Phase 3 clinical study with the primary objective of demonstrating the superiority of palbociclib (with or without goserelin) in combination with fulvestrant (Faslodex®) over fulvestrant (with or without goserelin)plus placebo in women with HR-positive, HER2-negative metastatic breast cancer, regardless of their menopausal status, whose disease had progressed after prior endocrine therapy.	
	Duration of main phase:	not applicable
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable

Hypothesis	The primary objective of this study is to demonstrate that the combination of palbociclib and fulvestrant is superior to the combination of placebo and fulvestrant in prolonging investigator-assessed PFS in women with HR+/HER2-negative metastatic breast cancer that has progressed on prior endocrine therapy, and regardless of their menopausal status.	
Treatments groups	Arm A (Investigational arm)	Palbociclib 125 mg/day orally for 3 weeks followed by 1 week off plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, every 28 days (+/- 7 days) thereafter starting from Day 1 of Cycle 1. Number of patients randomized: 347
	Arm B (Comparator arm):	Placebo orally daily for 3 weeks followed by 1 week off plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, every 28 days (+/- 7 days) thereafter starting from Day 1 of Cycle 1. Number of patients randomized: 174
Endpoints and definitions	Primary endpoint	Progression-Free Survival (PFS) as assessed by the Investigator
	Secondary endpoints	- Overall Survival (OS). - Objective Response (OR: CR or PR). - Duration of Response (DR). - Clinical Benefit Response (CBR: CR or PR or - SD ≥24 weeks). - Type, incidence, severity, seriousness and relationship to study medications of AEs and any laboratory abnormalities. - Trough plasma concentration of palbociclib, fulvestrant and goserelin (if applicable)in the subgroup of approximately 40 patients included in the initial safety assessment. - PRO endpoints such as health related quality of life scores [EuroQol (EQ-5D) Score. - Tumour tissue biomarkers, including genes (eg, copy numbers of CCND1 and CDKN2A, PIK3CA mutations), proteins (eg, Ki67, pRb, CCNE1), and RNA expression (eg, cdk4, cdk6).
Database lock	Study is ongoing	

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-Treat Population Data Cut-off Date = December -5-2014		
Descriptive statistics and estimate variability Effect estimate per comparison	Treatment group	Palbociclib plus Fulvestrant	Placebo plus Fulvestrant
	Number of subject	347	174
	PFS (median) [months]	9.2	3.8
	95% CI of median PFS [months]	7.5-NE	3.5-5.5

	Effect estimate per comparison of PFS	Comparison groups	Palbociclib + Fulvestrant vs. Placebo + Fulvestrant
		Hazard Ratio (HR)	0.422
		95% CI of HR	0.318-0.560
		1-sided P-value	p<0.000001
	OR (OR rate) [%]	10.4	6.3
	95% CI of OR rate [%]	7.4-14.1	3.2-11.0
	Effect estimate per comparison of OR	Comparison groups	Palbociclib + Fulvestrant vs. Placebo + Fulvestrant
		Odds Ratio	1.725
		95% CI of Odds Ratio	0.835-3.896
		1-Sided P-value	p=0.0791
	CBR (CBR rate) [%]	34.0	19.0
	95% CI of CBR rate [%]	29.0-39.3	13.4-25.6
	Effect estimate per comparison of CBR	Comparison groups	Palbociclib + Fulvestrant vs. Placebo + Fulvestrant
		Odds Ratio	2.189
		95% CI of Odds Ratio	1.391-3.523
		1-Sided P-value	p=0.0002
	DR (median) [months]	9.3	5.7
	95% CI of median DR [months]	4.0-NE	3.7-5.7
Notes	Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favour of Palbociclib +Fulvestrant. An Odds Ratio > 1 means better response in favour of Palbociclib + Fulvestrant. Confirmed objective response is considered for OR and CBR.		
Analysis description	**Other, Updated Analysis with Data Cut-off Date of 23 of October 2015**		
Analysis population and time point description	**Intent-to-Treat Population**		
Descriptive statistics and estimate variability Effect estimate per comparison	Treatment group	Palbociclib plus Fulvestrant	Placebo plus Fulvestrant
	Number of subject	347	174
	PFS (median) [months]	11.2	4.6

	95% CI of median PFS [months]	9.5-12.9	3.5-5.6
	Effect estimate comparison of PFS	Comparison groups	Palbociclib + Fulvestrant vs. Placebo + Fulvestrant
		Hazard Ratio (HR)	0.407
		95% CI of HR	0.398-0.620
		1-sided P-value	p<0.000001
	OR (OR rate) [%]	21.0	8.6
	95% CI of OR rate [%]	16.9, 25.7	4.9-13.8
	Effect estimate comparison of OR	Comparison groups	Palbociclib + Fulvestrant vs. Placebo + Fulvestrant
		Odds Ratio	2.78
		95% CI of Odds Ratio	1.56-5.60
		1-Sided P-value	p=0.0001
	CBR (CBR rate) [%]	66.3	39.7
	95% CI of CBR rate [%]	61.0-71.2	32.3-47.3
	Effect estimate comparison of CBR	Comparison groups	Palbociclib + Fulvestrant vs. Placebo + Fulvestrant
		Odds Ratio	3.02
		95% CI of Odds Ratio	2.05-4.57
		1-Sided P-value	p<0.0001
	DR (median) [months]	10.4	9.0
	95% CI of median DR [months]	8.3-NE	5.5-NE
Notes	Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favour of Palbociclib +Fulvestrant. An Odds Ratio > 1 means better response in favour of Palbociclib + Fulvestrant. Confirmed objective response is considered for OR and CBR.		

Table 34 - Summary of efficacy for Study 1008/PALOMA-2

Title: A Randomized, Multicenter, Double Blind Phase 3 Study of PD 0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women With ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti Cancer Treatment for Advanced Disease	
Study identifier	A5481008

Design	International, multicenter, randomized, double blind, placebo controlled, parallel group, Phase 3 clinical study comparing the efficacy and safety of palbociclib in combination with letrozole versus placebo in combination with letrozole in postmenopausal women with ER positive/HER2 negative advanced breast cancer (ABC).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	not applicable not applicable not applicable
Hypothesis	The primary objective of this study is to demonstrate that the combination of palbociclib with letrozole is superior to placebo plus letrozole in prolonging PFS in postmenopausal women with ER-positive/HER2-negative ABC who have not received any prior systemic anti-cancer therapies for their advanced/metastatic disease.	
Treatments groups	Arm A (Investigational arm)	Palbociclib, 125 mg, orally once daily (QD) on Day 1 to Day 21 of every 28 day cycle followed by 7 days off treatment; in combination with Letrozole, 2.5 mg, orally QD (continuously).
	Arm B (Comparator arm):	Placebo orally QD on Day 1 to Day 21 of every 28 day cycle followed by 7 days off treatment; in combination with Letrozole, 2.5 mg, orally QD (continuously).
Endpoints and definitions	Primary endpoint	Progression-Free Survival (PFS) as assessed by the Investigator
	Key Secondary endpoints	Overall Survival (OS) Objective Response (OR: Complete Response or Partial Response); Duration of Response (DR); Clinical Benefit Response (CBR) /Disease Control (DC) (CBR/DC: CR + PR + Stable disease ≥24 weeks); Corrected QT interval (QTc); Tumour tissue biomarkers, including genes (e.g Trough plasma concentration of PD 0332991; EuroQol (EQ 5D) Score
Database lock	Study is ongoing	

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-Treat Population Data Cut-off Date = February 26, 2016		
Descriptive statistics and estimate variability Effect estimate per comparison	Treatment group	Palbociclib plus Letrozole	Placebo plus Letrozole
	Number of subject	444	222
	PFS (median) [months]	24.8	14.5

	95% CI of median PFS [months]	22.1-NE* *NE: not estimable	12.9-17.1
	Effect estimate per comparison of PFS	Comparison groups	Palbociclib + Letrozole vs. Placebo + Letrozole
		Hazard Ratio (HR)	0.576
		95% CI of HR	0.463-0.718
		1-sided P-value	p<0.000001
	OR (OR rate) [%]	42.1	34.7
	95% CI of OR rate [%]	37.5-46.9	28.4-41.3
	Effect estimate per comparison of OR	Comparison groups	Palbociclib + Letrozole vs. Placebo + Letrozole
		Odds Ratio	1.40
		95% CI of Odds Ratio	0.98-2.01
		1-Sided P-value	p=0.0310
	CBR / DC (CBR/DC rate) [%]	84.9	70.3
	95% CI of CBR/DC rate [%]	81.2-88.1	63.8-76.2
	Effect estimate per comparison of CBR	Comparison groups	Palbociclib + Letrozole vs. Placebo + Letrozole
		Odds Ratio	2.39
		95% CI of Odds Ratio	1.58-3.59
		1-Sided P-value	p<0.0001
	DR (median) [months]	22.5	16.8
	95% CI of median DR [months]	19.8-28.0	14.2-28.5
Notes	Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of Palbociclib +Letrozole. An Odds Ratio > 1 means better response in favor of Palbociclib + Letrozole. Confirmed objective response is considered for OR and CBR.		

Title: Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial of fulvestrant (Faslodex) with or without PD-0332991 (palbociclib) ± goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy.		
Study identifier	A5481023	
Design	International, multicentre, 2:1 randomised, double-blind, placebo-controlled, parallel-group, Phase 3 clinical study with the primary objective of demonstrating the superiority of palbociclib (with or without goserelin) in combination with fulvestrant (Faslodex®) over fulvestrant (with or without goserelin)plus placebo in women with HR-positive, HER2-negative metastatic breast cancer, regardless of their menopausal status, whose disease had progressed after prior endocrine therapy.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	not applicable not applicable not applicable
Hypothesis	The primary objective of this study is to demonstrate that the combination of palbociclib and fulvestrant is superior to the combination of placebo and fulvestrant in prolonging investigator-assessed PFS in women with HR+/HER2-negative metastatic breast cancer that has progressed on prior endocrine therapy, and regardless of their menopausal status.	
Treatments groups	Arm A (Investigational arm)	Palbociclib 125 mg/day orally for 3 weeks followed by 1 week off plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, every 28 days (+/- 7 days) thereafter starting from Day 1 of Cycle 1. Number of patients randomized: 347
	Arm B (Comparator arm):	Placebo orally daily for 3 weeks followed by 1 week off plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, every 28 days (+/- 7 days) thereafter starting from Day 1 of Cycle 1. Number of patients randomized: 174
Endpoints and definitions	Primary endpoint	Progression-Free Survival (PFS) as assessed by the Investigator
	Secondary endpoints	- Overall Survival (OS). - Objective Response (OR: CR or PR). - Duration of Response (DR). - Clinical Benefit Response (CBR: CR or PR or - SD ≥24 weeks). - Type, incidence, severity, seriousness and relationship to study medications of AEs and any laboratory abnormalities. - Trough plasma concentration of palbociclib, fulvestrant and goserelin (if applicable)in the subgroup of approximately 40 patients included in the initial safety assessment. - PRO endpoints such as health related quality of life scores [EuroQol (EQ-5D) Score. - Tumour tissue biomarkers, including genes (eg, copy numbers of CCND1 and CDKN2A, PIK3CA mutations), proteins (eg, Ki67, pRb, CCNE1), and RNA expression (eg, cdk4, cdk6).
Database lock	Study is ongoing	
Results and Analysis		

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-Treat Population Data Cut-off Date = December -5-2014		
Descriptive statistics and estimate variability Effect estimate per comparison	Treatment group	Palbociclib plus Fulvestrant	Placebo plus Fulvestrant
	Number of subject	347	174
	PFS (median) [months]	9.2	3.8
	95% CI of median PFS [months]	7.5-NE	3.5-5.5
	Effect estimate per comparison of PFS	Comparison groups	Palbociclib + Fulvestrant vs. Placebo + Fulvestrant
		Hazard Ratio (HR)	0.422
		95% CI of HR	0.318-0.560
		1-sided P-value	p<0.000001
	OR (OR rate) [%]	10.4	6.3
	95% CI of OR rate [%]	7.4-14.1	3.2-11.0
	Effect estimate per comparison of OR	Comparison groups	Palbociclib + Fulvestrant vs. Placebo + Fulvestrant
		Odds Ratio	1.725
		95% CI of Odds Ratio	0.835-3.896
		1-Sided P-value	p=0.0791
	CBR (CBR rate) [%]	34.0	19.0
	95% CI of CBR rate [%]	29.0-39.3	13.4-25.6
	Effect estimate per comparison of CBR	Comparison groups	Palbociclib + Fulvestrant vs. Placebo + Fulvestrant
		Odds Ratio	2.189
		95% CI of Odds Ratio	1.391-3.523
		1-Sided P-value	p=0.0002
	DR (median) [months]	9.3	5.7
	95% CI of median DR [months]	4.0-NE	3.7-5.7

Notes	Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favour of Palbociclib +Fulvestrant. An Odds Ratio > 1 means better response in favour of Palbociclib + Fulvestrant. Confirmed objective response is considered for OR and CBR.		
Analysis description	**Other, Updated Analysis with Data Cut-off Date of March-16-2015**		
Analysis population and time point description	**Intent-to-Treat Population** **Data Cut-off Date = March-16-2015**		
Descriptive statistics and estimate variability Effect estimate per comparison	Treatment group	Palbociclib plus Fulvestrant	Placebo plus Fulvestrant
	Number of subject	347	174
	PFS (median) [months]	9.5	4.6
	95% CI of median PFS [months]	9.2-11.0	3.5-5.6
	Effect estimate comparison of PFS	Comparison groups	Palbociclib + Fulvestrant vs. Placebo + Fulvestrant
		Hazard Ratio (HR)	0.461
		95% CI of HR	0.360-0.591
		1-sided P-value	p<0.000001
	OR (OR rate) [%]	19.0	8.6
	95% CI of OR rate [%]	15.0-23.5	4.9-13.8
	Effect estimate comparison of OR	Comparison groups	Palbociclib + Fulvestrant vs. Placebo + Fulvestrant
		Odds Ratio	2.474
		95% CI of Odds Ratio	1.362-4.911
		1-Sided P-value	p=0.0010
	CBR (CBR rate) [%]	66.6	39.7
	95% CI of CBR rate [%]	61.3-71.5	32.3-47.3
	Effect estimate comparison of CBR	Comparison groups	Palbociclib + Fulvestrant vs. Placebo + Fulvestrant
		Odds Ratio	3.047
		95% CI of Odds Ratio	2.067-4.605
		1-Sided P-value	p<0.0001
	DR (median) [months]	9.3	7.6

	95% CI of median DR [months]	5.8-NE	5.5-9.3
Notes	Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favour of Palbociclib +Fulvestrant. An Odds Ratio > 1 means better response in favour of Palbociclib + Fulvestrant. Confirmed objective response is considered for OR and CBR.		

Analysis performed across trials (pooled analyses AND meta-analysis)

Critical visceral disease

According to current international treatment guidelines, endocrine therapy is not recommended in patients with critical, rapidly progressing or symptomatic visceral disease, due to a lower expectancy of a rapid tumour response or relevant tumour shrinkage compared with (cytotoxic) chemotherapies.

Studies PALOMA-3 and PALOMA-2 excluded patients with advanced/metastatic, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term, including patients with massive uncontrolled effusions (pleural, pericardial, peritoneal), pulmonary lymphangitis, and over 50% liver involvement.

The table below provides available data on time to response (TTR) and objective response rates (ORR) for the pivotal studies.

Table 35 – Efficacy in visceral subgroup compared with ITT (Studies 1023 and 1008)

	PALOMA-3				PALOMA-2			
	ALL Palbociclib + fulvestrant	ALL Placebo + fulvestrant	VISCERAL subgroup Palbociclib + fulvestrant	VISCERAL subgroup Placebo + fulvestrant	ALL Palbociclib + letrozole	ALL Placebo + letrozole	VISCERAL subgroup Palbociclib + letrozole	VISCERAL subgroup Placebo + letrozole
n	347	174	206	105	444	222	217	111
Visceral disease (% of pts)	59	60	100	100	49	50	100	100
OR* (%)	21	9	28	7	55	44	55	40
TTR* (months)	N/R	N/R	3.8	3.6	N/R	N/R	4.3	5.3
PFS (inv) (months)	11.2	4.6	9.2	3.5	24.8	14.5	19.2	12.9

Clinical studies in special populations

In pivotal Study 1008, 181/444 (41%) of palbociclib-treated patients were ≥65 years old. In pivotal Study 1023 the corresponding figures were 86/347 (25%). In total 34% of the palbociclib-treated patients in the two pivotal studies (1008 and 1023) together were 65 years or older, 8% were 75 years or older, 1% were 85 years or older.

Table 36 - Elderly patients in pivotal studies 1023 and 1008, and supportive study 1003

Controlled trials	Age 65-74 (Older subjects number /total number)		Age 75-84 (Older subjects number /total number)		Age 85+ (Older subjects number /total number)	
A5481023 (PALOMA-3)	96/521 (18.4)		30/521 (5.8)		3/521 (0.6)	
	Palbociclib+ FULV	Placebo+ FULV	Palbociclib+ FULV	Placebo+ FULV	Palbociclib+FULV	
	59	37	24	6	3	
A5481008 ph 3 (PALOMA-2)	195/666 (29.3)		60/666 (9)		7/666 (1.1)	
	Palbociclib+ LETROZ	Placebo +LETROZ	Palbociclib+ LETROZ	Placebo +LETROZ	Palbociclib +LETROZ	Placebo +LETROZ
	133	62	43	17	5	2
A5481003 ph 2 (PALOMA-1)	61/165 (37)		14/165 (8.5)		1/165 (0.6)	
	Palbociclib+ LETROZ	LETROZ	Palbociclib+ LETROZ	LETROZ	Palbociclib+LETROZ	
	29	32	7	7	1	
A5481003 Phase 2 Part 1 (N=66)	12	14	4	1	1	
A5481003 Phase 2 Part 2 (N=99)	17	18	3	6	0	

2.5.3. Supportive studies

Study 1003 (PALOMA-1)

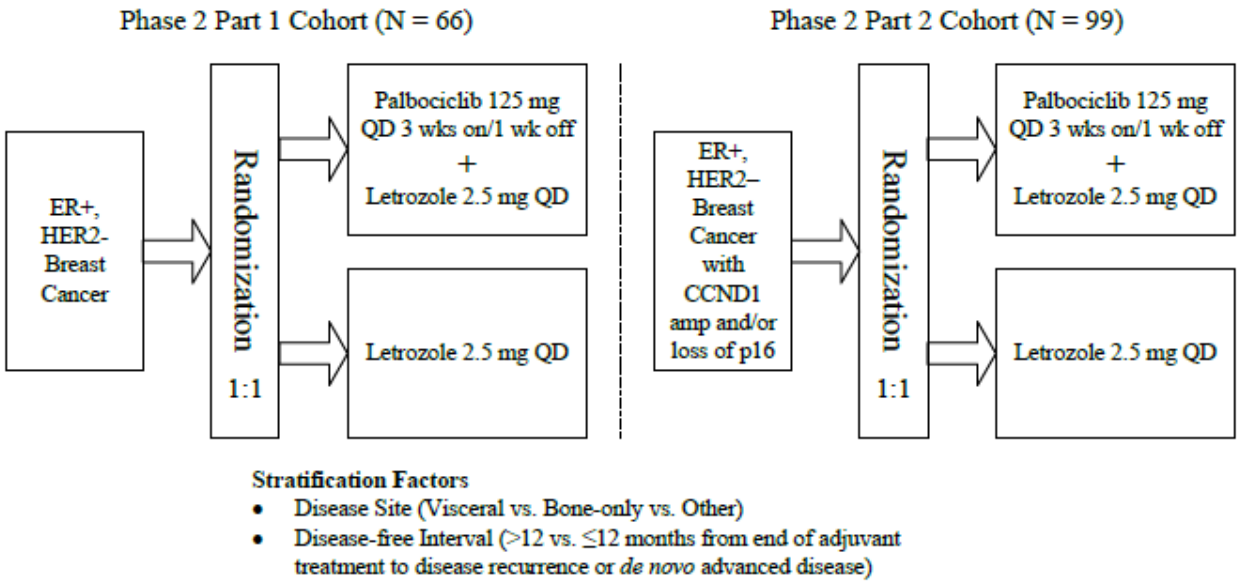
Phase 1/2, Open-Label, Randomized Study Of The Safety, Efficacy, And Pharmacokinetics Of Letrozole Plus Pd 0332991 (Oral Cdk 4/6 Inhibitor) And Letrozole Single Agent For The First-Line Treatment Of ER-Positive, HER2-Negative Advanced Breast Cancer In Postmenopausal Women

Study design, randomisation and treatments

The phase 1 stage enrolled 12 patients with the aim to confirm the tolerability of combining palbociclib with letrozole. Palbociclib 125 mg daily for 3 weeks followed by one week of rest as add-on to letrozole daily for 4 weeks showed acceptable tolerability and 4 partial responses were reported.

The initial Phase 2 study design included 150 patients randomized 1:1 to receive palbociclib plus letrozole (Arm A) or letrozole alone (Arm B). Letrozole was administered at standard dose according to label. Based upon evolving preclinical data suggesting that the tumours with CCND1 amplification and/or loss of CDKN2A/ p16INK4A gene were particularly sensitive to palbociclib, the design was revised. After a number of amendments the final study design was set as follows:

Figure 16 - Study 1003 – Final Phase 2 Design



Study participants

Key eligibility criteria included: Postmenopausal women with ER-positive, HER2-negative locally recurrent or metastatic breast cancer, measurable disease according to RECIST 1.0 or bone-only disease (Phase 2 only), ECOG performance status 0 or 1, adequate blood counts and organ function, and no prior/current brain metastases. For full inclusion/exclusion criteria, see below.

Inclusion Criteria

Patients must have met all of the following criteria for inclusion in the study:

1. Histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of 1) locally recurrent disease not amenable to resection or radiation therapy with curative intent, or 2) metastatic disease.

2. ER-positive tumour. Positivity was defined either as ≥10 fmol of tritium (H3)-oestrogen binding per mg of cytosol protein for dextran-coated charcoal and sucrose density methods, or ≥0.10 fmol of H3-estrogen binding per mg of DNA for immunofluorescence (IF)/enzyme-linked immunosorbent assay (EIA) technique. In case of use of immunohistochemistry (IHC), the report was to mention positive receptor status according to the standards of the laboratory.

3. HER2-negative breast cancer by FISH or IHC.

4. Paraffin-embedded tumour block(s) available for centralized assessment of Rb and other cell cycle-related proteins. Ph2P2 only: CCND1 amplification and/or loss of CDKN2A as determined by the central laboratory.

5. Measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST Version 1.0) or bone-only disease (Phase 2 only). Previously irradiated lesions were deemed measurable only if progression was documented at the site after completion of radiation.

6. Female patients, 18 years of age or older.

Postmenopausal status defined as:

• Prior bilateral surgical oophorectomy;

• Amenorrhea and age ≥60 years;

• Age <60 years and amenorrhea for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle stimulating hormone (FSH) and oestradiol in the postmenopausal ranges.

8. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

9. Resolution of all acute toxic effects of prior therapy or surgical procedures to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤1 (except alopecia or other toxicities not considered a safety risk for the patient).

10. Adequate organ function as defined by the following criteria:

• Absolute neutrophil count (ANC) ≥1500/μL;

• Platelets ≥100,000/μL;

• Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN), or AST and ALT ≤5 × ULN if due to underlying malignancy;

• Total serum bilirubin ≤1.5 × ULN regardless of liver involvement secondary to tumour. Inclusion of patients with increased serum indirect bilirubin due to Gilbert's syndrome was permitted;

• Serum creatinine ≤1.5 × ULN;

• QTc ≤470 msec (based on the mean value of the triplicate electrocardiograms [ECGs]).

11. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) had been informed of all pertinent aspects of the study.

12. Patients who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion Criteria

Patients who met any of the following exclusion criteria were not included in the study:

1. Brain metastases (even if treated and stable), spinal cord compression (history or presence of), carcinomatous meningitis, or leptomeningeal disease.

2. Major surgery within 3 weeks of first study treatment.

3. Prior treatment with:

• Any anticancer therapies for advanced disease, with the exception of radiation therapy to <25% of bone marrow at least 2 weeks prior to study treatment initiation;

• (neo)adjuvant letrozole with disease recurrence ≤12 months (Phase 2 only);

• Any CDK inhibitor.

4. Current treatment with:

• Any anticancer therapies for advanced disease;

• Any experimental treatment on another clinical study;

• Therapeutic doses of anticoagulant. Low-dose anticoagulants for deep vein thrombosis prophylaxis were allowed. Low-molecular-weight heparin was allowed. Aspirin was permitted.

5. Current use or anticipated need for:

• Food or drugs that are known strong CYP3A4 inhibitors (ie, grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, posaconazole, erythromycin, clarithromycin, tilithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, nefazodone, diltiazem, and delavirdine) – for both Phases 1 and 2;

• Drugs that are known strong CYP3A4 inducers (ie, carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's Wort) – for Phase 1 only.

6. Diagnosis of any secondary malignancy within the last 3 years, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.

7. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.

8. Active inflammatory bowel disease or chronic diarrhoea. Short bowel syndrome. Upper gastrointestinal surgery including gastric resection.

9. Known hypersensitivity to letrozole or to any of its excipients.

10. Known human immunodeficiency virus infection.

11. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the patient inappropriate for entry into this study.

Brain metastases, spinal cord compression (including history of), carcinomatous meningitis, or leptomeningeal disease were excluded. Overall, patients actually enrolled appear typical for a first-line, metastatic ER+ and HER2- negative breast cancer study. As expected in a small study, there were some imbalances in baseline factors of possible prognostic importance; these are outlined below.

Treatments

Phase 2:

In all cycles, letrozole 2.5 mg (Femara, filmcoated tablet) was administered on a continuous dosing regimen QD together with palbociclib (Arm A) or alone (Arm B). Letrozole was thus administered at standard dose according to label.

Palbociclib was provided in bottles containing either 25 mg or 100 mg capsules (isethionate salt) to patients. The capsules were distinguished by their size. Palbociclib was given according to the 3/1 schedule.

Outcomes/endpoints

Standard efficacy endpoints based on standard definitions were used, including PFS, overall survival (OS), time to progression (TTP),objective response (OR), duration of response (DOR). Clinical benefit response (CBR) was defined as the occurrence of complete response (CR), partial response (PR) or stable disease (SD) ≥24 weeks.

Screening/baseline tumour assessment was carried out within 4 weeks of start of treatment. Post-baseline tumour assessments were performed every 8 weeks. Bone scans were carried out at baseline and every 12 weeks thereafter. Objective tumour response was measured using RECIST (Version 1.0). All patients with responding tumours (CR or PR) had to have the response confirmed no sooner than 4 weeks after the initial documentation of response.

Recruitment

First patient screened: 15 September 2008.

Data cutoff date: 29 November 2013.

Between 25 September 2008 and 03 September 2009, a total of 12 women were enrolled in the Phase 1 part of the study at 3 sites in the United States. At the time of data cutoff for the Clinical Study Report (CSR) (29 November 2013), 2 patients (16.7%) were ongoing in the study.

Between 22 December 2009 and 12 May 2012, a total of 165 women were randomized in the Phase 2 part at 50 sites in 12 countries: Canada (2 sites), France (2 sites), Germany (8 sites), Hungary (7 sites), Ireland (4 sites), Italy (1 site), Russia (4 sites), South Africa (1 site), Republic of Korea (2 sites), Spain (5 sites), Ukraine (4 sites), and the United States(10 sites).

At the time of data cutoff for the CSR (29 November 2013), 19 patients (22.6%) and 8 patients (9.9%) were ongoing in the study in the palbociclib plus letrozole arm and letrozole alone arm, respectively.

Participant flow

In Phase 2 (Ph2P1+Ph2P2), 84 and 81 patients were randomized to the palbociclib plus letrozole arm and letrozole alone arm, respectively. One patient in the palbociclib plus letrozole arm and 4 patients in the letrozole alone arm were randomized but not treated.

Conduct of the study

Protocol deviations

In total 14/165 (8%) of patients in the phase 2 part pf Study 1003 had a protocol deviation defined as clinically significant, 4 of which were related to confirmation of post-menopausal status. It is considered unlikely that these deviations would have a major impact on the overall study results.

Changes in the Conduct of the Study or Planned Analyses

There were 7 amendments to the original study protocol (dated 27 March 2008) and there were 3 amendments to the original statistical analysis plan (SAP, dated 19 May 2008).

In summary, the protocol and SAP of study 1003 were amended significantly two times during study, first to divide the phase 2 study population into two cohorts where the second included only patients that were positive for factors believed to be predictive of response to the palbociclib treatment (Amendment #3, July 2010). The

second major change was to analyse the two cohorts together (Amendment #5, June 2012). In addition, the maturity of the PFS data was reduced (Amendment #7, July 2013).

Submission of all imaging studies (including photographs for superficial disease, if applicable) from patients in Phase 2 Part 2 to an independent core imaging laboratory for review was required from July 2010 (Amendment #3). From November 2011 (Amendment #6), analyses based on independent central review were introduced as a possibility in the efficacy analysis part of the protocol.

Results

Baseline data

There were imbalances in age and weight across study arms, potentially due to the small size of the study. Somewhat older and lighter (with regard to body weight) patients were included in the letrozole arm compared with the palbociclib + letrozole arm. The age difference in mean and medians of approximately 1 -1.5 year in both the overall phase 2 population and in cohort 2, could potentially favour the experimental arm, which also had fewer patients in pre-menopausal age.

Overall, the majority of patients had Stage IV disease (98%), ductal carcinoma (71%) and more than half of the patients had an ECOG performance status of 0. There was an imbalance between treatment arms in the time since diagnosis of breast cancer; the median time since diagnosis was 1.3 years (range: 0 to 27 years) in the palbociclib plus letrozole arm compared with 2.4 years (range: 0 to 40 years) in the letrozole alone arm. A higher percentage of patients in the palbociclib plus letrozole arm compared with the letrozole alone arm had Grade 3 tumours (36.9% versus 22.2%) and had progesterone receptor-positive disease (77.4% versus 65.4%).

In Phase 2 (Ph2P1+Ph2P2), the 2 treatment arms were generally balanced across the stratification factors of disease site and disease-free interval using the data based on randomization criteria. However, when using the CRF data, there were some imbalances between the 2 treatment arms:

• A lower percentage of patients had visceral disease in the palbociclib plus letrozole arm (44.1%) than in the letrozole alone arm (53.1%);

• A higher percentage of patients had bone only disease in the palbociclib plus letrozole arm (20.2%) than in the letrozole alone arm (14.8%). These discrepancies were due to the incorrect stratification factors being used at the time of randomization which were discovered retrospectively during data review and source data verification. Sensitivity analyses using CRF data was carried out to investigate the impact of the imbalances on the PFS results, using multivariate Cox proportional hazards models by investigator and BICR assessments. These indicated that the difference in disease site as per CRF with approximately 10% more visceral disease in the letrozole comparator arm will favour the experimental palbociclib+ letrozole arm in the comparison (BICR HR 0.4 for Non-visceral vs visceral). The difference in mean and medians of age of approximately 1 -1.5 years may on the other hand favour the comparator arm (BICR HR 0.5 for age ≥ 65 years vs. < 65 years. How these imbalances balance each other is difficult to discern, but adds uncertainty to the results.

There are imbalances across arms with regard to prior anti-cancer treatment. Mostly these are in the direction of the comparator arm having received more prior therapy compared to the palbociclib-containing experimental arm. E.g. a higher percentage of patients in the palbociclib + letrozole arm compared with the letrozole alone arm had received no prior systemic therapy (52 vs. 46% in the full Phase 2 population, 50 vs. 41% in Part 2 cohort.). Less pre-treatment generally implies more chance of response and could thus favour the experimental arm. The received types of prior chemotherapy were well-balanced across arms, however, as were the types and duration of prior anti-hormonal therapies.

Post-Study Systemic Therapy for Breast Cancer

Of the patients who had discontinued study treatment, 26% (17/65) in the palbociclib + letrozole arm compared with 15% (11/73) in the letrozole alone arm had not received next-line therapy.

Biomarker analysis

Enrolment of patients to the part 2 cohort (Ph2P2) was *a priori* defined as only to include biomarker positive patients without knowledge of the actual outcome of part 1 (Ph2P1). When Part 1 was analysed, however, it appeared as if the biomarker were non-predictive for outcome:

Table 37 - Hazard ratios by biomarker status in Phase 2, Part 1

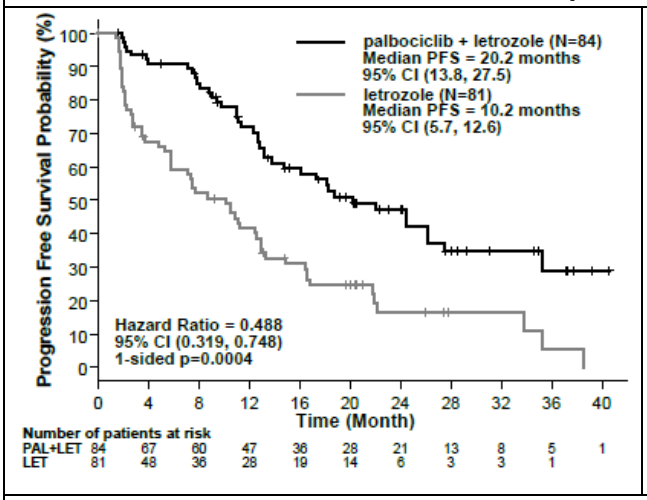
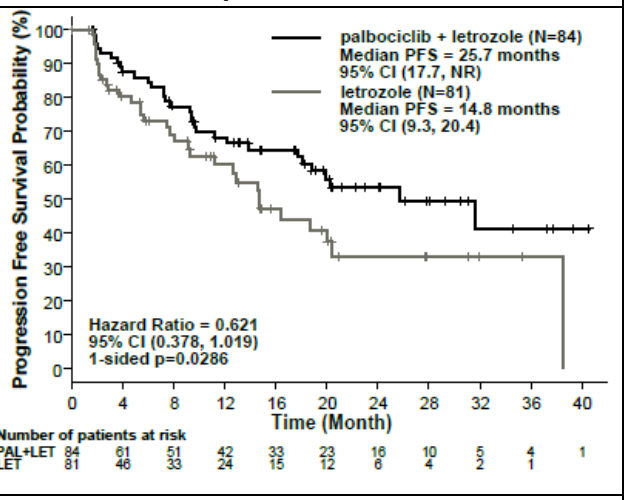
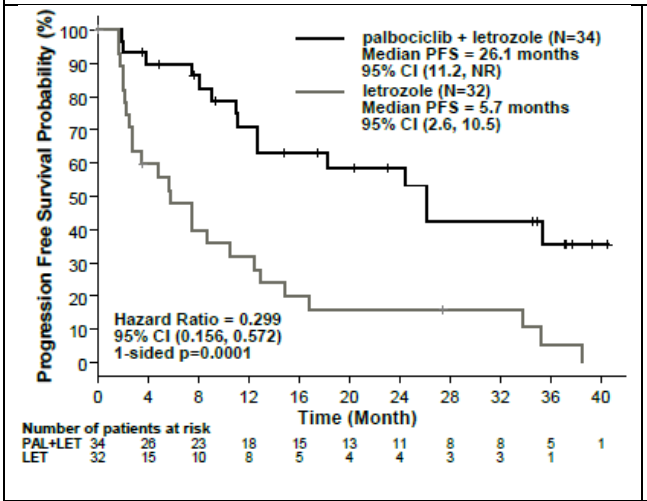
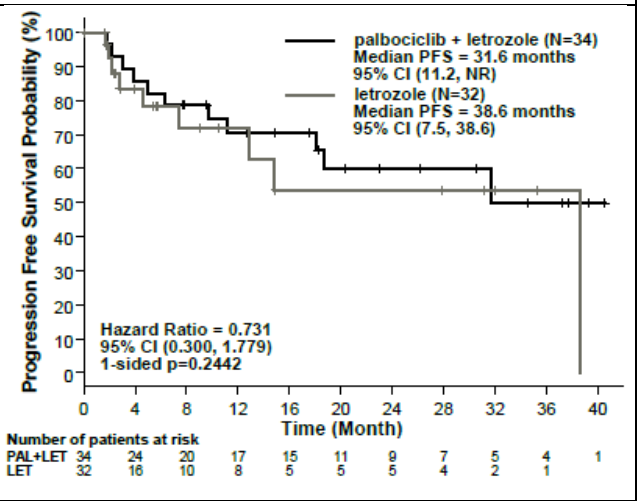
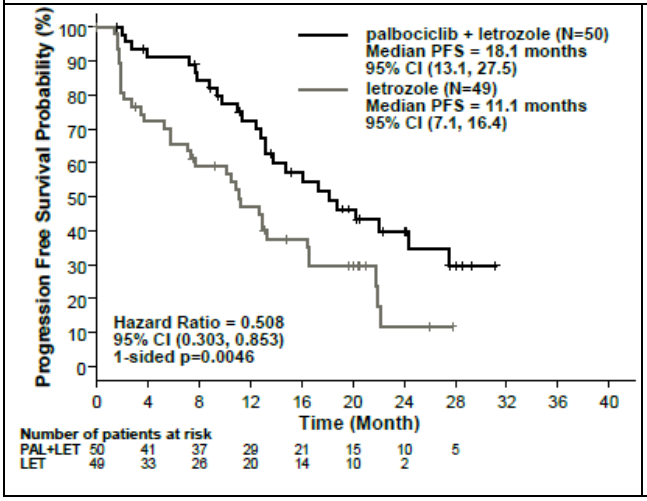
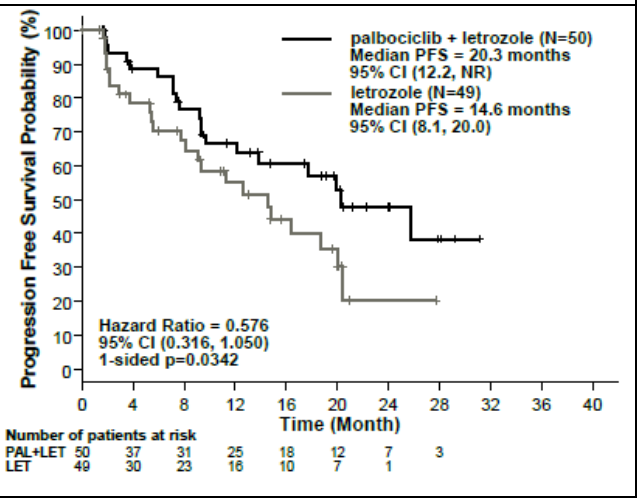
Biomarker status	Number of patients in the experimental + control arm	PFS (investigator assessment) HR (95% CI)
Positive	12 + 9	0.2 (95% CI 0.07; 0.71)
Negative	10 + 15	0.2 (95% CI 0.11; 0.71)
Unknown	12 + 8	0.9 (95% CI 0.18; 4.61)

Of note there was a small number of individuals and especially the poor and discrepant outcome in the biomarker unknown cohort.

Primary endpoint – Progression-free survival

The primary analysis of the primary objective was based on the investigator assessment of progressive disease. Blinded Independent Central Review (BICR) was also performed. See figure xxx below.

Figure 17 - KM plots of PFS, by investigator and BICR and by Part (Study 1003, ITT)

Investigator Assessment	Blinded Independent Central Review
Full Phase 2 (Part 1 + Part 2 cohorts)	
	
Phase 2 Part 1 cohort	
	
Phase 2 Part 2 cohort	
	

There is a marked difference between the investigator- and BICR-based curves of Ph2 Part1. The curve of the control arm is considerably lower while the curve of the experimental arm is somewhat better in the investigator-based compared with the BICR based analysis, indicative of major bias favouring the experimental arm in the investigator assessments. See further comments in the table below.

Summary of efficacy for Study 1003

Table 38 - Summary of main efficacy results for Study 1003 – PALOMA 1.

Title: PALOMA 1			
Study identifier	Study 1010 (Protocol number: A5481010)		
Design	Randomised, open label		
Hypothesis	Superiority		
Treatments groups	Experiment	Letrozole + palbociclib until PD or intolerance	
	Reference	Letrozol until PD or intolerance	
Endpoints and definitions	Primary endpoint	PFS (investigator)	
	Secondary endpoints	PFS (BICR), OS, ORR, HRQoL	
Database lock	29-November-2013		
Results and Analysis			
		Experiment	Control
Ph2P1 PFS (investigator)	Event rate Median, m. (95%CI)	15/34 26 (11; NR)	25/32 6 (3; 11)
	HR (95%) P-value	0.3 (stratified) <0.001	
Ph2P1 PFS (BICR)	Event rate Median, m. (95%CI)	11/34 32 (11; NR)	9/32 1.9 (1.9; 2.1)
	HR (95%) P-value	0.7 (0.3; 1.8) 0.2 (one sided)	
Comment: Note the major differences in event rates between investigator and BICR, especially in the control arm, **25 (inv.), 9 (BICR)** vs 15 and 11.			
Ph2P2 PFS (investigator)	Event rate Median, m. (95%CI)	26/50 18 (13; 28)	34/49 11 (7; 16)
	HR (95%) P-value	0.5 (0.36; 0.71) 0.005, one-sided	
Ph2P2 PFS (BICR)	Event rate Median, m. (95%CI)	20/50 20 (12; NR)	24/49 15 (8; 20)
	HR (95%) P-value	0.58 0.03, one-sided	

Comment: The discrepancy Investigator/BICR is clearly less pronounced than in Part 1, but directionally consistent, i.e. fewer BICR confirmed PD in the control arm.			
Ph2P1+2 PFS (investigator)	Event rate Median, m. (95%CI) HR (95%) P-value	41/84 20 (14; 28) 0.41 (stratified) <0.001	59/81 10 (6; 13)
Ph2P1+2 PFS (BICR)	Event rate Median, m. (95%CI) HR (95%) P-value	31/84 26 (18; NR) 0.6 (stratified) 0.029, one sided	33/81 15 (9; 20)
Comment: In the BICR analysis of the combined P1+2 stages, the p-value is borderline. The BICR confirmed PD rate is 31/41 (test) vs. 33/59 (control).			
Ph2P1+2 (BICR)	**ORR** (ITT) (measurable disease.)	30% 49%	21%, p=0.26 (two sided) 33%, p=0.14 (two sided)
Ph2P1+2	**Overall survival** Event rate Median (m) HR (95% CI)	 36% 38 0.8 (0.5; 1.3)	 38% 33

Investigator – BCIR Discordance analyses

Table 39 - Discordance of Investigator Assessment and Blinded Independent Central Review on PFS by Part (ITT)

Study1003, Phase 2:	Part 1		Part 2	
	Palb + letrozole (N= 34)	Letrozole alone (N= 32)	Palb + letrozole (N= 50)	Letrozole alone (N= 49)
n (%) where investigator declares PD where BCIR does not	7 (21)	16 (50)	12 (24)	11 (22)
n (%) where BCIR declares PD where investigator does not	16 (47)	7 (3)	6 (12)	1 (2)

A number of discordance analyses were made, a selection is shown in table 39 above. The pattern in Part 1 indicates a bias in the investigator assessments favouring the experimental arm, with 50% of PDs determined by investigator in the comparator arm were not confirmed by BCIR compared with only 21% in the experimental arm. Conversely, nearly half (47%) of the PDs in the experimental arm determined by the BCIR were not confirmed by the investigator compared with only 3% in the control arm. In addition, there were further tendencies of bias favouring the experimental arm in Part 1 with regard timing of PD declarations by investigator and BCIR, respectively, as for 5 (15%) patients in the experimental arm investigator declared PD more than 7 days later than BCIR, compared with only 2 (6%) in the comparator arm.

In Part 2 the figures were similar across arms with regard to investigator assessed PD not confirmed by BCIR (24 vs 22%), while a potential tendency of bias in favour of the experimental arm might be noted in the BCIR assessed PDs not confirmed by investigator.

In the search for explanations for the deviant findings between INV and BICR results in Ph2Part1, the Applicant found that an imbalance in the number of progressions based on new bone and non-target bone disease contributed to the disagreement between INV and BICR (INV: 13 vs. 40% in palbociclib + letrozole vs. letrozole alone arms; BICR 27 vs. 22% for BICR, respectively). After censoring INV progression events in both arms that were not called by the BICR at the time of PD and were based upon bone, the clinical benefit with the combination treatment on PFS was maintained (HR 0.443; 95% CI, 0.283 to 0.694). It is apparent that this does not explain the whole difference between assessments, however, considering the HRs 0.3 vs 0.7 in the original analysis by INV and BICR, respectively.

Taken together, these results indicate that Part 1 may be significantly biased and is therefore not suitable for licensure. The bias in the Phase 2 Part 1 cohort impacts also on the full Phase 2 results. Therefore only Part 2 results are considered relevant to the efficacy assessment. No number of sensitivity analyses (in the full phase 2 population) can compensate for the major bias identified in Part 1. Due to highly likely informative censoring, BICR data from Part 1 is not considered informative. It is noted that even if the likely informative censoring in BICR data could be overlooked, the BICR-based PFS results in the full Phase 2 population were not statistically significant (1-sided p=0.3, corresponding to 2-sided p= 0.6).

Secondary endpoint results in Phase 2 Part 2:

Overall survival: At an event rate of less 30% in the survival analysis, there is a weak trend in favour of the experimental arm: HR 0.8, 1-sided p=0.3.

Table 40 - Objective response rates (Study 1003, Phase 2 Part 2)

Objective response rate		Palbociclib + letrozole		Letrozole alone		1-sided p-value for difference
		n/N	%	n/N	%	
ITT	Investigator	21/50	42	19/49	39	0.45
	BICR	14/50	28	13/49	27	0.52
Measurable disease	Investigator	21/38	55	18/43	42	0.16
	BICR	14/31	45	13/37	35	0.28

2.5.4. Discussion on clinical efficacy

Study 1023 was a 2:1 randomized, double-blind, placebo-controlled, Phase 3 study comparing palbociclib vs. placebo as add-on to fulvestrant (+ goserelin in pre- and perimenopausal patients) in patients with hormone receptor (HR) positive, HER2-negative metastatic breast cancer, whose disease had progressed after prior endocrine therapy.

The treatment arms were well balanced with regard to the stratification factors either based on randomization or based on the CRF. Neither the inclusion/exclusion criteria violations nor the changes to the protocol and SAP appeared to have put the integrity of the study at risk. There were no objections to the overall study design. The baseline disease characteristics were similar across study arms. Small imbalances were noted but were not considered likely to affect the overall study results.

The study met its primary objective of prolonging investigator-assessed PFS at the interim analysis (data cut-off 05 Dec 2014), demonstrating a statistically significant prolongation in PFS and a clinical meaningful treatment effect. A number of pre-specified sensitivity analyses confirmed the results of the primary analysis.

Overall survival data were immature and thus non-informative with in total 28 deaths and event rates of 5% in both arms at the interim analysis. Therefore, two updated analyses were performed for investigator-based PFS, ORR, CBR and DOR at a median of 8.9 months follow-up (data cut-off 16 March 2015) and over 15 months (data cut-off 23 October 2015), respectively. In the second update, performed at an overall event rate of 64% (58 vs. 76%), the PFS HR was 0.50 (0.36-0.59). Median PFS was 11.2 vs. 4.6 months, i.e. a difference of 6.6 months. Thus in the updated analysis, the difference between arms has increased from 5.7 to 6.6 months.

In updated PFS subgroup analyses, all subgroup HR point estimates were below 1.0 and most had 95% confidence intervals below 1, indicating robustness of the results.

At a pre-specified interim OS analysis (data cut-off date of 23 Oct 2015) there were in total 112 deaths (21%) in both arms; 20.5 vs. 23.6% (experimental vs. control). No deaths in the palbociclib arm were due to toxicity. The formal statistical analysis of OS will be performed during the planned OS interim analysis and final analysis. At this time, there are no signs of a detrimental effect on OS. The final analysis of Overall Survival is projected to occur by Q4 (Dec) 2017. The Applicant has committed to submit these results by Q2 (June) 2018.

The difference in OR and CBR supports the PFS results.

Study 1008 was a 2:1 randomised double-blind, placebo-controlled, Phase 3 study comparing palbociclib vs. placebo as add-on to letrozole as first-line treatment of postmenopausal patients with ER-positive, HER2-negative advanced breast cancer.

The baseline characteristics appear overall balanced across arms. A 12% difference between study arms in ECOG performance status 0 was noted, but not considered important to the overall results.

The study met its primary objective of prolonging investigator-assessed PFS. The final PFS analysis (data cut-off 26 February 2016) was performed at an event rate of 50%, with 44% events in the palbociclib-containing arm and 61% in the placebo+ letrozole arm. The estimated HR was 0.58 (95% CI: 0.46-0.72; 1-sided $p<0.000001$) in favour of palbociclib plus letrozole, with a difference in PFS medians between arms of 10.3 months (24.8 vs. 14.5 months, with *non*-overlapping confidence intervals).

The results of a secondary PFS analysis based on Blinded Independent Central Review (BICR) support the primary investigator based analysis.

The results of the primary endpoint are supported by secondary outcome measures (ORR and DOR).

A planned OS interim analysis was performed at the time of the final PFS analysis based on 133 deaths, but the results were not presented because they were considered as being immature. The final OS analysis is planned at 390 events and will be submitted for regulatory assessment. Given the large treatment effect observed on PFS, and the assessment of non-PD deaths not raising any new safety concerns, a detrimental effect of palbociclib on OS is considered unlikely.

The frequency of Rb-negativity by IHC in Study 1008/ PALOMA-2 was non-trivial at 9%. A higher HR was observed in the small Rb-negative subpopulation compared with the Rb-positive group, and compared with the overall HR in the ITT. While alternative mechanisms of action may be hypothesised, in the presence of preclinical data suggesting requirement of intact an Rb-function for the activity of palbociclib, the presence of relevant clinical efficacy of palbociclib in the Rb-negative subgroup cannot be concluded without further study. Information on Rb is therefore given in the SmPC to inform the prescriber.

The updated indication sought based on Study 1008 and Study 1023 was worded as follows:

"IBRANCE is indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer:

- in combination with an aromatase inhibitor,
- in combination with fulvestrant in patients who have received prior endocrine therapy

In pre- or perimenopausal women the endocrine therapy should be combined with a luteinizing hormone releasing hormone (LHRH) agonist"

This proposed indication includes a number of extrapolations from the respective pivotal trials:

- from letrozole to any aromatase inhibitor (AI) (Study 1008)
- from goserelin to any LHRH agonist (Study 1023)
- from fulvestrant + LHRH in pre/perimenopausal patients (Study 1023), and from AI in postmenopausal patients (Study 1008), to combination with AI + LHRH in pre/perimenopausal women

The extrapolation from letrozole to aromatase inhibitors is considered acceptable based on the following facts:

- The PD effect of all AIs is the same (blocking the conversion of androgens to oestrogens by blocking the aromatase enzyme)
- AIs are used interchangeably in the clinic (depending on individual patient tolerability etc.)
- There are no DDI/PK issues between anastrozole or exemestane (not studied in clinical trials) and palbociclib that preclude the extrapolation (See PK section)

For the corresponding reasons, the extrapolation from goserelin to LHRH analogue is endorsed.

The extrapolation to AI + LHRH in premenopausal women can be accepted. Efficacy has been shown for palbociclib in combination with AI in postmenopausal patients, and in combination with fulvestrant + LHRH in pre/perimenopausal patients, supporting the extrapolation. Furthermore, AI + LHRH constitute an accepted alternative (to antioestrogens/SERMs) in premenopausal patients, including as first line therapy, according to current clinical practice and European and international therapy guidelines. From a mechanistic perspective, palbociclib acts downstream of the oestrogen receptor (ER), and effective inhibition of ER signalling is achieved with AI or fulvestrant (+LHRH) alike, as this is the basis for anti-tumour activity of these compounds. This further supports that palbociclib can be used as add-on, not only to fulvestrant +LHRH, but also to AI +LHRH.

Critical visceral disease

According to current international treatment guidelines, endocrine therapy is not recommended in patients with critical, rapidly progressing or symptomatic visceral disease, due to a lower expectancy of a rapid tumour response or relevant tumour shrinkage compared with (cytotoxic) chemotherapies.

This patient population was also excluded from Studies PALOMA-3 and PALOMA-2, and palbociclib is not a traditional cytotoxic chemotherapy agent, but acts through induction of growth arrest and senescence. Overall, the addition of palbociclib improved substantially on the clinical efficacy of the endocrine backbone, however. In both pivotal studies, ORR overall (ITT) was improved by 10-11%, and PFS by 5-10 months, respectively. In patients with visceral disease in PALOMA-3, the ORR was improved by 17% (from 7 to 24%), PFS was improved by 4.5 months (from 3.5 to 8 months) and Time to response (TTR) was improved by 1.7 months (from 5.4 to 3.7 months). For PALOMA-2, results on the visceral subgroup are currently only available for PFS, with an improvement by add-on palbociclib to letrozole of 6.3 months (from 19.2 to 12.9 months).

With regard to critical visceral disease, a rapid response to therapy is of importance. There is little published data on TTR for comparison. From the very limited literature identified, mainly phase 2 studies in different lines of therapy in the metastatic setting, the data showed that the TTR of 3.7 months observed for palbociclib + fulvestrant as second line treatment, is more similar to the TTR of endocrine therapies (around 4 months) than of the chemotherapy combinations reported (around 2 months).

Due to the limited information publicly available, and the many confounding factors such as line of therapy affecting cross-study comparisons, no firm conclusions can be drawn with regard to the time to response of palbociclib combinations relative to conventional chemotherapies, however. As the efficacy in general, as well as TTR for the palbociclib + fulvestrant combination, is clearly better for palbociclib combination therapy compared with the endocrine therapy alone, no restriction of indication is considered appropriate. Information has been introduced in the SmPC, however, to inform the prescriber of the ORR and TTR results for the visceral subgroups of studies 1008 and 1023 and that critical visceral disease was not studied.

2.5.5. Conclusions on the clinical efficacy

For Study 1023 (PALOMA-3) and Study 1008 (PALOMA-2), PFS results appear robust with regard to the level of statistical significance across analyses, the consistency of results in a number of PFS sensitivity analyses and in subgroups, and in terms of support from ORR and CBR analyses. Further data will be analysed for Study 1008 when the full CSR will be submitted by March 2017. The magnitude of effect in both pivotal studies is considered of clear clinical relevance, with 5 and 10 months improvement in median progression-free survival (HRs 0.42 and 0.58), respectively. While the data from both studies are still considered immature at a PFS event rate of 50% (both studies) and an OS event rate of 21% and 20%, respectively, no sign of a detrimental effect on OS has been observed at this point (PALOMA-3), and is considered unlikely given the large treatment effect on PFS (PALOMA-2).

The CHMP recommended that the final OS results from study 1023 should be submitted by June 2018.

The CHMP also recommended that the final OS results from study 1008 should be submitted by November 2020.

2.6. Clinical safety

The safety database consists of approximately 2000 individuals including 1600 patients with malignancies whereof the vast majority were treated in breast cancer studies (n~ 1500 [studies 1023, 1003, 1010 Phase 1/ Phase 2, 1034, 1008, and 1001]).

In addition and according to the A5481023 sNDA 90-Day Safety Update, approximately 10 000 patients received palbociclib in the US postmarketing setting from February 2015 through July 2015.

Study 1023 (PALOMA-3)

Disposition update as of 31 July 2015:

A total of 347 patients were randomised to the experimental arm of whom 345 received treatment while 174 patients were randomised to the control arm of whom 172 were treated as of 31 July 2015. A total of 60 % in the experimental arm and 79 % in the control arm were permanently discontinued. Hence, 39 % in the palbociclib plus fulvestrant arm and 19.5% in the control arm were ongoing as of 31 July 2015.

Patient exposure

The median number of cycles was fairly similar between the arms. The median treatment duration was about 5 months for both palbociclib and fulvestrant in the experimental arm and about 4 months for fulvestrant in the control arm.

The relative dose intensity with a mean of 87 % and a median of 92 % for palbociclib and 97 % and 100 % for fulvestrant respectively, may indicate an acceptable tolerability of the combination. However, as observed in the 1003 study, a high proportion of patients had at least one cycle delay (41 % with 22 % considered due to TEAEs), dose reduction (32 %) and/ or dose interruption (87 % with 54 % considered due to TEAEs) which may indicate certain tolerability concerns.

Of the now 724 patients exposed to palbociclib 125 mg QD (3/1) in advanced breast cancer, 205 has been treated for ≥12 months.

Update as of 31 July 2015:

The median duration of palbociclib treatment was 330 (1 – 596) days as compared to the control arm (137 [14 – 611] days). The median number of days on palbociclib was 221 (1 – 436) days vs. 102 (14 – 460) days for the control arm. The median relative dose intensity estimated for palbociclib was lower than that for placebo (89.8% [22% - 107%] and 99.5% [69% - 108%], respectively).

Adverse events

Table 41 - Overview of TEAEs All Causalities and All Cycles - As Treated Population (Study 1023)

Number of patients	Palbociclib plus Fulvestrant n (%)	Placebo plus Fulvestrant n (%)	Total n (%)
Number of patients			
Patients evaluable for AEs	345	172	517
Number of AEs	3045	1051	4096
Patients with AEs	337 (97.7)	153 (89.0)	490 (94.8)
Patients with SAEs	33 (9.6)	24 (14.0)	57 (11.0)
Patients with Grade 3 or 4 AEs	242 (70.1)	31 (18.0)	273 (52.8)
Patients with Grade 5 AEs [1]	3 (0.9)	2 (1.2)	5 (1.0)
Patients discontinued study due to AEs	2 (0.6)	3 (1.7)	5 (1.0)
Patient discontinued palbociclib/placebo due to AEs	13 (3.8)	7 (4.1)	20 (3.9)
Patients discontinued fulvestrant due to AEs	11 (3.2)	5 (2.9)	16 (3.1)
Patients temporarily discontinued palbociclib/placebo due to AEs	223 (64.6)	14 (8.1)	237 (45.8)
Patients temporarily discontinued fulvestrant due to AEs	83 (24.1)	6 (3.5)	89 (17.2)
Patients with palbociclib/placebo dose reduction of due to AEs	107 (31.0)	3 (1.7)	110 (21.3)
Patients with dose interruptions of fulvestrant due to AEs	3 (0.9)	0	3 (0.6)

Source: Section 14.3, Table 14.3.1.1.1 and Table 14.4.1.4.4
Abbreviations: AE: adverse event, n: number of patients affected, SAE: serious adverse event
Includes data up to 28 days after last dose of study drug.
Except for the Number of AEs patients are counted only once per treatment in each row.
Percentages are calculated in the reference to number of patients evaluable for AEs.
SAEs - according to the investigator's assessment.
Severity counts are based on the maximum severity or grade of events.
[1] Patient 10791002 died on study but no TEAE Grade 5 was recorded on CRF AE page.
MedDRA (v17.1) coding dictionary applied.

A higher proportion of AEs and Grade ≥3 were reported in the experimental arm compared to the control arm (98 % vs.89 % and 70 % vs. 18 % respectively). As opposed to what was observed in the 1003 study with

pablociclib in combination with letrozol, similarity in terms of SAEs and discontinuations were observed between the two arms.

Rather few patients were permanently discontinued. On the other hand, the high proportion of temporary discontinuations of palbiciclob in the combination arm is noted (65 % vs 8 % in the control arm).

Update as of 31 July 2015:

Exposure Category	Palbociclib + Fulvestrant (N=345)	Placebo + Fulvestrant (N=172)
Patients with at least 1 dose reduction,[e] n (%)	128 (37.1)	3 (1.7)
Patients with dose interruption,[f] n (%)	286 (82.9)	104 (60.5)
Patients with dose interruptions due to TEAEs, n (%)	193 (55.9)	13 (7.6)
Patients with cycle delay,[g] n (%)	187 (54.2)	22 (12.8)
Patients with cycle delay due to TEAEs, n (%)	143 (41.4)	4 (2.3)

Source A5481023 SU Tables 14.4.1.4.1 and 14.4.1.4.3.

CRF=Case Report Form; Max=maximum, Min=minimum; N=total number of patients; n=number of patients meeting prespecified criteria; Std Dev=standard deviation; SU=Safety Update; TEAEs=treatment-emergent adverse events.

a. Duration of treatment is defined as the total number of days calculated as last dose date – first dose date + 1.
b. Days on drug is defined as the total number of days on which the drug was actually administered.
c. Average daily dose administered = total dose administered/total days on drug.
d. Relative dose intensity = actual dose intensity/intended dose intensity × 100.
e. Dose reduction is defined as any dose reduction from the initial prescribed dose regardless of its duration. Note that dosing interruption is not counted as dose reduction.
f. Dose interruption is defined as 1) any missing dose recorded on the CRF, 2) any gap(s) within a cycle, 3) and/or patient did not complete 21 doses within a cycle.
g. Cycle delay is defined as a 2-day or longer delay in the cycle start date (Cycles 1 and 2) or a 7-day or longer delay in Cycles 3 and beyond.

Table 42 - Summary of All-Causality, TEAEs (All Cycles) Experienced by at Least 10 % of Patients in Either Treatment Arm of Study A5481023 as of 31 July 2015 by MedDRA PT Sorted by Descending Frequency in the Palbociclib Plus Fulvestrant Arm — All Treated Patients

	Number (%) of Patients (N=517)	
MedDRA PT[a]	Palbociclib + Fulvestrant (N=345)	Placebo + Fulvestrant (N=172)
Any TEAE	341 (98.8)	156 (90.7)
Neutropenia	228 (66.1)	4 (2.3)
Fatigue	142 (41.2)	50 (29.1)
Nausea	117 (33.9)	48 (27.9)
White blood cell count decreased	101 (29.3)	7 (4.1)
Anaemia	100 (29.0)	22 (12.8)
Headache	89 (25.8)	34 (19.8)
Leukopenia	89 (25.8)	2 (1.2)
Diarrhoea	81 (23.5)	33 (19.2)
Neutrophil count decreased	79 (22.9)	3 (1.7)
Constipation	69 (20.0)	27 (15.7)
Cough	66 (19.1)	23 (13.4)
Vomiting	65 (18.8)	26 (15.1)
Alopecia	62 (18.0)	11 (6.4)
Arthralgia	55 (15.9)	31 (18.0)
Back pain	55 (15.9)	30 (17.4)
Decreased appetite	55 (15.9)	14 (8.1)
Hot flush	54 (15.7)	29 (16.9)
Dyspnoea	46 (13.3)	15 (8.7)
Pain in extremity	46 (13.3)	26 (15.1)
Nasopharyngitis	45 (13.0)	14 (8.1)
Stomatitis	45 (13.0)	5 (2.9)
Thrombocytopenia	45 (13.0)	0 (0)
Dizziness	44 (12.8)	17 (9.9)
Pyrexia	44 (12.8)	9 (5.2)
Oropharyngeal pain	43 (12.5)	12 (7.0)
Insomnia	38 (11.0)	14 (8.1)
Rash	38 (11.0)	9 (5.2)
Platelet count decreased	35 (10.1)	0 (0)
Injection site pain	23 (6.7)	18 (10.5)

Data source: A5481023 SU Table 14.3.1.1.3.
MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=preferred term; SU=Safety Update; TEAE=treatment-emergent adverse event.
Note: Includes data up to 28 days after last dose of study drug.
a. Version 18.0.

Table 43 - TEAEs by MedDRA PT and Maximum CTCAE Grade by Descending Frequency (All Causalities and All Cycles) Reported in at Least 5% of Patients in Each Arm – As Treated Population (Study 1023)

MedDRA Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Missing or Unknown	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Palbociclib plus fulvestrant arm, N=345							
Patients with any AEs	22 (6.4)	73 (21.2)	202 (58.6)	37 (10.7)	3 (0.9)	0	337 (97.7)
Neutropenia	5 (1.4)	40 (11.6)	146 (42.3)	21 (6.1)	0	0	212 (61.4)
Fatigue	87 (25.2)	37 (10.7)	7 (2.0)	0	0	0	131 (38.0)
Nausea	74 (21.4)	26 (7.5)	0	0	0	0	100 (29.0)
WBC count decreased	12 (3.5)	39 (11.3)	39 (11.3)	2 (0.6)	0	0	92 (26.7)
Anaemia	41 (11.9)	39 (11.3)	8 (2.3)	0	0	0	88 (25.5)
Headache	60 (17.4)	12 (3.5)	1 (0.3)	0	0	0	73 (21.2)
Neutrophil count decreased	4 (1.2)	16 (4.6)	43 (12.5)	10 (2.9)	0	0	73 (21.2)
Leukopenia	3 (0.9)	20 (5.8)	47 (13.6)	0	0	0	70 (20.3)
Diarrhoea	54 (15.7)	12 (3.5)	0	0	0	0	66 (19.1)
Constipation	48 (13.9)	10 (2.9)	0	0	0	0	58 (16.8)
Alopecia	47 (13.6)	4 (1.2)	0	0	0	0	51 (14.8)
Hot flush	41 (11.9)	10 (2.9)	0	0	0	0	51 (14.8)
Vomiting	36 (10.4)	13 (3.8)	1 (0.3)	0	0	0	50 (14.5)
Arthralgia	35 (10.1)	9 (2.6)	1 (0.3)	0	0	0	45 (13.0)
Cough	37 (10.7)	8 (2.3)	0	0	0	0	45 (13.0)
Decreased appetite	32 (9.3)	9 (2.6)	3 (0.9)	0	0	0	44 (12.8)
Stomatitis	26 (7.5)	12 (3.5)	2 (0.6)	0	0	0	40 (11.6)
Thrombocytopenia	30 (8.7)	5 (1.4)	4 (1.2)	1 (0.3)	0	0	40 (11.6)
Back pain	23 (6.7)	13 (3.8)	3 (0.9)	0	0	0	39 (11.3)
Dizziness	34 (9.9)	2 (0.6)	1 (0.3)	0	0	0	37 (10.7)
Dyspnoea	19 (5.5)	17 (4.9)	0	1 (0.3)	0	0	37 (10.7)
Pain in extremity	26 (7.5)	8 (2.3)	0	0	0	0	34 (9.9)
Oropharyngeal pain	28 (8.1)	4 (1.2)	0	0	0	0	32 (9.3)
Rash	28 (8.1)	2 (0.6)	1 (0.3)	0	0	0	31 (9.0)
Pyrexia	26 (7.5)	3 (0.9)	1 (0.3)	0	0	0	30 (8.7)
Insomnia	21 (6.1)	5 (1.4)	1 (0.3)	0	0	0	27 (7.8)
Platelet count decreased	17 (4.9)	7 (2.0)	2 (0.6)	1 (0.3)	0	0	27 (7.8)
Oedema peripheral	24 (7.0)	2 (0.6)	0	0	0	0	26 (7.5)
MedDRA Preferred Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Missing or Unknown**	**Total**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Palbociclib plus fulvestrant arm, N=345							
Dyspepsia	17 (4.9)	8 (2.3)	0	0	0	0	25 (7.2)
Nasopharyngitis	16 (4.6)	9 (2.6)	0	0	0	0	25 (7.2)
Asthenia	18 (5.2)	5 (1.4)	0	0	0	0	23 (6.7)
Myalgia	21 (6.1)	2 (0.6)	0	0	0	0	23 (6.7)
Dry mouth	21 (6.1)	1 (0.3)	0	0	0	0	22 (6.4)
Dysgeusia	19 (5.5)	3 (0.9)	0	0	0	0	22 (6.4)
Abdominal pain	12 (3.5)	8 (2.3)	1 (0.3)	0	0	0	21 (6.1)
Muscle spasms	17 (4.9)	4 (1.2)	0	0	0	0	21 (6.1)
Upper respiratory tract infection	14 (4.1)	6 (1.7)	1 (0.3)	0	0	0	21 (6.1)
Musculoskeletal pain	14 (4.1)	5 (1.4)	1 (0.3)	0	0	0	20 (5.8)
Aspartate aminotransferase increased	9 (2.6)	5 (1.4)	5 (1.4)	0	0	0	19 (5.5)
Epistaxis	19 (5.5)	0	0	0	0	0	19 (5.5)
Injection site pain	15 (4.3)	3 (0.9)	1 (0.3)	0	0	0	19 (5.5)
Pruritus	16 (4.6)	3 (0.9)	0	0	0	0	19 (5.5)
Urinary tract infection	4 (1.2)	14 (4.1)	0	0	0	0	18 (5.2)
Placebo plus fulvestrant arm, N=172							
Patient with any AEs	66 (38.4)	54 (31.4)	28 (16.3)	3 (1.7)	2 (1.2)	0	153 (89.0)
Fatigue	31 (18.0)	13 (7.6)	2 (1.2)	0	0	0	46 (26.7)
Nausea	40 (23.3)	4 (2.3)	1 (0.6)	0	0	0	45 (26.2)
Diarrhoea	25 (14.5)	4 (2.3)	1 (0.6)	0	0	0	30 (17.4)
Headache	24 (14.0)	6 (3.5)	0	0	0	0	30 (17.4)
Arthralgia	24 (14.0)	4 (2.3)	0	0	0	0	28 (16.3)
Hot flush	23 (13.4)	5 (2.9)	0	0	0	0	28 (16.3)
Back pain	12 (7.0)	10 (5.8)	4 (2.3)	0	0	0	26 (15.1)
Constipation	21 (12.2)	3 (1.7)	0	0	0	0	24 (14.0)
Vomiting	19 (11.0)	1 (0.6)	1 (0.6)	0	0	0	21 (12.2)
Pain in extremity	11 (6.4)	5 (2.9)	3 (1.7)	0	0	0	19 (11.0)
Cough	14 (8.1)	4 (2.3)	0	0	0	0	18 (10.5)

MedDRA Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Missing or Unknown	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Placebo plus fulvestrant arm, N=172							
Anaemia	7 (4.1)	7 (4.1)	3 (1.7)	0	0	0	17 (9.9)
Dizziness	14 (8.1)	2 (1.2)	0	0	0	0	16 (9.3)
Injection site pain	16 (9.3)	0	0	0	0	0	16 (9.3)
Dry mouth	13 (7.6)	1 (0.6)	0	0	0	0	14 (8.1)
Decreased appetite	10 (5.8)	3 (1.7)	0	0	0	0	13 (7.6)
Insomnia	8 (4.7)	4 (2.3)	0	0	0	0	12 (7.0)
Myalgia	10 (5.8)	2 (1.2)	0	0	0	0	12 (7.0)
Pain	6 (3.5)	6 (3.5)	0	0	0	0	12 (7.0)
Abdominal pain upper	11 (6.4)	0	0	0	0	0	11 (6.4)
Dyspnoea	7 (4.1)	3 (1.7)	1 (0.6)	0	0	0	11 (6.4)
Muscle spams	10 (5.8)	1 (0.6)	0	0	0	0	11 (6.4)
Musculoskeletal pain	8 (4.7)	2 (1.2)	1 (0.6)	0	0	0	11 (6.4)
Alopecia	10 (5.8)	0	0	0	0	0	10 (5.8)
Chest pain	6 (3.5)	4 (2.3)	0	0	0	0	10 (5.8)
Depression	4 (2.3)	5 (2.9)	1 (0.6)	0	0	0	10 (5.8)
Pruritus	9 (5.2)	1 (0.6)	0	0	0	0	10 (5.8)
Abdominal pain	6 (3.5)	3 (1.7)	0	0	0	0	9 (5.2)
Anxiety	6 (3.5)	3 (1.7)	0	0	0	0	9 (5.2)
Musculoskeletal chest pain	6 (3.5)	3 (1.7)	0	0	0	0	9 (5.2)
Nasopharyngitis	6 (3.5)	3 (1.7)	0	0	0	0	9 (5.2)
Oedema peripheral	7 (4.1)	2 (1.2)	0	0	0	0	9 (5.2)
Oropharyngeal pain	7 (4.1)	2 (1.2)	0	0	0	0	9 (5.2)

Source: Section 14.3, Table 14.3.1.1.3
Abbreviations: AE: adverse event, CTCAE: Common Terminology Criteria for Adverse events, MedDRA: Medical Dictionary for regulatory Activities, N: number of patients, n: number of patients affected, WBC count: white blood cell count
Percentages are calculated in reference to N.
Includes data up to 28 days after last dose of study drug.
MedDRA (v17.1) coding dictionary applied.

TEAEs were most frequently reported in the SOCs Blood and lymphatic disorders (73 %), Gastrointestinal disorders (64 %), and General disorders and administration site conditions (61 %) in the experimental arm.

The most frequently reported TEAEs (≥20%) in the experimental arm were neutropenia (61 %), fatigue (38 %), nausea (29 %), WBC count decreased (27 %), anaemia (26 %), headache and neutrophil count decreased (21.2% each) and leukopenia (20%). In the control arm fatigue (27 %) and nausea (26 %) were reported.

According to the CSR, febrile neutropenia was reported in two patients (0.6 %) in the experimental arm (both Grade 3). There are no reports on hyper-/hypoglycaemia. A total of 17 % reported eye disorders, mainly vision blurred (5 %), lacrimation increased (4.3 %), dry eye (3 %) and eye irritation (0.6 %). All were of grade 1/2. No reports relevant to pancreas. One report judged as DILI was reported in the experimental arm.

The safety update (as of 31 July 2015) does not reveal any difference from what is observed in the above table. Most TEAEs were of Grade 1/2 except for neutropenia, neutrophil count decreased and leukopenia which were most commonly of Grade 3 (67%, 63% and 64% respectively).

Serious adverse events

SAEs were reported in about 10 % and 14 % in the experimental and control arms respectively. Most common in the experimental arm was pulmonary embolism and pyrexia (three patients each). Among the most common reported SAEs in the control arm were pleural effusion and ascites which is considered disease related.

ECG QT prolonged and febrile neutropenia are reported in one case each.

Update as of 31 July 2015 data cut-off date:

A total of 15.4 % experienced at least one SAE in the experimental arm vs. 18 % in the control arm. Most common SAEs in the experimental arm included pyrexia (5 patients [1.4%]), neutropenia (4 [1.2%]), pulmonary embolism (3 [0.9%]) as well as deep vein thrombosis, dyspnoea, febrile neutropenia, General

physical health deterioration, Pharyngitis, Pleural effusion, and suicide attempt (2 [0.6%] each). The remaining SAEs were experienced by one patient (0.3%) each.

Among patients experiencing SAEs of any severity grade in the experimental arm (N=53), Grade 3 SAEs were reported for more than half of the patients (55 %), and Grade 4 SAEs were reported for 15 %).

Deaths

A total of six (1.2 %) patients died during the study (up to 28 days after last dose). All were judged to be associated with the disease investigated.

Following the 28-day observation period after last dose, a total of 22 (4.3%) patients had died whereof 14 (4 %) patients in the experimental arm and 7 (4 %) patients in the control arm judged subsequent to the disease under study.

Update on deaths as of 31 July 2015 data cut-off date:

Table 44 - Summary of On-Study Deaths Reported in Study A5481023 as of 31 July 2015 — All Treated Patients

	Number (%) of Patients		
	Palbociclib + Fulvestrant (N=345)	Placebo + Fulvestrant (N=172)	Total (N=517)
Number of deaths[a]	4 (1.2)	3 (1.7)	7 (1.4)
Cause of death			
Disease under study	4 (1.2)	2 (1.2)	6 (1.2)
Study treatment toxicity	0 (0)	0 (0)	0 (0)
Other	0 (0)	1 (0.6)[b]	1 (0.2)

Data source: A5481023 SU Table 14.3.3.1.
N=total number of patients; SU=Safety Update.
a. Deaths occurred during the period from the start of treatment up to and including 28 days after the last dose.
b. Subject No. 12891002 experienced intracerebral haemorrhage likely caused by arterio-venous malformation.

Hence, no additional patient had died on study in the experimental arm during the eight months since previous data cut-off date while one patient in the control arm died (considered due to disease under study).

Laboratory findings

Haematology

Almost all patients in the experimental arm with hematologic laboratory test results available for evaluation had abnormal white blood cell counts (98 %) and absolute neutrophil counts (95 %) as compared to 22 % and 8 % respectively for the control arm.

In the experimental arm, anaemia and thrombocytopenia were reported in 76 % and 57 % of the patients vs. 36 % and 8 % in the control arm respectively.

Clinical Chemistry

No major concern is raised relevant to clinical chemistry.

Hy's Law

One patient in each treatment arm met the laboratory criteria for a potential Hy's Law case although neither case was eventually considered to be a Hy's Law case as these patients also had elevations in alkaline phosphatase as well as alternative explanations for the laboratory changes.

Safety in special populations

Age

The vast majority were < 65 years of age. A total of about 25 % of the study population were ≥ 65. In terms of TEAEs, SAEs and discontinuations, no major difference between the two age groups were observed in either arm. Patients < 18 years were not eligible in the study.

Race

The vast majority was Caucasian (73 %) and the second largest was Asian (overall about 20 %).

Gender

Not performed as all patients enrolled were female.

Discontinuation and dose adjustments due to AES

Table 45 - Summary of All-Causality TEAEs (All Cycles) Associated With Permanent Discontinuation from Treatment by MedDRA PT Experienced by Patients Receiving Palbociclib Plus Fulvestrant in Study 1023 as of 05 December 2014 – All Treated Patients (Study 1023)

MedDRA PT[a]	Number (%) of Patients Receiving Palbociclib + Fulvestrant (N=345)
Any TEAE	13 (3.8)
Anaemia	2 (0.6)
Neutropenia	2 (0.6)
Thrombocytopenia	2 (0.6)
Alanine aminotransferase increased	1 (0.3)
Bone pain	1 (0.3)
Disease progression	1 (0.3)
Disseminated intravascular coagulation	1 (0.3)
Drug-induced liver injury	1 (0.3)
Dyspnoea	1 (0.3)
Erysipelas	1 (0.3)
Nausea	1 (0.3)
Skin lesion	1 (0.3)
Vocal cord paralysis	1 (0.3)

Data source: A5481023 CSR Table 14.3.1.5.1.
CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=preferred term; TEAE=treatment-emergent adverse event.
Note: Includes data up to 28 days after last dose of study drug.
a. Version 17.1.

Update with data cut-off date 31 July 2015:

MedDRA PT[a]	Number (%) of Patients Receiving Palbociclib + Fulvestrant (N=345)
Any TEAE	19 (5.5)
Fatigue	2 (0.6)
Thrombocytopenia	2 (0.6)
Anaemia	1 (0.3)
Alanine aminotransferase increased	1 (0.3)
Bone pain	1 (0.3)
Breast mass[b]	1 (0.3)
Disease progression	1 (0.3)
Drug-induced liver injury	1 (0.3)
Dyspnoea	1 (0.3)
Endometrial cancer[b]	1 (0.3)
Erysipelas	1 (0.3)
General physical health deterioration	1 (0.3)
Liver disorder	1 (0.3)
Nausea	1 (0.3)
Neutropenia	1 (0.3)
Pneumonia	1 (0.3)
Rectal cancer[b]	1 (0.3)
Seizure	1 (0.3)
Suicide attempt	1 (0.3)
Vocal cord paralysis	1 (0.3)
White blood cell count decreased	1 (0.3)

Data source: A5481023 SU Table 14.3.1.5.1.
MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=preferred term; SU=Safety Update; TEAE=treatment-emergent adverse event.
Note: Includes data up to 28 days after last dose of study drug.
a. Version 18.0.
b. New primary cancer.

Table 46 - Summary of All-Causality TEAEs (All Cycles) Associated With Temporary Discontinuation from Treatment by MedDRA PT and Maximum Severity Grade by Decreasing Frequency (Grades 1-4) for at Least 2 Patients Receiving Palbociclib Plus Fulvestrant (Study 1023)

	Number (%) of Patients (N=517)									
	Palbociclib + Fulvestrant (N=345)					Placebo + Fulvestrant (N=172)				
MedDRA PT[a]	Grade 1	Grade 2	Grade 3	Grade 4	Grades 1-4	Grade 1	Grade 2	Grade 3	Grade 4	Grades 1-4
Any TEAE	5 (1.4)	7 (2.0)	186 (53.9)	26 (7.5)	224 (64.9)	1 (0.6)	4 (2.3)	9 (5.2)	0 (0)	14 (8.1)
Neutropenia	0 (0)	0 (0)	139 (40.3)	17 (4.9)	156 (45.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Neutrophil count decreased	0 (0)	0 (0)	45 (13.0)	5 (1.4)	50 (14.5))	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
WBC count decreased	3 (0.9)	6 (1.7)	18 (5.2)	1 (0.3)	28 (8.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Leukopenia	0 (0)	2 (0.6)	19 (5.5)	0 (0)	21 (6.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea	1 (0.3)	5 (1.4)	0 (0)	0 (0)	6 (1.7)	0 (0)	0 (0)	1 (0.6)	0 (0)	1 (0.6)
Thrombocytopenia	3 (0.9)	1 (0.3)	1 (0.3)	1 (0.3)	6 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anaemia	0 (0)	3 (0.9)	2 (0.6)	0 (0)	5 (1.4)	0 (0)	0 (0)	1 (0.6)	0 (0)	1 (0.6)
Diarrhoea	2 (0.6)	3 (0.9)	0 (0)	0 (0)	5 (1.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fatigue	0 (0)	2 (0.6)	3 (0.9)	0 (0)	5 (1.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting	1 (0.3)	3 (0.9)	1 (0.3)	0 (0)	5 (1.4)	0 (0)	0 (0)	1 (0.6)	0 (0)	1 (0.6)
Dizziness	2 (0.6)	1 (0.3)	1 (0.3)	0 (0)	4 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pyrexia	3 (0.9)	0 (0)	1 (0.3)	0 (0)	4 (1.2)	0 (0)	1 (0.6)	0 (0)	0 (0)	1 (0.6)
ALT increased	1 (0.3)	0 (0)	2 (0.6)	0 (0)	3 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Influenza like illness	3 (0.9)	0 (0)	0 (0)	0 (0)	3 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Platelet count decreased	0 (0)	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal pain	0 (0)	1 (0.3)	1 (0.3)	0 (0)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Arthralgia	0 (0)	2 (0.6)	0 (0)	0 (0)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AST increased	1 (0.3)	0 (0)	1 (0.3)	0 (0)	2 (0.6)	0 (0)	0 (0)	1 (0.6)	0 (0)	1 (0.6)
Asthenia	1 (0.3)	1 (0.3)	0 (0)	0 (0)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bronchitis	0 (0)	2 (0.6)	0 (0)	0 (0)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Constipation	1 (0.3)	1 (0.3)	0 (0)	0 (0)	2 (0.6)	1 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.6)
Gastrointestinal infection	1 (0.3)	1 (0.3)	0 (0)	0 (0)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pain in extremity	0 (0)	2 (0.6)	0 (0)	0 (0)	2 (0.6)	0 (0)	1 (0.6)	0 (0)	0 (0)	1 (0.6)
Stomatitis	1 (0.3)	1 (0.3)	0 (0)	0 (0)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Data source: A5481023 CSR Table 14.3.1.5.3.2.
ALT=alanine aminotransferase increased; AST=aspartate aminotransferase increased; CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=preferred term; TEAE=treatment-emergent adverse event; WBC=white blood cell.
Notes: Includes data up to 28 days after last dose of study drug.
Each patient is counted once in each row based on the highest severity grade reported for the event.
a. Version 17.1.

Cutoff date: 05 December 2014

Update with data cut-off date 31 July 2015:

The overall proportion of TEAEs associated with temporary discontinuation was 69 % in the experimental arm vs. about 13 % in the control arm. Most commonly was neutropenia (48 %) and Neutrophil count decreased (17 %) as well as white blood cell count decreased (8 %) and leukopenia (7 %). All but one TEAE of neutropenia were of Grade 3/4 severity.

Table 47 - Summary of All-Causality TEAEs (All Cycles) Associated With Dose Reduction or Modification by MedDRA PT and Maximum Severity Grade Sorted by Decreasing Frequency (Grades 1-4) for at Least 2 Patients Receiving Palbociclib Plus Fulvestrant (Study 1023)

	Number (%) of Patients (N=517)									
	Palbociclib + Fulvestrant (N=345)					Placebo + Fulvestrant (N=172)				
MedDRA PT[a]	Grade 1	Grade 2	Grade 3	Grade 4	Grades 1-4	Grade 1	Grade 2	Grade 3	Grade 4	Grades 1-4
Any TEAE	2 (0.6)	14 (4.1)	74 (21.4)	17 (4.9)	107 (31.0)	1 (0.6)	1 (0.6)	1 (0.6)	0 (0)	3 (1.7)
Neutropenia	1 (0.3)	7 (2.0)	54 (15.7)	11 (3.2)	73 (21.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Neutrophil count decreased	0 (0)	1 (0.3)	12 (3.5)	7 (2.0)	20 (5.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
WBC count decreased	1 (0.3)	4 (1.2)	4 (1.2)	0 (0)	9 (2.6)	0 (0)	1 (0.6)	0 (0)	0 (0)	1 (0.6)
Thrombocytopenia	2 (0.6)	1 (0.3)	1 (0.3)	0 (0)	4 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Leukopenia	0 (0)	0 (0)	3 (0.9)	0 (0)	3 (0.9)	1 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.6)
Stomatitis	0 (0)	1 (0.3)	1 (0.3)	0 (0)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Data source: A5481023 CSR Table 14.3.1.5.2.1.
CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=preferred term; TEAE=treatment-emergent adverse event; WBC=white blood cell.
Notes: Includes data up to 28 days after last dose of study drug.
Each patient is counted once in each row based on the highest severity grade reported for the event.
a. Version 17.1.

A total of approximately 32% in the experimental arm had their palbociclib dose reduced. According the 1023 CSR, 29 % had their dose reduced from 125 mg QD to 100 mg QD and about 8 % from 125mg/100 QD mg to 75 mg QD. Palbociclib dose was reduced at least twice for 5 % of the patients.

Update with data cut-off date 31 July 2015:

A total of 128 patients (37.1%) in the experimental arm had their palbociclib dose reduced as of 31 July 2015: 34 % had their dose reduced from 125 mg QD to 100 mg QD, and 12 % had their dose reduced from 125 mg to 100 mg QD and further to 75 mg QD. Palbociclib dose was reduced at least twice for 31 patients (9.0%) in that treatment arm. In addition, 13 patients (3.8%) had their palbociclib dose regimen changed from Schedule 3/1 to Schedule 2/2 (2 weeks on palbociclib treatment followed by 2 weeks off treatment).

Study 1008 (PALOMA-2) – Top Line Results

Patient exposure

Table 48 - Drug Exposure and Dose Intensity of Palbociclib, Placebo and Letrozole: All Cycles Combined – As Treated Set (Study 1008)

	Palbociclib plus Letrozole N=444	Placebo* plus Letrozole N=222
Palbociclib or placebo		
Number of cycles		
Mean (SD)	17.8 (8.85)	15.3 (9.77)
Median (range)	21.0 (1.0, 37.0)	15.0 (1.0, 38.0)
Treatment duration (days) [a]		
Median (range)	603.0 (1.0, 1037.0)	413.0 (10.0, 1071.0)
Average Daily dose administered (mg) [b]		
Mean (SD)	116.8 (13.19)	124.8 (2.12)

	Palbociclib plus Letrozole N=444	Placebo* plus Letrozole N=222
Median (range)	125.0 (76.6, 125.2)	125.0 (104.7, 125.6)
Relative dose intensity (%) [c]		
Mean (SD)	86.8 (14.47)	98.2 (5.52)
Median (range)	93.0 (40.3, 109.5)	99.6 (56.1, 104.5)
Letrozole		
Number of cycles		
Mean (SD)	17.8 (8.85)	15.3 (9.77)
Median (range)	21.0 (1.0, 37.0)	15.0 (1.0, 38.0)
Treatment duration (days) [a]		
Median (range)	617.0 (1.0, 1037.0)	420.0 (10.0, 1075.0)
Average Daily dose administered (mg) [b]		
Mean (SD)	2.5 (0.00)	2.5 (0.00)
Median (range)	2.5 (2.5, 2.5)	2.5 (2.5, 2.5)
Relative dose intensity (%) [c]		
Mean (SD)	99.1 (2.41)	99.2 (2.02)
Median (range)	99.9 (73.4, 100.2)	100.0 (79.0, 100.0)

Source: Table 14.4.1.4.1, Table 14.4.1.4.2, Table 14.4.1.4.3, and Table 14.4.1.4.4
Abbreviations: N=number of patients; SD=Standard deviation;
* Placebo doses are shown as palbociclib equivalents
a. Duration of treatments is defined as the total number of dosing days from first to and including last day of each study treatment.
b. Average daily dose administered = (total dose administered)/(total days on drug).
c. Relative Dose Intensity is the actual dose intensity divided by the intended dose intensity multiplied by 100%.

Adverse events

Table 49 - Summary of All-Causality TEAEs (As-Treated Population)

	Palbociclib Plus Letrozole N = 444 n (%)	Placebo Plus Letrozole N = 222 n (%)
Any AE	439 (98.9)	212 (95.5)
Any serious AE	87 (19.6)	28 (12.6)
Any Grade 3 or 4 AE	344 (77.5)	56 (25.2)
Any Grade 5 AE	10 (2.3)	4 (1.8)
Permanently discontinued study due to AE	11 (2.5)	4 (1.8)
Permanently discontinued palbociclib or placebo due to AE	41 (9.2)	12 (5.4)
Permanently discontinued letrozole due to AE	27 (6.1)	11 (5.0)
Temporarily discontinued palbociclib or placebo due to AE	332 (74.8)	35 (15.8)
Temporarily discontinued letrozole due to AE	77 (17.3)	22 (9.9)
Dose reduction of palbociclib or placebo due to AE	160 (36.0)	3 (1.4)

Source: Table 14.3.1.1.1.
Includes data up to 28 days after last dose of study drug.
Serious adverse events – according to investigator's assessment.
Abbreviations: AE=adverse event, N=number of patients in treatment arm, n=number of patients meeting criteria.

Table 50 - Summary of All-Causality TEAEs by PT and Maximum CTCAE Grade Reported by ≥10% of Patients in Either Treatment Group in Descending Frequency Order (As-Treated Population)

	Palbociclib Plus Letrozole (N = 444)						Placebo Plus Letrozole (N = 222)					
Preferred Term	Total n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Any AE[a]	439 (98.9)	19 (4.3)	74 (16.7)	276 (62.2)	60 (13.5)	10 (2.3)	212 (95.5)	49 (22.1)	105 (47.3)	49 (22.1)	5 (2.3)	4 (1.8)
Neutropenia	294 (66.2)	9 (2.0)	40 (9.0)	207 (46.6)	38 (8.6)	0	7 (3.2)	3 (1.4)	2 (0.9)	1 (0.5)	1 (0.5)	0
Fatigue	166 (37.4)	100 (22.5)	58 (13.1)	8 (1.8)	0	0	61 (27.5)	45 (20.3)	15 (6.8)	1 (0.5)	0	0
Nausea	156 (35.1)	127 (28.6)	28 (6.3)	1 (0.2)	0	0	58 (26.1)	43 (19.4)	11 (5.0)	4 (1.8)	0	0
Arthralgia	148 (33.3)	103 (23.2)	42 (9.5)	3 (0.7)	0	0	75 (33.8)	61 (27.5)	13 (5.9)	1 (0.5)	0	0
Alopecia	146 (32.9)	134 (30.2)	12 (2.7)	0	0	0	35 (15.8)	33 (14.9)	2 (0.9)	0	0	0
Diarrhoea	116 (26.1)	77 (17.3)	33 (7.4)	6 (1.4)	0	0	43 (19.4)	28 (12.6)	12 (5.4)	3 (1.4)	0	0
Cough	111 (25.0)	88 (19.8)	23 (5.2)	0	0	0	42 (18.9)	32 (14.4)	10 (4.5)	0	0	0
Leukopenia	106 (23.9)	8 (1.8)	32 (7.2)	63 (14.2)	3 (0.7)	0	1 (0.5)	1 (0.5)	0	0	0	0
Anaemia	103 (23.2)	36 (8.1)	43 (9.7)	23 (5.2)	1 (0.2)	0	20 (9.0)	9 (4.1)	7 (3.2)	4 (1.8)	0	0
Back pain	96 (21.6)	55 (12.4)	35 (7.9)	6 (1.4)	0	0	48 (21.6)	29 (13.1)	19 (8.6)	0	0	0
Headache	95 (21.4)	77 (17.3)	17 (3.8)	1 (0.2)	0	0	58 (26.1)	45 (20.3)	9 (4.1)	4 (1.8)	0	0
Hot flush	93 (20.9)	75 (16.9)	18 (4.1)	0	0	0	68 (30.6)	57 (25.7)	11 (5.0)	0	0	0
Neutrophil count decreased	87 (19.6)	3 (0.7)	17 (3.8)	59 (13.3)	8 (1.8)	0	7 (3.2)	3 (1.4)	3 (1.4)	1 (0.5)	0	0
Constipation	86 (19.4)	68 (15.3)	16 (3.6)	2 (0.5)	0	0	34 (15.3)	26 (11.7)	7 (3.2)	1 (0.5)	0	0
Asthenia	75 (16.9)	33 (7.4)	32 (7.2)	10 (2.3)	0	0	26 (11.7)	14 (6.3)	12 (5.4)	0	0	0
White blood cell count decreased	72 (16.2)	6 (1.4)	20 (4.5)	46 (10.4)	0	0	4 (1.8)	2 (0.9)	2 (0.9)	0	0	0
Vomiting	69 (15.5)	51 (11.5)	16 (3.6)	2 (0.5)	0	0	37 (16.7)	28 (12.6)	6 (2.7)	3 (1.4)	0	0
Pain in extremity	68 (15.3)	46 (10.4)	21 (4.7)	1 (0.2)	0	0	39 (17.6)	28 (12.6)	8 (3.6)	3 (1.4)	0	0
Stomatitis	68 (15.3)	49 (11.0)	18 (4.1)	1 (0.2)	0	0	13 (5.9)	12 (5.4)	1 (0.5)	0	0	0
Decreased appetite	66 (14.9)	46 (10.4)	17 (3.8)	3 (0.7)	0	0	20 (9.0)	15 (6.8)	5 (2.3)	0	0	0
Dyspnoea	66 (14.9)	42 (9.5)	19 (4.3)	5 (1.1)	0	0	30 (13.5)	20 (9.0)	7 (3.2)	3 (1.4)	0	0
Insomnia	66 (14.9)	44 (9.9)	22 (5.0)	0	0	0	26 (11.7)	18 (8.1)	8 (3.6)	0	0	0
Dizziness	63 (14.2)	56 (12.6)	4 (0.9)	2 (0.5)	0	0	33 (14.9)	30 (13.5)	3 (1.4)	0	0	0
Nasopharyngitis	62 (14.0)	46 (10.4)	16 (3.6)	0	0	0	22 (9.9)	19 (8.6)	3 (1.4)	0	0	0
Rash	61 (13.7)	43 (9.7)	16 (3.6)	2 (0.5)	0	0	22 (9.9)	20 (9.0)	2 (0.9)	0	0	0
Upper respiratory tract infection	59 (13.3)	23 (5.2)	36 (8.1)	0	0	0	25 (11.3)	15 (6.8)	10 (4.5)	0	0	0
Dry skin	55 (12.4)	53 (11.9)	2 (0.5)	0	0	0	13 (5.9)	12 (5.4)	1 (0.5)	0	0	0
Pyrexia	55 (12.4)	45 (10.1)	10 (2.3)	0	0	0	19 (8.6)	18 (8.1)	1 (0.5)	0	0	0
Myalgia	53 (11.9)	48 (10.8)	5 (1.1)	0	0	0	20 (9.0)	18 (8.1)	2 (0.9)	0	0	0
Urinary tract infection	53 (11.9)	3 (0.7)	45 (10.1)	5 (1.1)	0	0	17 (7.7)	1 (0.5)	16 (7.2)	0	0	0
Abdominal pain	50 (11.3)	36 (8.1)	10 (2.3)	4 (0.9)	0	0	12 (5.4)	8 (3.6)	4 (1.8)	0	0	0
Oedema peripheral	50 (11.3)	44 (9.9)	6 (1.4)	0	0	0	14 (6.3)	14 (6.3)	0	0	0	0
Dysgeusia	45 (10.1)	38 (8.6)	7 (1.6)	0	0	0	11 (5.0)	11 (5.0)	0	0	0	0
Dyspepsia	41 (9.2)	32 (7.2)	9 (2.0)	0	0	0	27 (12.2)	20 (9.0)	6 (2.7)	1 (0.5)	0	0
Anxiety	36 (8.1)	21 (4.7)	15 (3.4)	0	0	0	25 (11.3)	15 (6.8)	10 (4.5)	0	0	0

Source: Table 14.3.1.1.3.
Includes data up to 28 days after last dose of study drug.
MedDRA (v18.1) coding dictionary applied.
Abbreviations: AE=adverse event, CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients meeting prespecified criterion.
a. The category "Any AE" included all patients without consideration of the 10% cutoff used in this table.

Table 51 - Summary of All-Causality Treatment-Emergent CTCAE Grade 3, 4, and 5 AEs by PT Reported by ≥1% of Patients in Either Treatment Group in Descending Frequency Order (As- reated Population)

	Palbociclib Plus Letrozole (N = 444)				Placebo Plus Letrozole (N = 222)			
Preferred Term	All Grade 3 to 5 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grade 3 to 5 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Any AE[a]	346 (77.9)	276 (62.2)	60 (13.5)	10 (2.3)	58 (26.1)	49 (22.1)	5 (2.3)	4 (1.8)
Neutropenia	245 (55.2)	207 (46.6)	38 (8.6)	0	2 (0.9)	1 (0.5)	1 (0.5)	0
Neutrophil count decreased	67 (15.1)	59 (13.3)	8 (1.8)	0	1 (0.5)	1 (0.5)	0	0
Leukopenia	66 (14.9)	63 (14.2)	3 (0.7)	0	0	0	0	0
White blood cell count decreased	46 (10.4)	46 (10.4)	0	0	0	0	0	0
Anaemia	24 (5.4)	23 (5.2)	1 (0.2)	0	4 (1.8)	4 (1.8)	0	0
Hypertension	15 (3.4)	15 (3.4)	0	0	13 (5.9)	13 (5.9)	0	0
Aspartate aminotransferase increased	11 (2.5)	11 (2.5)	0	0	2 (0.9)	2 (0.9)	0	0
Alanine aminotransferase increased	10 (2.3)	9 (2.0)	1 (0.2)	0	0	0	0	0
Asthenia	10 (2.3)	10 (2.3)	0	0	0	0	0	0
Fatigue	8 (1.8)	8 (1.8)	0	0	1 (0.5)	1 (0.5)	0	0
Febrile neutropenia	8 (1.8)	7 (1.6)	1 (0.2)	0	0	0	0	0
Back pain	6 (1.4)	6 (1.4)	0	0	0	0	0	0
Diarrhoea	6 (1.4)	6 (1.4)	0	0	3 (1.4)	3 (1.4)	0	0
Pulmonary embolism	6 (1.4)	4 (0.9)	1 (0.2)	1 (0.2)	5 (2.3)	3 (1.4)	1 (0.5)	1 (0.5)
Thrombocytopenia	6 (1.4)	5 (1.1)	1 (0.2)	0	0	0	0	0
Dyspnoea	5 (1.1)	5 (1.1)	0	0	3 (1.4)	3 (1.4)	0	0
General physical health deterioration	5 (1.1)	5 (1.1)	0	0	1 (0.5)	0	1 (0.5)	0
Pneumonia	5 (1.1)	5 (1.1)	0	0	2 (0.9)	1 (0.5)	0	1 (0.5)
Syncope	5 (1.1)	5 (1.1)	0	0	3 (1.4)	3 (1.4)	0	0
Urinary tract infection	5 (1.1)	5 (1.1)	0	0	0	0	0	0
Vomiting	2 (0.5)	2 (0.5)	0	0	3 (1.4)	3 (1.4)	0	0
Headache	1 (0.2)	1 (0.2)	0	0	4 (1.8)	4 (1.8)	0	0
Pain in extremity	1 (0.2)	1 (0.2)	0	0	3 (1.4)	3 (1.4)	0	0

Source: Table 14.3.1.8.1.
Includes data up to 28 days after last dose of study drug.
Highest grade reported for each patient.
MedDRA (v18.1) coding dictionary applied.
Abbreviations: AE=adverse event, CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients meeting criterion.
a. The category "Any AE" included all patients without consideration of the ≥1% cutoff used in this table.

Serious Adverse Events

Table 52 Summary of All-Causality Treatment-Emergent Serious Adverse Events (≥2 Patients in Either Treatment Group) by Maximum CTCAE Grade (As-Treated Population)

	Palbociclib Plus Letrozole N = 444 n (%)						Placebo Plus Letrozole N = 222 n (%)					
Preferred Term	Total n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Any AE[a]	87 (19.6)	2 (0.5)	17 (3.8)	46 (10.4)	11 (2.5)	10 (2.3)	28 (12.6)	2 (0.9)	6 (2.7)	12 (5.4)	4 (1.8)	4 (1.8)
Febrile neutropenia	7 (1.6)	0	1 (0.2)[b]	5 (1.1)	1 (0.2)	0	0	0	0	0	0	0
Pleural effusion	4 (0.9)	0	3 (0.7)	1 (0.2)	0	0	1 (0.5)	0	0	1 (0.5)	0	0
Pneumonia	4 (0.9)	0	1 (0.2)	3 (0.7)	0	0	2 (0.9)	0	0	1 (0.5)	0	1 (0.5)
Pulmonary embolism	4 (0.9)	0	0	2 (0.5)	1 (0.2)	1 (0.2)	3 (1.4)	0	0	1 (0.5)	1 (0.5)	1 (0.5)
Acute kidney injury	3 (0.7)	0	0	3 (0.7)	0	0	0	0	0	0	0	0
Disease progression	3 (0.7)	0	0	0	0	3 (0.7)	0	0	0	0	0	0
Malignant melanoma	3 (0.7)	1 (0.2)	0	2 (0.5)	0	0	0	0	0	0	0	0
Pyrexia	3 (0.7)	1 (0.2)	2 (0.5)	0	0	0	0	0	0	0	0	0
Urinary tract infection	3 (0.7)	0	1 (0.2)	2 (0.5)	0	0	0	0	0	0	0	0
Alanine aminotransferase increased	2 (0.5)	0	1 (0.2)	1 (0.2)	0	0	0	0	0	0	0	0
Anaemia	2 (0.5)	0	0	2 (0.5)	0	0	0	0	0	0	0	0
Aspartate aminotransferase increased	2 (0.5)	0	0	2 (0.5)	0	0	0	0	0	0	0	0
Atrial fibrillation	2 (0.5)	0	2 (0.5)	0	0	0	0	0	0	0	0	0
Cellulitis	2 (0.5)	0	0	2 (0.5)	0	0	0	0	0	0	0	0
Deep vein thrombosis	2 (0.5)	0	1 (0.2)	1 (0.2)	0	0	1 (0.5)	0	1 (0.5)	0	0	0
Pain	2 (0.5)	0	1 (0.2)	1 (0.2)	0	0	1 (0.5)	0	1 (0.5)	0	0	0
Pancreatitis acute	2 (0.5)	0	0	1 (0.2)	1 (0.2)	0	0	0	0	0	0	0
Pathological fracture	2 (0.5)	0	0	1 (0.2)	1 (0.2)	0	0	0	0	0	0	0
Sepsis	2 (0.5)	0	0	1 (0.2)	1 (0.2)	0	0	0	0	0	0	0
Syncope	2 (0.5)	0	0	2 (0.5)	0	0	0	0	0	0	0	0
Vomiting	2 (0.5)	0	2 (0.5)	0	0	0	2 (0.9)	0	1 (0.5)	1 (0.5)	0	0
Diverticulitis	0	0	0	0	0	0	2 (0.9)	0	0	2 (0.9)	0	0

Source: Table 14.3.1.3.2.
Includes data up to 28 days after last dose of study drug.
MedDRA (v18.1) coding dictionary applied.
Abbreviations: AE=adverse event; CTCAE= Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients meeting criteria.
a. The category "Any AE" included all patients with a serious AE without consideration of the ≥2 patients cutoff used in this table.
b. Reported case of Grade 2 Febrile neutropenia is currently under review since the CTCAE criteria may not have been met for this event.

AEs associated with permanent discontinuation

Table 53 Summary of All-Causality TEAEs Associated With Permanent Discontinuation for ≥2 Patients in Either Treatment Group (As-Treated Population)

Preferred Term	Palbociclib Plus Letrozole N = 444 n (%)	Placebo Plus Letrozole N = 222 n (%)
Any AE	43 (9.7)	13 (5.9)
Neutropenia	5 (1.1)	0
Disease progression	3 (0.7)	0
Alanine aminotransferase increased	3 (0.7)	0
Diarrhoea	2 (0.5)	0
Fatigue	2 (0.5)	2 (0.9)
Aspartate aminotransferase increased	2 (0.5)	0
Neutrophil count decreased	2 (0.5)	0
Malignant melanoma	2 (0.5)	0
Acute kidney injury	2 (0.5)	0

Source: Table 14.3.1.5.1.
Includes data up to 28 days after last dose of study drug.
MedDRA (v18.1) coding dictionary applied.
Abbreviations: AE=adverse event, MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in population; n=number of patients meeting criterion.

Deaths

Table 54 - Summary of Deaths (As-Treated Population)

	Palbociclib Plus Letrozole (N = 444) n (%)	Placebo Plus Letrozole (N = 222) n (%)
Number of deaths from start of treatment to last dose including 28 days after last dose	10 (2.3)	4 (1.8)
Cause of death		
Disease under study	3 (0.7)	2 (0.9)
Other/unknown	7 (1.6)	2 (0.9)
Number of deaths during follow-up period occurring more than 28 days after last dose	85 (19.1)	34 (15.3)
Cause of death		
Disease under study	78 (17.6)	32 (14.4)
Other/unknown	7 (1.6)	2 (0.9)

Source: Table 14.3.3.1.
Deaths are from the Notice of Death Case Report Form page.
Abbreviations: N=number of patients; n=number of patients meeting prespecified criteria.

A total of ten patients (2.3 %) died while on study (defined as up to 28 days after last dose) in the experimental arm vs. four (1.8 %) in the control arm (3/10 and 2/4 due to disease under study in the respective arms).

The 7 deaths on study (within 28 days of last study dose) that were not due to progressive breast cancer included one case with treatment-related pneumonia, with death due to pulmonary failure, which should be considered as treatment-related. In addition, one case with death due to cardiogenic shock on Day 2 of treatment should be considered possibly related, since autopsy could not identify a cause.

With regard to the 7 deaths during follow up (beyond 28 days after last dose of study treatment), the evaluation of the cases did not reveal signs of a relationship with the study treatment.

Study 1003 (PALOMA-1)

The safety data from this Phase I/II study is considered providing merely support to the safety profile of palbociclib as identified in the two confirmatory studies 1023 and 1008.

Patient exposure

In terms of treatment duration for palbociclib in the combined Phase II population (Ph2P2) the median time was about 15 months. The relative dose intensity with a mean of 94 % and a median of 95 % indicates an acceptable tolerability.

Adverse events

Table 55 - Overview of TEAEs (All Causalities) - Phase 2: As Treated Set (Study 1003)

	Phase 2 (Ph2P1+Ph2P2)		Ph2P1		Ph2P2	
	Palbociclib + Letrozole (N=83)	Letrozole (N=77)	Palbociclib + Letrozole (N=33)	Letrozole (N=29)	Palbociclib + Letrozole (N=50)	Letrozole (N=48)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients evaluable for AEs	83	77	33	29	50	48
Number of AEs	914	438	431	201	483	237
Patients with AEs	83 (100.0)	65 (84.4)	33 (100.0)	25 (86.2)	50 (100.0)	40 (83.3)
Patients with SAEs	18 (21.7)	5 (6.5)	8 (24.2)	2 (6.9)	10 (20.0)	3 (6.3)
Patients with Grade 3 or 4 AEs	64 (77.1)	16 (20.8)	28 (84.8)	4 (13.8)	36 (72.0)	12 (25.0)
Patients with Grade 5 AEs	1 (1.2)	0	0	0	1 (2.0)	0
Patients discontinued due to AEs	12 (14.5)	2 (2.6)	8 (24.2)	1 (3.4)	4 (8.0)	1 (2.1)
Patients discontinued palbociclib due to AEs	12 (14.5)	0	8 (24.2)	0	4 (8.0)	0
Patients discontinued letrozole due to AEs	12 (14.5)	2 (2.6)	8 (24.2)	1 (3.4)	4 (8.0)	1 (2.1)
Patients temporarily discontinued palbociclib due to AEs	52 (62.7)	1 (1.3)	26 (78.8)	0	26 (52.0)	1 (2.1)*
Patients temporarily discontinued letrozole due to AEs	12 (14.5)	3 (3.9)	5 (15.2)	0	7 (14.0)	3 (6.3)
Patients with dose reduction of palbociclib due to AEs	32 (38.6)	0	15 (45.5)	0	17 (34.0)	0

Source: Table 14.3.1.1.1.b.
* This is an error reported in the CRF.
Includes data up to 28 days after last dose of study drug.
Except for the Number of Adverse Events, patients are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
Abbreviations: AE=Adverse event, CRF=Case Report Form; Ph2P1=Phase 2 Part 1; Ph2P2=Phase 2 Part 2; Ph2P1+Ph2P2=Phase 2 combined; SAE=Serious adverse event.

A longer treatment duration of the combination arm compared to the control arm is recognised (median about 15 and 8 months respectively). Overall a higher proportion of AEs, SAEs, Grade ≥3 (main contributors neutropenia and leukopenia), AEs that led to permanent or temporary discontinuation and dose reductions were reported in the experimental arm compared to the control arm. The one patient with a Grade 5 event died from PD. Note the difference between Part 1 and 2 with respect to discontinuations.

All patients in the experimental arm reported at least one TEAE as compared with the letrozole arm (100 % vs. 86 %).

The following common TEAEs were reported substantially more common i.e. >10% difference, for the experimental arm than those for the control arm: neutropenia (75% vs. 5%, respectively), leukopenia (43% vs. 3.9%), fatigue (41% vs. 23%), anaemia (35% vs. 6.5%), nausea (30% vs. 14%), alopecia (22% vs. 2.6%), decreased appetite (21% vs. 6.5%), thrombocytopenia (19% vs. 2.6%), dyspnoea (18% vs. 8%), vomiting (18% vs. 4%), and upper respiratory tract infection (13% vs. 2.6%).

In study 1003, one case of hyperglycemia (Grade 2) and one case of hypoglycemia (Grade 1) were reported in the combination arm in the Phase 2 combined population.

Please refer also to Discussion on Adverse Events of Special Interest (study 1003 and study 1023) below.

Serious adverse events

A total of 24% in the experimental arm and about 8% in the control arm experienced at least one SAE in the Phase 2 portion of the study as of that data cut-off date (02 January 2015). Most SAEs were reported for single patients, except pulmonary embolism that was reported for four patients (4.8 %) and back pain in two patients (2.4 %).

One patient in the experimental arm of the Ph2P2 cohort experienced ischaemic colitis judged as treatment-related SAE.

Deaths

One patient died in the combination arm during the Phase 2 portion which was judged as due to disease progression. No patients died in the letrozole monotherapy arm.

About 30 patients died during follow up (> 28 days after last dose). The vast majority were due to PD with a similar distribution between the two arms.

Safety in special populations

Age

The overall proportions of TEAEs and permanent discontinuations due to TEAEs were similar between the two age groups in the experimental arm. SAEs were more frequently experienced by patients ≥65 years of age compared to the patients < 65 years of age in both treatment arms.

The proportion of Grade 3/4 TEAE in the experimental arm was lower in patients ≥ 65 years of age (76 %) than that in patients < 65 years of age (85 %).

Race

The vast majority were caucasian (91 % and 90 % in the experimental arm and control arm respectively).

Gender

No analysis by gender was performed for the safety data as all patients enrolled were women.

Discontinuation and dose adjustments due to AES

In the experimental arm 16 % of the patients in the Phase 2 combined, permanently discontinued vs. 2.6 % in the control arm. The main reason was as expected neutropenia (6 %) followed by fatigue (2.4 %). In the control arm one patient each permanently discontinued due to arthralgia and nausea. The magnitude of patients that permanently discontinued due to AES does not convey any concern and is deemed acceptable.

The proportion of temporary discontinuations (64 %) was considered high. Not surprising the most common reported TEAES were events of myelosuppression. Overall a total of 54% experienced hematologic TEAEs leading to temporary discontinuation from treatment.

A total of 37% in the experimental arm experienced TEAEs leading to palbociclib dose reduction in the Phase 2 portion of the study. Most commonly reported TEAEs leading to dose reduction were neutropenia (29%), leukopenia (7%), thrombocytopenia (2.4%) and fatigue (2.4%).

Adverse events of special interest (Studies 1023 and 1003)

Based on data of palbociclib in non-clinical studies, the following events of special clinical interest have been identified: myelosuppression (neutropenia-related and thrombocytopenia-related events), QT interval prolongation, eye disorders including cataracts, respiratory disorders including interstitial lung disease and pneumonitis and venous thromboembolic disorders.

Myelosuppression

Neutropenia

A total of 76 % and 79 % reported neutropenia as TEAEs in study 1003 and 1023 respectively. Grade 3 and 4 events of neutropenia were 51% and 6 % respectively in study 1003 with no cases of febrile neutropenia, neutropenic sepsis or neutropenic infection reported. The corresponding figures in study 1023 were 53 % and 9 % respectively where there were two cases of febrile neutropenia reported in the experimental arm and one in the control arm. Both were associated with a Grade 4 event.

In study 1003, regardless of the severity grade the median time from first dose to onset of first episode of neutropenia was shorter than one treatment cycle (i.e. 28 days [for palbociclib 3 w on; 1 w off]). The minimum median time for any grade of neutropenia to onset was about 13 days.

Most patients in the experiemental arm who were reported for neutropenia did not concomitantantly have infection related TEAEs. The types of infections/ infestations observed for those that were reported to have concommitant infections (38 %) were mainly of Grade 1 or 2 with no cases of Grade 4 or 5. Most common were upper respiratory tract infections (nasopharyngitis, bronchitis, pharyngitis, sinusitis and rhinitis).

In study 1023, about 50 % of the patients in the experimental arm had had neutropenia of Grade 3 maximum severity and 9 % had Grade 4 maximum severity in the palbociclib plus fulvestrant arm. For any grade neutropenia, the shortest time from first dose to onset was similar between the treatment arms about 14 days.

As observed in the 1003 study, the median time from first dose to onset of first neutropenia episode regardless of grade was 15 days.

The median duration of Grade ≥3 neutropenia and Grade 4 neutropenia was 15 days and 9 days respectively.

The duration of neutropenia by patient regardless of severity grade was longer than one treatment cycle in the vast majority of patients (92 %) in the experimental arm.

Considering the overall high incidence and severity (mainly Grade 3) of neutropenia, it is notable that overall few cases of febrile neutropenia/ neutropenic sepsis/ neutropenic infection have been reported. Given the fairly low proportion of permanent discontinuations, it may be assumed that neutropenia can be managed with measures like dose reductions and dose interruptions. Based on cumulative, and 'by treatment duration' data provided by the Applicant, there is also no indication of a cumulative toxicity of palbociclib with regard to either neutropenia or febrile neutropenia. About 10 % received G-CSF in the studies.

Febrile neutropenia will continue to be monitored in ongoing clinical studies and in the RMP (important identified risk of myelosuppression).

Thrombocytopenia

In the 1003 (Phase 2 combined) a total of 23 % of the patients in the experimental arm experienced thrombocytopenia vs. 2.6 % in the control arm. Grade 3 and 4 were 1.5 % and 0.6 % respectively.

In the 1023 study, 19 % of the patients in the experimental arm experienced thrombocytopenia while none in the control arm. A total of six patients had a maximum of Grade 3 and two patients had a maximum of Grade 4.

It is noted that no events of bleeding were reported in association with thrombocytopenia.

QT interval prolongation

From non-clinical observations, a potential of palbociclib for QT prolongation and hemodynamic effects was identified from in vitro assays and/or in vivo cardiovascular dog studies.

Furthermore the palbociclib exposure-response relationships for the ECG endpoints (RR and QTc intervals) were developed using data from Studies 1001, 1002, and 1003. The exposure-response relationships for RR and QTC intervals was described by linear mixed effects models, indicated no effect on heart rate of palbociclib and a rather flat QT-exposure relationship.

In study 1003, one patient in the experimental arm and two patients in the control arm had a maximum increase of≥ 60 msec from baseline. No patients had >500 msec as maximum postbaseline value.

In study 1023, a total of 73 patients in the experimental arm and 74 patients in the control arm were evaluable i.e. had both baseline and postbaseline ECG data. None of the patients in the experimental arm had a postbaseline QTcF of ≥500 msec. The proportion of patients with a postbaseline QTcB of ≥500 msec was higher in the palbociclib plus fulvestrant arm (5.5%) than that in the placebo plus fulvestrant arm (1.4%). The proportions of patients with a >60 msec maximum increase from baseline in QTcF were similar between the two treatment arms. The proportion of patients with a >60 msec maximum increase from baseline in QTcB was higher in the experimental arm compared to the control arm.

No TEAEs of syncope, cardiac arrest, convulsion, sudden death, death, Torsade de pointes, ventricular fibrillation, ventricular flutter and ventricular tachycardia have been reported.

From the clinical perspective, observations in the 1003 and 1023 study do not reveal any clear causality between QT prolongation and the addition of palbociclib to either letrozole or fulvestrant.

QTc Substudy

Study 1008 included a QTc analysis substudy that was conducted as the definitive QTc prolongation evaluation for the palbociclib program.

QTc Analysis Substudy Conclusions

- In the QTc analysis population, QTcS was the best correction factor to account for the effect of heart rate on QT interval, followed by QTcF and QTcB.

- In the QTc analysis population, no patients from either treatment arm had a post-baseline absolute mean maximum QTcS or QTcF ≥500 msec or an increase from QTcS or QTcF baseline value ≥60 msec during the intensive QTc assessment period.

- A random effect analysis of the QTc data in the QTc analysis population demonstrated that the upper bounds of the 1-sided 95% CI for the mean change from clock time-matched baseline for QTcS and QTcF were all <8 msec at all time-points in the QTc assessment period.

Thus, no indication of a QT-prolongation effect was found in this QT substudy inStudy 1008/PALOMA-2, intended as the definitive QT prolongation evaluation for the palbociclib programme. It should be noted that no thorough QT study has been performed, however, and that supratherapeutic doses have not been clinically evaluated. From a PK point of view, the risk of achieving an exposure four times the normal exposure (i.e. the exposure level where a preclinical study indicated a QT-signal) appears low, however. Theoretically possible, but unlikely, scenarios include:

- Concomitant inhibition of the enzymes CYP3A4 och SULT2A1 mainly responsible for the elimination. (Inhibition of only one is not expected to lead to a 4 x increase in exposure)
- Severe hepatic impairment (A PAM is requested)
- Normal variability, considered unlikely to achieve 4 x increase in exposure.

QT prolongation is included in the RMP as an Important Potential Risk.

Eye disorders including cataracts

From non-clinical findings, cataracts/lens degeneration was identified in rats in association with altered glucose metabolism (glycosuria and/or hyperglycaemia). A further association was found between glucose metabolism and pancreatic islet vacuolation.

Hyperglycemia/ Diabetes

In the Phase 2 portion of the 1003 study, one patient in the experimental arm experienced Grade 2 hyperglycaemia which was considered unrelated to treatment.

In the 1023 study, a total of three patients (0.9%) in the experimental arm and two patients (1.2%) in the control arm experienced hyperglycaemia.

Hyperglycaemia was proposed as Important Potential Risk in the RMP which was endorsed. In addition, the Applicant states that prospective monitoring of hemoglobin A1c was added to characterise whether or not palbociclib affected glucose metabolism. No hemoglobin A1c data to report was available as of data cutoff date. This will be separately reported. A study addressing this issue is on-going.

Respiratory disorders including interstitial lung disease and pneumonitis

From non-clinical observations, clinical and microscopic findings in single- and repeat-dose rat toxicity studies were suggestive of a potential for palbociclib to affect the respiratory system.

Respiratory associated TEAEs were overall more common in the combinations arms in study 1003 and study 1023 (48 % and 35 % as compared to their comparators (26 % for letrozole and 27 % for fulvestrant). The most frequently reported events in study 1003 were dyspnoea (18 %), cough (13 %) and epistaxis (11 %) and in study 1023 cough (13 %), dyspnoea (11 %), oropharyngeal pain (9 %), and epistaxis (5.5%).

The individual types of TEAEs and the distribution thereof are fairly similar between the two studies. Interstitial lung disease/Pneumonitis was included in the RMP as Important Potential Risk which was supported.

Venous thromboembolic disorders

The increased risk of pulmonary embolism associated with malignancy alone which may yet increase with the administration of chemotherapy, endocrine treatment (venous thromboembolic events are known adverse drug reactions to both letrozole and fulvestrant) as well with other drugs is well known. Notwithstanding, there were

six events of pulmonary embolism reported in the experimental arm in study 1003 while none in the letrozole alone arm. Likewise in study 1023 there were events (three cases) in the experimental arm while none in the control arm. This may be, as suggested by the Applicant, due to differential treatment duration.

Of note, on study 1008 (Phase III palbociclib/letrozole vs. letrozole alone), there were six events (1.4 %) of pulmonary embolism in the experimental arm while five (2.3 %) in the control arm.

Immunological events

This has not been addressed in the dossier and will not be required.

2.6.1. Discussion on clinical safety

The safety database consists of approximately 2000 individuals including 1600 patients with malignancies whereof the vast majority were treated in breast cancer studies (n~ 1500 [studies 1023, 1003, 1010 Phase 1/ Phase 2, 1034, 1008, and 1001]).

In terms of exposure, in the 1003 study relative dose intensity for palbociclib was high (mean of 94 %, median of 95 %) while to lesser extent in the 1023 study (mean of 87 %, median of 90 %) although indicative of an acceptable tolerability for the respective combinations The add on of palbociclib to either letrozole or fulvestrant appears not to convey any major concerns in regard to any added or heightened safety issue deriving from the accompanying treatments.

The treatment duration was longer in study 1003 (median about 15 months for palbociclib/ letrozole arm vs. 8 months for the letrozole alone arm) than in study 1023 (median 5 months for palbociclib/ fulvestrant vs. 4 months for fulvestrant alone) although bearing in mind the different settings of the two studies i.e. 1st and 2nd line respectively.

Study 1023

A higher proportion of AEs (98 % vs. 89 %), Grade 3/4 (70 % vs. 18 %), AEs that led to temporary discontinuation and dose reductions (31 % vs. 1.7 %) were reported for the experimental arm compared to the control arm.

It is recognised that few patients permanently discontinued the study or permanently discontinued palbociclib/ placebo or fulvestrant due to AEs. From a tolerability perspective this is reassuring. On the other hand, the high proportion of temporary discontinuations of palbiciclob in the combination arm is noted 65 % vs 8 % in the control arm. A total of 24 % temporarily discontinued fulvestrant in the experimental arm vs. about 4 % in the control arm.

A substantially higher proportion of patients in the experimental arm (65 %) had TEAEs that led to temporary discontinuation from treatment as compared to control arm (8 %).

The main causes leading to temporary discontinuations were as expected, haematology related. The vast majority of the overall TEAEs leading to this measure were judged treatment related (61 %).

Study 1008 Summary of Top Line Results

The Applicant has provided top line results from the confirmatory Phase III 1008 study investigating palbociclib+letrozole vs. placebo+letrozole. Almost all reported an AE (98.9 % and 95.5 % in the experimental and control arm respectively). In comparison between the two palbociclib+ letrozole arms in studies 1008 and 1003 (Ph2P1+PhP2), a fairly similar proportion was observed in terms of SAEs (19.6 % vs. 21.7 %), Grade 3/4

(77.5 % vs. 77.1 %), discontinuation due to AEs (2.5 % vs. 14.5 %), temporary discontinuation of palbociclib (74.8 % vs. 62.7 %) and dose reduction of palbociclib (36.0 % vs. 38.6 %).

The most common TEAEs in the palbociclib+ letrozole arm included neutropenia, fatigue, nausea, arthralgia, alopecia, diarrhoea, cough, leukopenia and anaemia.

Relevant to the high proportion of reports of neutropenia (66.2 % all grades, 46.6 % Grade 3), it is noted that febrile neutropenia was reported in a limited proportion (1.8 %). This is in line with what was observed in study 1023 (0.9 %). In study 1003 there were no reports of febrile neutropenia.

In regard to pulmonary embolism, six patients (1.4 %) in the experimental arm experienced pulmonary embolism (one fatal) while five (2.3 %) in the control arm (one fatal).

A total of ten patients (2.3 %) died while on study (defined as up to 28 days after last dose) in the experimental arm vs. four (1.8 %) in the control arm (3/10 and 2/4 due to disease under study in the respective arms). Of the14 non-PD deaths, one death of pulmonary failure due to pneumonia is considered related to the palbociclib therapy; and one case of fatal cardiogenic shock on Day 2 of treatment of unknown cause is considered possibly related. No new safety concerns were raised based on the analysis of deaths in study 1008.

From a safety perspective based on the data provided, it is agreed that the adverse events observed appears to be in line with what has previously been reported in studies 1003 and 1023. No new safety concern, trend or signal has been identified at this point.

Study 1003 (Phase 2 [Ph2P1+Ph2P2])

Overall, the safety observations in study 1003 is consistent with study 1023 and what at this point is known from the 1008 top line results i.e. an acceptable low proportion of permanent discontinuations vs. the high proportion of temporary discontinuations, dose reductions and delays.

Also in terms of TEAEs, Grade 3 and 4 events and SAEs the safety profile is consistent with the observations from the two Phase III studies with the main cause being events of myelosuppression and largely neutropenia. No cases neutropenic sepsis or neutropenic infection was reported in the Phase 2 portion of the study.

Regardless of the severity grade the median time from first dose to onset of first episode of neutropenia was shorter than one treatment cycle (i.e. 28 days [for palbociclib 3 w on; 1 w off]). The minimum median time for any grade of neutropenia to onset was about 13 days. From the safety perspective 2 week on/ 2 week off regimen appears more appealing.

The overall median duration of neutropenia by patient and any severity grade reported for the experimental arm was 147 days across all cycles with duration > 7 days for the vast majority of patients (94 %). The median duration of Grade ≥3 and Grade 4 events across all cycles was 48 days and 8 days respectively.

Overall comments on studies 1023, 1008 and 1003

More recent safety data has been requested during the procedure and for study 1023 the Applicant has submitted an A5481023 90-Day Safety Update (to support the A5481023 supplemental NDA (sNDA) to the FDA) with 31 July 2015 as data cut-off date. Additional safety up-dates have been provided with cut-off date February 26 2016 for study 1023 (SAEs) and for studies 1008 and 1003 (data on AEs, laboratory test values and SAEs).

Overall the safety profile is generally consistent through all studies. A more complete summary of clinical safety of study 1008 will be available by March 2017.

The add-on of palbociclib to letrozole or fulvestrant is associated with an overall rather substantial increase in events of myelosuppression largely neutropenia (mainly Grade 3) which has led to a high proportion of patients undergoing temporary dose interruptions, dose delays and dose reductions in the respective experimental arms.

It is notable however, that overall few cases of febrile neutropenia/ neutropenic sepsis/ neutropenic infection have been reported (none in study 1003). Considering the fairly low proportion of permanent vs. the high proportion of temporary discontinuations, it may be assumed that neutropenia can be managed with measures like dose reductions and dose interruptions. Based on cumulative, and 'by treatment duration' data, there is also no indication of a cumulative toxicity of palbociclib with regard to either neutropenia or febrile neutropenia. Febrile neutropenia will continue to be monitored in ongoing clinical studies and in the RMP (important identified risk of myelosuppression).

Of note, two cases of fatal hepatic toxicity have recently been reported with palbociclib associated to letrozole (Vuppalanchi R. et al [2016]: Pseudocirrhosis and liver failure in patients with metastatic breast cancer after treatment with palbociclib [Hepatology. doi:10.1002/hep.28720]).

In addition to these two cases, there were 3 out of 179 cases of hepatotoxicity with palbociclib. However, based on these limited data in patients with hepatic metastasis, no clear relation between palbociclib and hepatic pseudocirrhosis can be evidenced. Consequently, for the time being, no modification of the SmPC will be required. The hepatotoxicity should be closely monitored through the MA.

Pooled chemistry laboratory values as well as pooled hepatic laboratory values of subjects treated in studies 1003 and 1023 were generally comparable between the palbociclib arms vs the comparator arms. Nonetheless, hypocalcemia and hypophosphataemia occurred more frequently in the palbociclib arm (respectively 30.6 % versus 18.6% and 39.2% versus 19.7%), but at mild/moderate grade (1 or 2).

In study 1003 differences in the reporting frequencies of some adverse event parameters were observed between palbociclib treated subjects ≥ 65 years of age compared to those <65 years of age. This is thought to be most likely related to variability due to the relatively small number of subjects represented in each age group. In the larger and thus more representative study 1023, there was no notable difference in the incidence of SAEs. In regard to treatment duration by age-groups (median), no apparent difference between age group < 65 and ≥65-74 is noted. The number of patients ≥ 75 years of age were limited in both study 1003 (n=8) and 1023 (n=27) which preclude any firm conclusion to be drawn in this age group. No specific measures in the SmPC or RMP are proposed. This is considered acceptable.

2.6.2. Conclusions on the clinical safety

The add-on of palbociclib to letrozole or fulvestrant is associated with an overall rather substantial increase in toxicity relative the respective comparators. The main underlying cause behind this is the palbociclib associated myelosuppression essentially neutropenia which however appears not to be translated into a corresponding high proportion of febrile neutropenia. Given the acceptable levels of exposure achieved and the fact that the magnitude and severities of the TEAEs reported did not translate into a corresponding high proportion of permanent discontinuations or a concerned high number of non-disease related deaths, it is concluded that palbociclib in its proposed combinations with supportive measures of dose adjustments as appropriate, is reasonably tolerable.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Myelosuppression (Neutropenia, Anaemia, Thrombocytopenia)
Important potential risks	QT prolongation Interstitial lung disease/Pneumonitis Hyperglycaemia Reproductive and Developmental Toxicity
Missing information	Male patients Hepatic impairment Renal impairment Long-term use

Pharmacovigilance plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
A5481027 A multicentre, randomized, double-blind, phase 3 study of palbociclib plus letrozole versus placebo plus letrozole for the treatment of previously untreated Asian postmenopausal women with ER-positive, HER2-negative advanced brast cancer Category 3	To evaluate the effect of palbociclib on hyperglycaemia	Hyperglycaemia	Ongoing	April 2019
A5481013 A phase 1, open-label, single dose, parallel-cohort study to evaluate the pharmacokinetics of	To evaluate the pharmacokinetics of palbociclib in patients with impaired hepatic function	Hepatic impairment	Ongoing	December 2017

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
palbociclib in subjects with impaired hepatic function Category 3				
A5481014 A phase 1, open-label, single dose, parallel-group study to evaluate the pharmacokinetics of palbociclib in subjects with impaired renal function Category 3	To evaluate the pharmacokinetics of palbociclib in patients with impaired renal function	Renal impairment	Ongoing	June 2017

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Myelosuppression (Neutropenia, Anaemia, Thrombocytopenia)	SmPC sections 4.2, 4.4 and 4.8	None
QT prolongation	SmPC sections 5.2 and 5.3	None
Interstitial lung disease/Pneumonitis	No risk minimisation measures are considered necessary at present	None
Hyperglycaemia	SmPC section 5.3	None
Reproductive and Developmental Toxicity	SmPC sections 4.6 and 5.3	None
Male patients	None	None
Hepatic impairment	SmPC sections 4.2 and 5.2	None
Renal impairment	SmPC sections 4.2 and 5.2	None
Long-term use	No risk minimisation measures are considered necessary at present	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

The applicant compared the structure of palbociclib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers palbociclib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ibrance is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Breast cancer is a heterogeneous disease with subtypes having varied responses to anti-hormonal and chemotherapy treatments. Breast tumour types can be distinguished by their hormonal receptor status, with one third of tumours being ER-negative and two thirds of tumours being ER-positive.

ER-positive tumours make up 65% of tumours in women aged 35 to 65 years and 82% of tumours in women older than 65 years[16]. These cancers are largely oestrogen driven in postmenopausal women where the main source of the tumour's oestrogen is from conversion of androgens to oestrogens via aromatase enzyme action. Modification of oestrogen activity or synthesis represents the treatment of choice for postmenopausal women with hormone receptor-positive advanced breast cancer, particularly for those with slowly progressive disease and limited tumour-related symptoms

3.1.2. Available therapies and unmet medical need

Recommendations from the American Society of Clinical Oncology Clinical Practice Guidelines, the European School of Oncology-European Society for Medical Oncology (ESO-ESMO) 2nd International Consensus Guidelines for Advanced Breast Cancer (ABC2), and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommend endocrine therapy as the preferred first-line treatment option for hormone receptor-positive, HER2-negative advanced breast cancer (except for immediately life-threatening disease or when concerns exist regarding endocrine resistance). The choice between endocrine therapies for the initial treatment is often driven by prior adjuvant endocrine therapy, potential side effects, time to progression on prior therapy, as well as the patient's menopausal status.

Currently, first-line treatment in the ER-positive, HER2-negative advanced breast cancer postmenopausal population typically includes endocrine therapies, such as letrozole, anastrozole, exemestane, fulvestrant, and tamoxifen6 with time to progression and prolongation of PFS ranging from 5 to 15 months.

Presently, second and subsequent lines of therapy in the hormone receptor-positive advanced breast cancer population typically include endocrine therapies, such as tamoxifen, fulvestrant, steroidal or nonsteroidal AIs, progestins, and androgens. In the pivotal studies for the present application, letrozole and fulvestrant were used as endocrine backbone therapy and comparators.

In addition, postmenopausal women with hormone receptor-positive, HER2-negative breast cancer that have progressed after treatment with letrozole or anastrozole may also receive everolimus (Afinitor) in combination with exemestane.

Chemotherapy should be reserved for cases of rapidly progressive disease or proven endocrine resistance.

3.1.3. Main clinical studies

Three main clinical studies Study 1023 (PALOMA-3), Study 1008 (PALOMA-2) and Study 1003 (PALOMA-1) were submitted in support of a proposed indication for palbociclib in combination with letrozole and fulvestrant, respectively.

3.2. Favourable effects

PALOMA-3 (in combination with fulvestrant)

An interim analysis was performed at a median of 5.6 months follow-up and an overall event rate of 37% (100/347 and 93/174 in experimental and comparator arm, respectively). At this point, the study met its primary objective of prolonging investigator-assessed PFS with hazard ratio (HR) 0.42 (95% CI: 0.32, 0.56; stratified 1-sided p-value <0.000001) in favour of palbociclib plus fulvestrant. The median PFS was 9.2 months

(95% CI: 7.5, not estimable) for palbociclib plus fulvestrant and 3.8 months (95% CI: 3.5, 5.5) for placebo plus fulvestrant, and the difference in medians between arms was 5.7 months.

In a number of pre-specified sensitivity analyses HR remained stable around 0.4 in all analyses, indicating robustness of the results.

A blinded independent central review (BICR) was performed on a randomly sampled subset constituting 40% (n=211) of the Intention-to-treat (ITT) population, showing HR 0.27, with similar median PFS in the control arm at 3.7 months, but median not reached in the palbociclib arm.

Two updated efficacy analyses were performed based on investigator assessment. The latter occurred at a median follow-up of over 15 months in both study arms, and an overall event rate of 64% (58 vs. 76%). This showed a PFS HR of 0.50 (0.36-0.59) and median the PFS was 11.2 vs. 4.6 months, i.e. a difference of 6.6 months in favour of the palbociclib-containing arm.

In updated PFS subgroup analyses all subgroup HR point estimates were below 1.0 and most had 95% confidence intervals below 1, indicating robustness of the results. Pre-/perimenopausal patients and postmenopausal patients had similar HRs, 0.46 and 0.52, respectively, both with confidence intervals below 1.0. Patients who had received 0 lines of therapy in the metastatic setting had a somewhat higher HR point estimate (0.59) than those with 1 or 2 previous lines of therapy for metastatic disease (0.46 and 0.48), but with 95% confidence interval below 1.0.

In the updated analysis the difference in objective response rate (ORR), 21 vs 9% (non-overlapping confidence intervals, 1-sided p= 0.0001), and Clinical Benefit rate (CBR), 66 vs.40% (non-overlapping confidence intervals, 1-sided p<0.0001), supports the PFS results. Duration of response (DOR) was numerically but not statistically significantly longer in the experimental arm compared with the comparator arm, 10.4 vs. 9.0 months.

At a pre-specified interim analysis of overall survival (OS) (data cut-off date of 23 Oct 2015), the event rate was 21.5% of the total 521 patients (20.5% vs. 23.6%, for palbociclib plus fulvestrant arm and placebo plus fulvestrant arm, respectively). No death in the palbociclib-containing arm was due to toxicity.

With regard to Patient-reported outcomes (PROs), a time to event analysis was pre-specified for deterioration in pain (TTD), defined as first occurrence of an increase of at least 10 points in pain on study. Statistically convincing and plausible results were achieved with a difference in median time to deterioration of 8.0 vs 2.8 months, HR 0.6, p <0.001.

PALOMA-2 (in combination with letrozole)

The final PFS analysis was performed at an event rate of 50%. The estimated HR was 0.58 (95% CI: 0.46-0.72; 1-sided p<0.000001) in favour of palbociclib plus letrozole. The median PFS was 24.8 months (95% CI: 22.1-NE) for palbociclib plus letrozole and 14.5 months (95% CI: 12.9-17.1) for placebo plus letrozole, with a difference in PFS medians between arms of 10.3 months (with non-overlapping confidence intervals).

The results of the primary endpoint are supported by secondary outcome measures. For objective response rate, based on confirmed responses, a difference between arms of 11% was noted, together with a 15% difference in disease control rate (CR+PR+SD $\geq$ 24 weeks). The difference in median duration of response) in responding patients with measurable disease at baseline appeared clinically relevant at 5.7 months.

A planned overall survival (OS) interim analysis was performed at the time of the final PFS analysis based on 133 deaths (20% event rate), but the results were not presented as being immature. The median follow-up time for the palbociclib plus letrozole arm was 23.0 months (95% CI: 22.6-23.4) and for the placebo plus letrozole arm

was 22.3 months (95% CI: 21.9-22.9). There was one treatment-related death (infection), and one possibly related death in the palbociclib arm.

The frequency of Rb-negativity by IHC in Study 1008/ PALOMA-2 was 9%. A higher HR was observed in the small Rb-negative subpopulation (n=51) at 0.675 (95% CI: 0.308, 1.481) compared with the Rb-positive group (n= 512), HR 0.531 (95% CI: 0.416, 0.680).

Indication

Extrapolations from letrozole to any aromatase inhibitor, and from goserelin to any GnRH/LHRH analogue, are both considered acceptable based on mechanistic rationales supported by the clinical interchangeability of the products in question, together with a lack of PK and drug-drug interaction concerns for the products that were not studied. (see Discussion on Clinical Efficacy).

The proposed extrapolation to combination of palbociclib with AI + LHRH in pre/perimenopausal women, from combination with fulvestrant + LHRH in pre/perimenopausal women and from combination with AI in postmenopausal women, is considered acceptable based on the benefit observed in the pivotal studies, and on AI+LHRH being an established first line treatment option in premenopausal patients according to international guidelines. Also from a mechanistic perspective, the extrapolation is supported, since effective inhibition of oestrogen receptor (ER) signalling is achieved by both endocrine regimens and palbociclib acts downstream of the ER.

PALOMA-1 (in combination with letrozole)

For reasons described under “Discussion of clinical efficacy”, PFS results are considered likely to be without major bias only in the second part of the phase 2 trial (Ph2P2), presented below.

Part 2

At an overall event rate of 61% (26/50 and 34/49 in experimental and comparator arm, respectively), the investigator assessed PFS showed a hazard ratio (HR) of 0.51 at a 1-sided p-value of <0.005 with a median difference of 7 months (18 vs. 11).

In the blinded independent central review (BICR) analysis, corresponding figures were 20/50 and 24/49, with an HR of 0.58 and a 1-sided p-value of 0.03 and a median difference of 5 months (20 vs. 15).

At an event rate of 30% in the overall survival (OS) analysis, there is a weak trend in favour of the experimental arm in Part 2: HR 0.8, 1-sided p=0.3.

Objective response rate (ORR) was similar in BICR-based ITT analysis, 28.0 vs 26.5% (n: 14/50 vs 13/49) 1-sided p=0.5, and numerically higher in the experimental arm in in BICR-based analysis of patients with measurable disease, 45 vs 35% (n: 14/31 vs 13/37), 1-sided p=0.3.

3.3. Uncertainties and limitations about favourable effects

Retinoblastoma protein status

According to pre-clinical data, palbociclib lacks functional efficacy in Rb-negative cancer cell lines and animal models, demonstrating the importance of intact Rb function for the efficacy of palbociclib. Loss of Rb itself is rarely seen in ER positive breast cancer. The frequency of Rb-negativity by IHC in Study 1008 (PALOMA-2) was non-trivial at 9%, however, and the HR in this subgroup (n=51) had a wide confidence interval overlapping 1.0. In light of the preclinical background, the presence of relevant efficacy of palbociclib in this group cannot be

concluded. It is acknowledged that alternative mechanisms of action may be hypothesised, and confounding of preclinical experiments related to the immortalisation of cell lines affecting Rb-status has been suggested, but these theories cannot be used to dismiss the actual preclinical findings. It is also noted that preclinical models of Rb-function are commonly based on genetic determination Rb-status, while in clinical studies protein expression by immunohistochemistry (IHC) is most frequently used, potentially impacting results differently. Considering the possibility that patients may have their tumours molecularly screened, providing information that includes Rb-status, information has been introduced in the SmPC to inform the prescriber, including results from preclinical models and the available clinical data. Furthermore, in order to potentially solve this uncertainty, the Applicant has committed to perform a non-clinical study investigating the activity of palbociclib *in vitro* and *in vivo*, as explants from human IHC Rb positive and IHC Rb negative fresh tumour samples, and if possible also based on genetic determination of Rb status.

Critical visceral disease

In patients with critical, rapidly progressing or symptomatic visceral disease, a rapid and high likelihood of response to therapy is of importance. Chemotherapy is therefore recommended for this group of patients, who were excluded from the PALOMA-3 and PALOMA-2 studies. In both studies, the addition of palbociclib substantially improved on both the PFS and ORR of the endocrine backbone, also in patients with (non-critical) visceral disease. Smaller /no improvement was observed for the clinically important Time to tumour response (TTR) in the visceral subgroups, however, and the observed TTRs around 4 months are difficult to contextualise due to the limited published data on TTRs of chemotherapies available for comparison. Information has therefore been introduced in the SmPC to inform the prescriber of the ORR and TTR results for the visceral subgroups of PALOMA-3 and PALOMA-2 studies, and that critical visceral disease was not studied.

OS immaturity

OS data for both pivotal phase 3 studies are immature have not been presented due to immaturity (20-21% event rate). Given the large treatment effect observed on PFS, and the assessment of deaths, which did not raise any new safety concerns, a detrimental effect of palbociclib on OS is considered unlikely, however.

3.4. Unfavourable effects

The most frequently reported TEAEs were associated with myelosuppression largely neutropenia leading to a magnitude of temporary dose interruptions, dose delays and dose reductions. Other frequently reported TEAEs were fatigue, infections, nausea, arthralgia, stomatitis, vomiting, diarrhea and alopecia. Most of the TEAEs were of Grade 1 or Grade 2 maximum severity except for neutropenia and leukopenia reported most commonly as a Grade 3 TEAE (for details please refer to the Effects Table).

The safety findings observed in 1023, 1008 and 1003 including recent safety up-dates seem overall consistent which is reassuring.

Considering the overall high incidence and severity of neutropenia, it is of note that overall few cases of febrile neutropenia/ neutropenic sepsis/ neutropenic infection have been reported.

Given the fairly low proportion of permanent vs. the high proportion of temporary discontinuations, it may be assumed that neutropenia can be managed with measures like dose reductions and dose interruptions. Based on cumulative, and 'by treatment duration' data provided by the Applicant, there is also no indication of a cumulative toxicity of palbociclib with regard to either neutropenia or febrile neutropenia.

3.5. Uncertainties and limitations about unfavourable effects

Palbociclib may have the potential to alter glucose homeostasis in humans in association with effects on the endocrine pancreas with effects on the eye, teeth, kidney, and adipose tissue considered secondary to the endocrine changes/glucose dysregulation.

3.6. Effects Table

Table 56 - Effects Table for palbociclib: hormone receptor positive, HER2 negative breast cancer

Favourable Effects	Experimental arm	Control arm	Difference between arms	HR	P-value 2-sided*	Comment
Study 1023/PALOMA-3 (updated analysis)					**23 October 2015 cut-off**	
N	347	174	-	-	-	2:1 rand.
PFS Investigator (BICR not performed in update)	Median 11.2 m Event rate 58%	Median 4.6 m Event rate 76%	Median 6.6 m	0.50	<0.000002	Clinically meaningful, stat. robust. Supported by primary analysis (Inv. HR 0.42, BICR HR 0.3) and sub-groups
Study 1008/PALOMA-2						
N	444	222				
PFS Investigator	Median 24.8 m Event rate 44%	Median 14.5 m Event rate 62%	Median 10.3 m	0.58	p<0.000002	Clinically meaningful, stat significant. Supported by BICR HR 0.65 and sub-groups
Unfavourable effects	**Experimental arm**	**Control Arm**		**Comment**		
Study 1023/PALOMA 3						
Grade 3 or 4	70.1	18.0				
Study 1003/PALOMA-1						
Grade 3/4	77.1	20.8				
Study 1008/ PALOMA-2 Top Line results						
Grade 3/4	77.5	25.2				

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A prolongation of progression-free survival by 6-10 month's in the early metastatic settings of breast cancer is of clear clinical value.

The main safety risk associated with palbociclib is bone marrow suppression, essentially neutropenia that led to dose delay and dose reductions in about 1/3 patients. This type of toxicity is commonly encountered in oncology practice and easily managed, especially as neutropenic infections were uncommon. There is also no indication of a cumulative toxicity.

3.7.2. Discussion on the benefit-risk assessment

Study 1023 (PALOMA-3) and Study 1008 (PALOMA-2) are both immature with regard to overall survival (OS), at event rates of 21% and 20%, respectively. For both studies, PFS results appear robust with regard to the level of statistical significance across analyses, the consistency of results in a number of PFS sensitivity analyses and in subgroups, and in terms of support from ORR and CBR analyses. Given the large treatment-effect on PFS, and that the evaluation of deaths on study and during follow-up did not raise concerns, a detrimental effect of palbociclib on OS is considered unlikely. The proposed indication includes a number of extrapolations from the respective pivotal trials. These extrapolations were considered acceptable based on the mechanism of action of palbociclib and the inhibition of downstream effectors of ER as well as based on the current accepted treatment paradigms published in European guidelines on breast cancer. Both pivotal studies are relatively immature, however, and the lack of mature data on overall survival will be addressed post-authorisation.

The safety findings observed in studies 1023, 1008 and 1003 seem indeed consistent. The add-on of palbociclib to letrozole or fulvestrant is associated with an overall rather substantial increase in events of myelosuppression largely neutropenia (mainly Grade 3) which has led to a high proportion of patients undergoing temporary dose interruptions, dose delays and dose reductions in the respective experimental arms.

It is notable however, that overall few cases of febrile neutropenia/ neutropenic sepsis/ neutropenic infection have been reported. Considering the fairly low proportion of permanent vs. the high proportion of temporary discontinuations, it may be assumed that neutropenia can be managed with measures like dose reductions and dose interruptions. Based on cumulative, and 'by treatment duration' data, there is also no indication of a cumulative toxicity of palbociclib with regard to either neutropenia or febrile neutropenia.

Given the magnitude of the clinical benefit observed and the relatively general low grades of the TEAEs reported which did not result in a high proportion of febrile neutropenia, permanent discontinuations or non-disease related deaths, it is concluded that palbociclib in combination with an aromatase inhibitor or in combination with fulvestrant is reasonably tolerable.

3.7.3. Balance of benefits and risks

The CHMP concludes that the magnitude of the treatment effect on progression-free survival and the manageable toxicity contribute to a positive B/R balance.

3.8. Conclusions

The overall B/R of Ibrance is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers that the risk-benefit balance of Ibrance is favourable in the following indication:

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

- *in combination with an aromatase inhibitor;*
- *in combination with fulvestrant in women who have received prior endocrine therapy (see section 5.1).*

In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Other conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

The applicant compared the structure of palbociclib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers palbociclib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.