Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Palbociclib

Proprietary Product Name: Ibrance

Sponsor: Pfizer Pty Ltd Australia

Date of first round report: 1 September 2016
Date of second round report: 30 January 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
%CV	Percent Coefficient of Variation
%RE	Percent Relative Error
ABC	advanced breast cancer
ADI	average dose intensity
ADME	Absorption, distribution, metabolism and elimination
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
AT	All Treated As Treated Set
ATC	Absolute thrombocyte count
$AUC_{extrap\%}$	The Area Under The Plasma Concentration-Time Curve From The Time of Last Measurable Concentration To Infinity Divided By AUC_{inf}
AUC_{inf}	Area Under The Plasma Concentration-Time Curve From Time 0 To Infinity
AUC_{last}	Area Under The Plasma Concentration-Time Curve From Time 0 To Time Of Last Measurable Concentration
AUC_{24}	Area Under The Plasma Concentration-Time Curve From Time 0 To 24 Hours
BALB	Baseline albumin
BALK	Baseline alkaline phosphatase
BAST	Baseline Alanine Aminotransferase
BAST	Baseline Aspartate Aminotransferase

Abbreviation	Meaning
BICR	Blinded Independent Central Review
BLQ	Below The Lower Limit of Quantification
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Response
CCND1	Cyclin D1
CDKN2A	Cyclin-Dependent Kinase Inhibitor 2A (also known as 'p16INK4A')
CDK	Cyclin-Dependent Kinase
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent Clearance
C_{max}	Maximum Observed Plasma Concentration
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Predose Concentration
CYP	CytochromeP450
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DLT	Dose-Limiting Toxicity

Abbreviation	Meaning
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic Acid
EIA	Enzyme-Linked Immunosorbent Assay
eNCA	Electronic Noncompartmental Analysis
EOT	End Of Treatment
ER	Estrogen Receptor
ER positive	Oestrogen receptor postivie
FISH	Fluorescence In Situ Hybridization
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSF	Granulocyte Colony-Stimulating Factor
GGT	Gamma Glutamyltransferase
H3	Tritium
HER2	Human Epidermal Growth Factor Receptor 2 (ErbB2)
HPLC/MS/MS	High Pressure Liquid Chromatography Tandem Mass Spectrometry
HR	Hazard Ratio
IB	Investigator's Brochure
IC50	Half-Maximal Inhibitory Concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IF	Immunofluorescence
IHC	Immunohistochemistry
IND	Indeterminate

Abbreviation	Meaning
IOBU-SDMC	Internal Oncology Business Unit-Safety Data Monitoring Committee
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
Ki	Concentration for half-maximal inactivation
Ki67	Nuclear protein identified by the Ki67 monoclonal antibody
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
mBPI-sf	Modified Brief Pain Inventory–Short Form
MCF	Michigan Cancer Foundation
MedDRA	Medical Dictionary For Regulatory Activities
MRAUCinf	metabolite to parent ratio AUCinf
MRAUClas	metabolite to parent ratio AUClast
MRC_{max}	metabolite to parent ratio of C_{max}
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
NCBI	National Center For Biotechnology Information
NC	Not Calculated
NCI	National Cancer Institute
NR	Not Reached
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival

Abbreviation	Meaning
p16INK4A	Cyclin-Dependent Kinase Inhibitor 2A
PALOMA	Palbociclib Ongoing trials in the Management of Breast Cancer
PD	Progressive Disease
PFS	Progression-Free Survival
Ph2P1	Phase II Part 1
Ph2P1+Ph2P2	Phase II Combined
Ph2P2	Phase II Part 2
PK	Pharmacokinetic(s)
popPK	population pharmacokinetics
PR	Partial Response
pRb	Retinoblastoma Susceptibility Gene Product
PrD	progressive disease
PRO	Patient Reported Outcome
QC	Quality Control
QD	Once Daily
QT	Time From Beginning Of QRS Complex To End Of T Wave In The Electrocardiogram
QTc	Corrected QT Interval
QTcB	Corrected QT Interval According To Bazett
QTcF	Corrected QT Interval According To Fridericia
QTcS	Corrected QT Interval According To Study-Specific Criteria
r2	Goodness-of-fit statistic from the regression
RANKL	Receptor Activator Of Nuclear Factor Kappa-B Ligand
Rb	Retinoblastoma
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase II Dose

Abbreviation	Meaning
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SCLC	small cell lung carcinoma
SNP	Single Nucleotide Polymorphism
SOC	System Organ Class
SOP	Standard Operating Procedure
sSAP	Supplemental Statistical Analysis Plan (for Biomarkers)
SSID	Study Subject Identification Number
Std Dev	Standard Deviation
$t_{½}$	Terminal Plasma Half-Life
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time To Maximum Plasma Concentration
TTP	Time To Progression
ULN	Upper Limit Of Normal
Vz/F	Apparent Volume Of Distribution
VGPR	Very Good Partial Response
WBC	White Blood Cell

1 Submission details

1.1 Identifying information

Submission number	PM 2016-01317-1-4
Sponsor	Pfizer Australia Pty Ltd
Trade name	Ibrance
Active substance	Palbociclib

This is an application to register a new chemical entity.

1.2 Drug class and therapeutic indication

This medicine is a first in class and stated to be a reversible, small molecule inhibitor of cyclin-dependent kinases (CDK) CDK4/ (cyclin D1) and CDK6/cyclin D2. CDK4/6 are downstream of multiple signalling pathways which lead to cellular proliferation, and palbociclib is postulated to prevent cellular proliferation by preventing G1 to S phase progression of the cell cycle.

The proposed indications taken from the Draft PI and Letter of Application dated 25 April 2016 are:

> *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 or metastatic breast cancer:*
>
> - with letrozole as initial endocrine-based therapy in postmenopausal women
> - with fulvestrant in women who have received prior therapy

1.3 Dosage forms and strengths

The following is taken from the Product Information:

Ibrance is supplied as hard gelatin capsules containing 75 mg, 100 mg or 125 mg of palbociclib as the freebase and the following excipients: microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, silicon dioxide and magnesium stearate.

1.4 Dosage and administration

The recommended dose of Ibrance is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days.

When coadministered with palbociclib, the recommended dose of letrozole is 2.5 mg taken orally once daily continuously throughout the 28-day cycle. Please refer to the full prescribing information of letrozole.

When coadministered with palbociclib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, 29, and once monthly thereafter. Please refer to the full prescribing information of fulvestrant.

Ibrance should be taken with food.

Patients should be encouraged to take their dose at approximately the same time each day. Continue the treatment as long as the patient is deriving clinical benefit from therapy.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Ibrance capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Prior to the start and throughout treatment with the combination palbociclib plus fulvestrant, pre/perimenopausal women should be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to local clinical practice.

1.4.1 Dose Modifications

Dose modification of Ibrance is recommended based on individual safety and tolerability.

Management of some adverse reactions may require temporary dose interruptions/delays, and/or dose reductions, or permanent discontinuation as per dose reduction schedules provided in Tables 1-3 below (same as Tables 6, 7 and 8 in Precautions and Adverse Effects in PI Attachment 1).

Table 1: Recommended dose modifications

Table 6. IBRANCE Recommended Dose Modifications for Adverse Events

Dose Level	Dose
Recommended dose	125 mg/day
First dose reduction	100 mg/day
Second dose reduction	75 mg/day*

*If further dose reduction below 75 mg/day is required, discontinue the treatment.

Table 2: Dose modifications and management Haematologic toxicities

Table 7. IBRANCE Dose Modification and Management – Haematologic Toxicities[a]

Monitor complete blood counts prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 14 of the first 2 cycles, and as clinically indicated.	
CTCAE Grade	**Dose Modifications**
Grade 1 or 2	No dose adjustment is required.
Grade 3	Day 1 of cycle: Withhold IBRANCE, repeat complete blood count monitoring within 1 week. If recovered to Grade ≤2, resume at the *same dose*. If Grade 3, hold initiation of next cycle until recovery to Grade ≤2. Resume at the *same dose*. If Grade 4, hold initiation of next cycle until recovery to Grade ≤2. Resume at the *next lower dose*. Day 14 of first 2 cycles: Continue IBRANCE at current dose. Repeat complete blood count on Day 21. If Grade 3 on Day 21, start subsequent cycles at the *same dose*. If Grade 4 on Day 21, start subsequent cycles at the *next lower dose*. Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia in the subsequent cycles.
Grade 3 neutropenia with fever ≥38.5°C and/or infection	Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose*.
Grade 4	Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose*.

Grading according to CTCAE 4.0 (Grade 1: ANC < LLN - 1500/mm^3; Grade 2: ANC 1000 - <1500/mm^3; Grade 3: ANC 500 - <1000/mm^3; Grade 4: ANC <500/mm^3).

ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; LLN-lower limit of normal.

[a] Table applies to all haematologic adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

Table 3: Dose modifications and management Non-haematologic toxicities

Table 8. IBRANCE Dose Modification and Management – Non-Haematologic Toxicities

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade ≥3 non-haematologic toxicity (if persisting despite medical treatment)	Withhold until symptoms resolve to: Grade ≤1; Grade ≤2 (if not considered a safety risk for the patient) Resume at the *next lower dose*.

Grading according to CTCAE 4.0
CTCAE=Common Terminology Criteria for Adverse Events.

No dose modifications are required on the basis of the patient's age, sex or body weight (see Pharmacokinetics).

Dosage Adjustment in Renal Impairment

No dose adjustments are required for patients with mild to moderate renal impairment (creatinine clearance [CrCl] ≥ 30 mL/min). Ibrance has not been studied in patients with severe renal impairment (CrCl <30 mL/min) or requiring haemodialysis (see Pharmacology – Pharmacokinetics – *Renal Impairment*).

Dosage Adjustment in Hepatic Impairment

No dose adjustments are required for patients with mild hepatic impairment (total bilirubin ≤1 x upper limit of normal [ULN] and aspartate aminotransferase [AST] >1 x ULN, or total bilirubin >1.0-1.5 x ULN and any AST). Ibrance has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and any AST) (see Pharmacology – Pharmacokinetics – *Hepatic Impairment*).

Dosage Adjustment in the Elderly

No dose adjustment is necessary in patients ≥ 65 years of age (see Pharmacology Pharmacokinetics *Elderly ≥ 65 years*).

2 Background

2.1 Information on the condition being treated

In Australia in 2016, breast cancer is predicted to be the 3rd most commonly diagnosed cancer overall, and the most common cancer diagnosed in Australian women (based on an analysis of the Australian Cancer Registry by the Australian Institute of Health and Welfare). In 2016, it was estimated that 3,073 Australian people will die from breast cancer (27 men and 3,046 women), making it the 4th most common cause of death from cancer.

Breast cancer is a heterogeneous disease and comprises several subtypes. Treatment options are determined mainly by whether the cancer is hormone receptor-positive (oestrogen receptor [ER] and/or progesterone receptor [PR]-positive) and whether or not human epidermal growth factor 2 (HER2) is overexpressed ('HER2-positive'). No Australian-specific data are available, but from the US SEER database, of breast cancers assessable for ER status, 73% were ER-positive/HER2-negative[1]). Women with metastatic disease will present either following relapse

[1] Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2012,

after diagnosis and treatment at an earlier stage (potentially including adjuvant endocrine or chemotherapy and/or radiotherapy) or with metastatic disease at diagnosis. Recent figures are not available, but the estimated rate of presentation with de novo metastatic disease is 6-10% (Harris et al, 1993).

Despite the use of systemic therapies which have resulted in improvements in overall survival, metastatic breast cancer is still regarded as an incurable condition, with a median survival after diagnosis of approximately 18-24 months (Wood et al, 2005). The aims of treatment are to improve survival, and to improve or maintain quality of life.

This application seeks registration for the treatment of postmenopausal women with advanced or metastatic HR-positive, HER2-negative breast cancer therefore the remainder of this background section will focus on agents available to treat this population with this particular subtype and stage of disease. Those with ER-positive/HER2-positivedisease have a different prognosis and treatment options.

The main treatment options for patients with metastatic ER-positive, HER2-negative breast cancer are systemic: endocrine therapy, chemotherapy, and targeted therapies (in combination). Additional modalities include palliative radiation therapy, surgery and supportive care measures such as analgesia. The choice of therapy depends upon the extent and location of metastases, the rate of disease progression and also symptom burden. For those with rapidly progressing disease and/or significant disease burden especially visceral metastases, chemotherapy (single agent or in combination) is usually commenced. Where there is no pending visceral crisis, endocrine therapy is the treatment of choice.

2.1.1 Endocrine therapies

Postmenopausal women have low levels of endogenous oestrogen, with the main source being derived from androgen conversion by aromatase enzymatic activity. Endocrine therapies aim to reduce or stop oestrogen production (for example, ovarian suppression, aromatase inhibitors), block signaling through the oestrogen receptor (for example, tamoxifen and fulvestrant) or antagonize ER (for example, fulvestrant). For women who are pre- or perimenopausal, suppression of ovarian function, either with LHRH analogues or bilateral oophorectomy, is required before commencing agents such as aromatase inhibitors and fulvestrant.

The choice of treatment incorporates consideration of any prior adjuvant therapies used/in use at the time relapse is identified. Generally those with de novo metastatic breast cancer or those relapsing >12 months after completion of adjuvant endocrine therapy would be offered first line endocrine therapy; while those relapsing within 12 months of completing adjuvant endocrine therapy or progressing on first line endocrine therapy would be eligible for second line endocrine therapy.

An aromatase inhibitor, either letrozole or anastrozole, is the initial treatment of choice. Exemestane is approved for second line use, either alone or in combination with everolimus (see below). Tamoxifen was demonstrated to be inferior to letrozole (Phase III Study 025- see TGA PI) but can be used first line where there are significant co-morbidities or prior intolerance preventing use of an aromatase inhibitor.

2.2 Current treatment options

The following list is confined to endocrine therapy-based regimens approved for use in postmenopausal women, either endocrine therapy alone or in combination with targeted

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National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015.

therapies, as this is the population in whom registration is being sought, with palbociclib being proposed as an add-on to two currently approved endocrine therapies (letrozole in the first line setting; fulvestrant after progression on prior endocrine therapy).

Currently approved endocrine treatment options in Australia for postmenopausal women with metastatic ER-positive, HER2-negativebreast cancer are:

2.2.1 First line (all approved for first line usage and beyond except toremifene)

2.2.1.1 Non-steroidal aromatase inhibitors

Letrozole is indicated for the 'treatment of advanced breast cancer in postmenopausal women with oestrogen/progesterone-receptor-positive disease' (TGA PI)

Anastrozole is indicated for the 'treatment of advanced breast cancer in postmenopausal women with oestrogen/progesterone-receptor-positive disease' (TGA PI)

2.2.1.2 Selective oestrogen receptor modulators (SERMs)

'Tamoxifen is indicated for the treatment of breast cancer. '(TGA PI)

Toremifene Fareston is indicated for first line treatment of hormone-dependent metastatic breast cancer in postmenopausal patients. Fareston is not recommended for patients with oestrogen receptor negative tumours. (TGA PI)

Comment: Toremifene is seldom used in Australia.

LHRH analogue

Goserelin is approved in Australia for the treatment of women with 'locally advanced or metastatic breast cancer in pre-menopausal women suitable for hormonal manipulation.' (TGA PI)

Comment:

1. The initial treatment of choice in postmenopausal women would be an aromatase inhibitor, either letrozole or anastrozole. If neither of these were tolerated then tamoxifen can be used.
2. Goserelin is not used as a single agent in this setting due to its limited efficacy, but is used in combination with tamoxifen in premenopausal women and also permits these women to commence aromatase inhibitors and fulvestrant which all require postmenopausal oestradiol levels to be efficacious. Comparisons of LHRH analog alone and in combination with aromatase inhibitors have not been studied. Caution has to be exercised to ensure that postmenopausal oestradiol levels are actually achieved.

2.2.1.3 Second line or beyond

Selection of second line endocrine therapy, subject to this being still the most appropriate option, may include the steroidal aromatase inhibitor, exemestane, alone or in combination with the mammalian target of rapamycin (mTOR) inhibitor, everolimus. Further options include fulvestrant monotherapy – combination therapies are being investigated within clinical trials.

Steroidal aromatase inhibitor

Exemestane is approved for the following indication: 'Aromasin is indicated for the treatment of oestrogen receptor-positive advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy.' (TGA PI)

Everolimus, was approved as second line therapy for 'Postmenopausal women with hormone receptor-positive, HER2 negative advanced breast cancer in combination with exemestane after

failure of treatment with letrozole or anastrozole.' (TGA PI)

Comment: Everolimus and exemestane in combination are associated with significant toxicities including pneumonitis, nausea, vomiting, stomatitis, diarrhoea as well as neutropenia, anaemia, thrombocytopenia and the risk of infection. Hyperglycaemia also may occur. These may be severe, dose-limiting and also have a detrimental effect on quality of life.

Fulvestrant was approved by the TGA on 6 March 2006 with the following indication: 'Faslodex is indicated for the treatment of postmenopausal women with hormone-receptor positive, locally advanced or metastatic breast cancer who have progressive disease following prior tamoxifen therapy.' (TGA PI). Fulvestrant is an oestrogen receptor antagonist that blocks ER dimerization and DNA binding, increases ER turnover, and inhibits nuclear uptake of the receptor.

Comments:

1. From a clinical perspective, this could include women who have received tamoxifen in the last 12 months in the adjuvant setting, or as treatment for their metastatic disease. In clinical practice in Australia, fulvestrant is usually offered following progression on an aromatase inhibitor as this is considered the standard of care for the treatment of metastatic ER-positive disease in postmenopausal women.
2. Initial trials submitted for registration compared a regimen using 250 mg of fulvestrant versus anastrozole and demonstrated comparable clinical outcomes; the EFECT study (not submitted for TGA evaluation) demonstrated comparability with the steroidal aromatase inhibitor, exemestane (Chia et al, 2008) As the results from the CONFIRM study comparing 250 mg versus 500 mg demonstrated improved PFS and OS with 500 mg (TGA Product Information), this is the dose used. 500 mg is the fulvestrant dose proposed for use in combination with palbociclib in the indication being sought in this submission.

Progestins

Megestrol acetate is approved as follows: 'Palliative treatment of recurrent inoperable or metastatic carcinoma of the breast (see DOSAGE). It should not be used in lieu of currently accepted procedures such as surgery, radiation or chemotherapy.' (TGA PI)

Comment: This is used occasionally as a palliative treatment after progression on all other treatments. There are significant side effects including the risk of thrombo-embolic events, fluid retention and weight gain.

2.2.1.4 Other

The use of oestrogens and androgens is not standard practice. Numerous clinical trials are underway comparing the addition of targeted therapies with endocrine therapies.

2.3 Clinical rationale

Despite improvements in overall survival with the use of systemic therapies, metastatic breast cancer is still regarded as an incurable condition, with a median survival after diagnosis of approximately 18-24 months (Wood et al, 2005). The goal of therapy in any setting is prolongation of progression-free and overall survival, and improvement in quality of life as well as to defer the need for subsequent treatments, which include chemotherapy with its associated toxicities and limited clinical benefit.

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 (Harvey et al, 1999), and the role of oestrogens in breast cancer aetiology and progression is well established. Even with the use of letrozole and other endocrine therapies, progression-free survival for postmenopausal women with hormone

receptor-positive, HER2-negative breast cancer at first relapse is generally less than one year, and less than eight months upon progression after prior therapy. Resistance to endocrine treatment may be present from the outset, or emerge during endocrine treatment. Once this occurs, the mainstay is chemotherapy with its relatively low response rates and significant toxicities and for most agents the patient requires regular trips to an outpatient setting for intravenous administration. Thus there is significant unmet need for an agent that improves response rates, duration of response, progression-free survival and overall survival and maintains quality of life for patients with this common cancer.

Palbociclib is a first in class CDK4/6 inhibitor and is stated to inhibit G1 to S phase progression of the cell cycle. Cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. In vitro studies demonstrate that palbociclib reduces cellular proliferation of oestrogen receptor (ER)-positive breast cancer cell lines by blocking progression of the cell from G1 into S phase of the cell cycle. In ER-positive breast cancer cell lines, sensitivity to palbociclib and its effects upon cell cycle and growth inhibition were associated with the presence of retinoblastoma (Rb) and upregulation of cyclin D1 as well as decreased CDKN2A. These gene expression findings are also associated with the luminal (ER positive) versus basal-like subtypes (ER-negative/PR-negative/HER2-ve) of breast cancer.

These results, together with published data about the interaction of oestrogens and CDKs and the important role of cell cycle-related proteins in the genesis and maintenance of breast cancer, provided a rationale for testing palbociclib in combination with agents such as letrozole. The clinical exploration of this combination is also supported by the safety profile of palbociclib.

Studies A5481010, A5481003 and A5481008 examined palbociclib in combination with letrozole for the treatment of postmenopausal patients with ER-positive, HER2-negative advanced (locally advanced or metastatic) breast cancer. Letrozole has been selected as background treatment as it is approved, considered a standard of care and commercially available for first line endocrine treatment. The combination with fulvestrant is proposed for those whose disease has progressed after initial endocrine therapy, and seeking to utilise the different mechanism of action of fulvestrant compared with aromatase inhibitors and improve the progression-free survival observed with fulvestrant alone.

There are no approved therapies for use in combination with aromatase inhibitors, nor in combination with fulvestrant in the first line and subsequent settings, respectively; thus this constitutes a novel treatment approach for the treatment of women diagnosed with metastatic HR-positive breast cancer.

2.4 Formulation

2.4.1 Formulation development

The Clinical Overview stated the following:

'The commercial formulation of palbociclib is an immediate-release free base capsule for oral administration at 3 palbociclib dosage strengths of 75 mg, 100 mg, and 125 mg. This formulation is being used in ongoing Phase III clinical trials and is administered under fed conditions. During the clinical development program, early clinical trials (Studies 1001, 1002, 1003, 1004, and 1010 [Phase I portion]) used hand-filled capsules containing the palbociclib isethionate salt drug substance (hereafter referred to as the isethionate capsule) at 5-mg , 25-mg , and 100-mg strengths. In these early trials, including Study 1003, the isethionate capsule was administered under minimal fasting conditions. The isethionate salt and drug product was not designed to be commercialized. Furthermore, their pharmaceutical properties were not acceptable for the commercial product. Additionally, an intravenous solution, an oral suspension, an oral solution, and capsule formulations with different dissolution levels and

active pharmaceutical ingredient particle sizes were developed to support bioavailability and clinical pharmacology studies, but not used in efficacy studies.'

Comment: It is noted that the 'pivotal' Phase I/II Study being submitted in support of the first line proposed usage used a formulation that differs from that used in the later Phase III trials, and also that the administration in that study was under 'minimally fasted conditions' - the recommendation, following results of 2 pharmacokinetic studies and resulting in a protocol amendment during Study 1008, now is to take palbociclib with food as this apparently 'eliminated the occurrence of low-liers' (Clinical Overview).

2.4.2 Excipients

Ibrance is supplied as hard gelatin capsules containing 75 mg, 100 mg or 125 mg of palbociclib as the freebase and the following excipients: microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, silicon dioxide and magnesium stearate.

The sponsor states in the following in the letter of application

The Ibrance formulation excipient lactose monohydrate is produced from bovine milk. The magnesium stearate is of vegetable origin. Gelatin in the capsule shells is produced from bovine bones and bovine hides. Module 3.2.A provides statements and declarations from the capsule shell, lactose and magnesium stearate suppliers. Module 3.2 .R. provides information on the ingredients of animal origin including the summary tables and EDQM TSE Certificates of Suitability for gelatin, compliant to the Ph. Eur monograph 1483: Products with risk of transmitting agents of animal spongiform encephalopathies.

2.5 Regulatory history

2.5.1 Australian regulatory history

This is the first submission for registration of palbociclib, a first in class CDK4/6 inhibitor, in Australia.

A presubmission meeting was held with the sponsor in October 2015, followed by subsequent communications. A review of the agreed minutes and letter from the sponsor dated 20 November 2015 indicates that there was extensive discussion between the TGA and the sponsor about possible strategies for efficient evaluation of the data

At the time of undertaking this evaluation and preparing this clinical evaluation report, according to the timelines provided by the sponsor in the cover letter, no regulatory agency would have received the full CSR for Study 1008 evaluation and all existing approvals for the first line usage at this time are conditional in nature, requiring confirmation from this Study (see below).

2.5.2 Orphan drug designation

Consistent with metastatic ER-positive breast cancer not being a rare disease, no orphan drug designation was sought.

2.5.3 Related submissions

N/A

2.5.4 Overseas regulatory history

2.5.4.1 USA

The current FDA label for Ibrance is as follows:

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

- letrozole as initial endocrine based therapy in postmenopausal women (1), or
- fulvestrant in women with disease progression following endocrine therapy.

The indication in combination with letrozole is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Timeline of regulatory approval and postmarketing requirements by the FDA

The Food and Drug Administration (FDA) granted palbociclib breakthrough therapy designation in April, 2013 based on preliminary evidence of clinical activity in women with metastatic ER-positive breast cancer.

On 3 February, 2015, the FDA granted accelerated approval for the following indication (taken from the FDA label):

Ibrance is a kinase inhibitor indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. This indication is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

The following postmarketing commitment was required by the FDA (taken from the approval letter dated 3 February 2015).

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

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

On 19 February, 2016 the FDA granted approval for Ibrance as indicated for the treatment of hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer in combination with fulvestrant in women with disease progression following endocrine therapy

The following postmarketing commitment was required by the FDA (taken from the approval letter dated 19 February 2016).

3040-1 Submit the final overall survival analysis with datasets from Trial A5481023, PALOMA-3 A double-blind, phase III trial of fulvestrant with or without palbociclib in pre- and post-menopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer

that progressed on prior endocrine therapy.

2.5.4.2 Canada

On 16 March 2016, Health Canada approved the use of Ibrance as follows:

Ibrance, indicated:

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

has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for Ibrance please refer to Health Canada's Notice of Compliance with conditions – drug products web site: http//www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

The following is taken from the Health Canada Summary Basis of Decision, accessed from the Health Canada website 25 July 2016 http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd-smd-2016-Ibrance-182048-eng.php.

On March 16, 2016, Health Canada issued a Notice of Compliance under the Notice of Compliance with Conditions (NOC/c) Guidance to Pfizer Canada Inc. for the drug product Ibrance. The product was authorized under the NOC/c Guidance on the basis of the promising nature of the clinical evidence, and the need for further follow-up to confirm the clinical benefit. Patients should be advised of the fact that the market authorization was issued with conditions.

Confirmatory studies

Study 1008 (PALOMA-2): A randomised, multi centre, double-blind, Phase III Study of Ibrance 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 anti-cancer treatment for advanced disease.

To confirm the clinical benefit of Ibrance for the treatment of these patients, as initial endocrine-based therapy for their metastatic disease, Pfizer Canada Inc. will submit the following:

The sponsor will submit as a Supplemental New Drug Submission-Confirmatory (SNDS-C) Study:

- High level results for Study 1008 (PALOMA-2). These results will be provided at their earliest availability. Pfizer has indicated that it will withdraw the indication should the primary endpoint of the Phase III trial not reach statistical significance.

The final study report for Study 1008 (PALOMA-2). This report will be submitted at its earliest availability.'

Comment: This conditional approval is restricted to those with metastatic ER-positive breast cancer that is, not locally advanced disease or hormone receptor-positive disease.

2.5.4.3 European Union

An application was lodged with the EMA on 30 July 2015 for the following indications:

Ibrance in combination with endocrine therapy is indicated for the treatment of

HR-positive, 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 sponsor provided an updated indication under consideration by the Rapporteurs pending assessment of the top-line summary of Study 1008 as providing adequate support.

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 or with fulvestrant in postmenopausal women, and with an aromatase inhibitor or with fulvestrant plus a luteinizing hormone-releasing hormone (LHRH) agonist in pre- or perimenopausal women.

A recommendation regarding marketing authorization by the Committee for Medicinal Products for Human Use (CHMP) is awaited.

2.5.4.4 Switzerland

An application was lodged with SwissMedic on 8 December 2015 for the same indication as sought in this application. No further details were provided.

2.6 Guidance and references used

Amir E, Miller N, Geddie W, et al. (2012) Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. J Clin Oncol **30**:587–592.

Chia, S., W. Gradishar, L. Mauriac, et al. 2008. 'Double-blind, randomised placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT.' J Clin Oncol 26(10):1664-1670.

Harris JR, Morrow M, Bonadonna G. Cancer of the breast. In: De Vitta VT Jr, Hellman S, Rosenberg SA, editors. Cancer. Principles and Practice in Oncology. 4th edition. Philadelphia, PA: JB Lippincott; 1993. p. 1264-1332.

Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. 2014;106(5) doi: 10.1093/jnci/dju055.

McCain, First-in-Class CDK4/6 Inhibitor Palbociclib Could Usher in a New Wave of Combination Therapies for HR+, HER2− Breast Cancer J Pharmacy and Therapeutics 2015 Aug; 40(8):511-20

Wood WC, Muss HB, Solin LJ, Olopade OI. Malignant Tumors of the Breast. In: DeVita VT Jr, Hellmann S, Rosenberg SA, editors. Cancer, Principle and Practice of Oncology, 7th Edition, Lippincott Williams and Wilkins; 2005; 1415-1477.

Health Canada website 25 July 2016 http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd-smd-2016-Ibrance-182048-eng.php.

2.7 Evaluator's commentary on the background information

ER-positive breast cancer is the most common subtype of this common cancer, and in the inoperable, locally advanced and metastatic settings is a serious, life-threatening illness. There is significant unmet need for new agents that are well tolerated and which improve clinical outcomes including PFS, OS, physical function and wellbeing in patients with this incurable stage of breast cancer. Palbociclib is an oral agent with a new mechanism of action, therefore potentially additionally offering convenience.

The proposed indications potentially encompasses a large proportion of patients newly diagnosed with locally advanced or metastatic ER-positive and/or PR-positive breast cancer and those with disease progression on currently available endocrine therapies, if it were approved. Given this is a new agent with a new mechanism of action, and is intended for the treatment of a common cancer, there need to be data and evidence to demonstrate efficacy and safety

satisfactorily for approval for either of the proposed indications.

The sponsor has elected to lodge an application with a 'top line summary' (TLS) from Study 1008, the pivotal Phase III study and is seeking registration for both indications in this application.

It is to be noted that Australia does not have a provisional registration pathway, and that the two overseas approvals for the first line usage to date have both been conditional (USA and Canada), requiring confirmation of clinical benefit from a large, randomised Phase III trial (PALOMA-2), and that the full CSR for this trial is not available for full clinical evaluation at this time, and has not been submitted to any regulator anywhere in the world.

3 Contents of the clinical dossier

3.1 Scope of the clinical dossier

Additional information requested by the Clinical Evaluator included the minutes from the presubmission meeting with the TGA in October 2015.

A request was made for the sponsor to provide the latest EMA reports and any questions from the EMA, together with the sponsor's responses to those questions answers in order to facilitate a more efficient review.

3.1.1 Clinical Studies

- 1 Phase I/II study: Study A5481003 CSR (safety updated in Summary of Clinical Safety (SCS), 90-day safety update, individual patient data)
- 1 Phase III study: Study A5481023 (Study 1023) with a CSR with data cut-off date 5 Dec 2014, and 2 updates of efficacy with data cut-off dates of 16 March, 23 Oct 2015; 1 safety update (90-day safety update as of cut-off date of 31 July 2015 updates the data in CSR and SCS)
- Top line summary and Tables from 1 Phase III Study A5481008 (Study 1008) (cut-off 26 Feb 2016) and 90-day safety update narratives blinded
- 90-day safety update includes data blinded as to treatment allocation from Study A5481027, an ongoing double-blind, placebo-controlled study of palbociclib in combination with letrozole for the treatment of previously untreated Asian postmenopausal women with ER-positive, HER2-negative advanced breast cancer; draft CIOMS blinded to treatment allocation also provided but not evaluable;
- Limited safety update from Study A5481010 An ongoing Phase I/II Study of the Efficacy, Safety and Pharmacokinetics of palbociclib as a single agent in Japanese Patients with Advanced Solid Tumors or in Combination With Letrozole for the First-Line Treatment of Postmenopausal Japanese Patients with ER (+) HER2 (-) Advanced Breast Cancer
- Data from 90-day safety update for Study A5481034 an ongoing expanded access study of palbociclib in combination with letrozole in advanced breast cancer; a Table of Contents with some limited hyperlinks, as well as some CIOMS watermarked draft are provided for some of these adverse events.

No Integrated Safety Summary was provided

3.1.2 Summary of Clinical Safety (SCS)

- This included safety reports:

  - for a total of 1640 patients with malignant disease, including advanced breast cancer, in 8 Pfizer-sponsored Phase I-III clinical studies of palbociclib;
    - Studies 1001, 1002, and 1010 Phase I Part 1 1003, 1023, 1004, 1034 and 1008;
  - from 17 Investigator-initiated research (IIR) studies;
- The safety summaries for all studies were updated by the 90-day safety update:
  - Almost but not entirely for Study A5481023;
  - in part for Studies 1003, 1010 [new data, more patients Ph1P2 and Phase II], and 1034 as well as the 17 IIR studies, Studies A5481003, A5481010, plus a further investigator-initiated studies
- This was superseded by the top-line summary for Study A5481008.
  - This was not the SCS document to which the 90-day safety summary referred (see below).

3.1.3 90-day safety update

- This document provided a cumulative safety information as of 31 July 2015 for those studies that were included in the Study 1023 sNDA SCS (Studies 1023, 1003, 1010 [Ph1P2 and Phase II], and 1034 as well as 17 IIR studies). That is, this provided a comparative update for the Summary of Clinical Safety which accompanied the supplementary new drug application (extension of indications) submitted to the FDA for Study 1023 sNDA and provided analyses of safety data from 7 Pfizer-sponsored Phase I-III clinical studies of palbociclib.
  - This is not the same Summary of Clinical Safety provided to the TGA which included 8 Pfizer-sponsored Phase I-III clinical studies of palbociclib. As a result:
    - no hyperlinks to the SCS included in this application were correct;
    - it could not be assumed that the SCS datasets to which it referred were identical to those provided to the TGA;
- Additional safety data were included from Studies 1008, 1027 and 25 IIR studies;
  - This was superseded by the top-line summary for Study A5481008.
- The 6-month Periodic Safety Update review included was superseded by the full 12-month document provided separately in the dossier.

3.1.4 Safety narratives/CIOMS

- Draft CIOMS from numerous Phase I, II and III Investigator-initiated trials (non-Pfizer) in a range of solid tumours, including use in the metastatic and adjuvant settings, and as monotherapy and in combination with chemotherapy, endocrine therapy. Some of these are blinded, other reports not; these data were accompanied by a Narrative Table of Contents but the absence hyperlinks limited the utility of this document.

3.1.5 Postmarketing data

- The first annual Periodic Safety Update Report 03-Feb-15 to 02-Feb-16;
- Safety specification of the Risk Management Plan

3.1.6 Product Information

- All data for the studies provided had been superseded by the data with later cut-offs in the dossier

3.1.7 Other data provided but not evaluated

Data from Study A5481004, a Phase I/II Open-Label Study of the Safety and Efficacy of PD-0332991 in combination with bortezomib and dexamethasone in patients with refractory multiple myeloma were provided but were not evaluated as the use in combination with 2 drugs and in a different disease does not provide supportive evidence for registration for the proposed usage. Should there be a submission for the treatment of myeloma or use with this combination in future, this study would require evaluation.

Data from the ongoing Phase III Study A5481027 was not evaluable for safety due to all events, draft CIOMS being blinded as to treatment allocation. Should this be submitted in support of an application in future, it would require a full evaluation at that time.

3.2 Paediatric data

No paediatric data are included which is acceptable given breast cancer is seldom seen in the paediatric age group.

3.3 Good clinical practice

This sponsor has stated that the studies were designed and monitored in accordance with the CRO's standard operating procedures (SOPs), which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki as amended by the 59th World Medical Association General Assembly in 2008.

Comment: It is noted in the FDA report for the original new drug application, that the Office of Scientific Investigations undertook an audit of the four highest accruing sites for Study 1003, and while it is stated in the FDA report that 'Major issues' were identified at one of the sites, individual assessments of each deviation, 'no patient was placed at significant risk and key study outcomes were not affected…a sensitivity analysis was performed removing all the patients from site 1001 (and) this analysis does not change the conclusions of the study as presented …' (FDA Medical review, p18, Supplement Number 000 accessed online 28 July 2016)

3.4 Evaluator's commentary on the clinical dossier

3.4.1 First line proposed usage:

The studies providing efficacy and safety data in the first line usage are a completed Phase I/II Study and an ongoing Phase III study. No clinical study report is available for the Phase III study which has not been previously evaluated by the TGA, and the data provided in the Phase III 'Top line summary' is very limited (see evaluation of Study A5481008 in Section 7 for further details):

- summaries of only 4/11 secondary endpoints are included;
- no secondary analyses based on blinded independent review for either the primary endpoint nor any secondary endpoints.

- The safety narratives/draft CIOMS provided for the Phase III study are all blinded to treatment allocation and therefore are not evaluable;
- the Statistical Analysis Plan provided is not finalized and does not incorporate all the amendments made during the study;

This is essentially the 'pivotal study' for this usage and the information provided are not considered sufficient in scope or detail to satisfactorily demonstrate safety and efficacy to support registration for an indication with very wide anticipated usage if approved in the 3rd most common cancer in Australia. It is noted this was a concern raised by the TGA prior to the dossier being submitted, and it is the view of the clinical evaluator following evaluation of the data provided.

3.4.2 Second line and beyond usage in combination with fulvestrant

Studies in support of the second-line usage with fulvestrant include a CSR for a Phase III study, and the 90-day update included in the dossier updates both the information in the main CSR and also the draft PI provided with the application. The information currently provided is not sufficient, but subject to the sponsor providing adequate responses to the clinical questions in section 12 as well as an updated PI, this could be considered adequate to support an application for second line usage for the treatment following progression in this common cancer.

3.4.3 Product Information draft

Only limited evaluation was possible as:

- All safety and efficacy data for the studies provided had been updated with the data with later cut-offs in the dossier

Overall the dossier does not provide an organised, well-coordinated presentation of the data for evaluation by the TGA. This is largely due to the inclusion of multiple updates of just some efficacy and safety outcomes for the pivotal studies (for example, Study 1023 and Study 1008) without integration into the summaries or the draft PI, the provision of documents intended to supplement and update other agencies at a different stage of evaluation, and the lack of any integrated safety summaries.

In particular, the 90-day safety update provided to the US provides a partial update to the Summary of Clinical Safety submitted to the FDA, which included fewer studies and which is different from the Summary of Clinical Safety included. As a result, although is hyperlinked to that document as a source reference for these data, none of the hyperlinks refer the evaluator to the corresponding data and it cannot be assumed that the data in the US SCS and the SCS submitted here are identical.

The TGA requested that the sponsor provide any reports from the European Medicines Agency, and the questions posed by that agency and the sponsor's responses to those questions.

The current draft cannot be evaluated fully and requires substantial updating and resubmission for evaluation.

4 Pharmacokinetics

4.1 Studies providing pharmacokinetic information

Table 4 shows the Pharmacokinetics studies submitted.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	Absorption	A5481016	Effect of multiple doses of itraconazole on the PKs of a single dose of palbociclib
	BA	A5481015	Absolute oral BA of palbociclib IR relative to IV administration
		A5481009	Relative BA of IR capsules formulated using differing particle sizes or an oral solution compared to an isethionate capsule
	BE of different formulations	A5481020	Bioequivalence of final Phase III formulation to the isethionate salt or initial Phase III form
		A5481022	The effect of particle size and lubrication level on the BA of palbociclib
		A5481040	The effect of particle size and lubrication level on the BA of palbociclib
	Food Effect	A5481021	Effects of high-, moderate- and low-fat meals on the BA of palbociclib
		A5481036	Comparison of final Phase III and HFI forms under fasted and fed conditions
	Dose proportionality	A5481032	Dose proportionality of 4 single oral dose levels of palbociclib in Japanese subjects
	Mass Balance	A5481011	ADME of palbociclib
PopPK	Target population	PMAR-EQDD-A548b-DP4-269	Palbociclib popPK in patients with cancer
PK in special popn	Target population	A5481003	PK of palbociclib and letrozole when administered in combination in postmenopausal women with advanced breast cancer
		A5481001	Single-dose and steady-state PK of oral palbociclib administered QD in

PK topic	Subtopic	Study ID	*
			patients with advance solid tumours
		A5481010	Single and multiple dose PKs of palbociclib when given as a single agent to Japanese cancer patients
	Hepatic impairment	A5481013	No information provided by Sponsor
PK inter-actions	Rifampin	A5481017	Effect of multiple doses of rifampin on the PK of a single oral 125 mg dose of palbociclib
	Modafinil	A5481039	Effect of multiple doses of modafinil on the PK of a single oral 125 mg dose of palbociclib
	Midazolam	A5481012	Effect of multiple doses of palbociclib on the PKs of a single, oral dose of midazolam
	Tamoxifen	A5481026	Effect of multiple doses of tamoxifen on the PK of a single oral 125 mg dose of palbociclib
	Effect of gastric pH	A5481038	PKs of palbociclib under fed conditions when given with and without famotidine, rabeprazole sodium, or Mi-Acid Maximum Strength Liquid
		A5481018	PKs of palbociclib under fasted conditions in absence and presence of rabeprazole

* Indicates the primary PK aim of the study. † Bioequivalence (BE) of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication. Popn populations BA Bioavailability

4.1.1 Summary of pharmacokinetics

Comment: It should be noted that 11 of the 21 studies that provided information regarding the PKs of palbociclib were undertaken in populations of solely Black or predominantly Black subjects. In addition, nine of these studies included only males and in the 2 studies in which females participated they represented less than 6% of the total population.

4.1.1.1 Analytical Methods

For the initial studies, a validated analytical method comprising liquid chromatography with tandem mass spectrometry (LC-MS/MS) was used to determine palbociclib levels in plasma. The lower limit of quantitation (LLOQ) for palbociclib was 2.50 ng/mL, and the standard curve range was 2.50 ng/mL to 2,500 ng/mL, using a sample volume of 25 µL. Following on from this

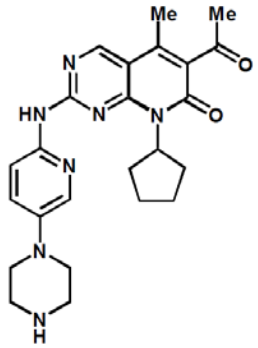
a second validated LC-MS/MS method was used to measure both palbociclib and its lactam metabolite, PF-05089326, in human plasma PK samples. The LLOQs for palbociclib and PF-05089326 were 1.00 ng/mL and 0.100 ng/mL, respectively. The standard curve ranges were 1.00 ng/mL to 250 ng/mL and 0.100 ng/mL to 25.0 ng/mL for palbociclib and PF-05089326, respectively, using a sample volume of 50 µL.

4.1.1.2 Physicochemical characteristics of the active substance

The following information regarding the physiochemical characteristics of palbociclib is taken from the proposed PI.

Australian Approved Name: Palbociclib
Chemical Structure (Figure 1).

Figure 1: Chemical structure



Chemical Name: 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

Molecular Formula: C24H29N7O2
Molecular Weight: 447.54 Daltons
CAS Registry: 571190-30-2

Description: Palbociclib is a yellow to orange powder with a pKa of 7.4 (secondary piperazine nitrogen) and 3.9 (pyridine nitrogen). The solubility of palbociclib in aqueous media decreases over the range pH 4.3 to pH 9.0. At or below pH 4, palbociclib behaves like a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly. The partition coefficient (1-octanol /water) at pH 7.4 is 0.99.

4.2 Pharmacokinetics in healthy subjects

4.2.1 Absorption

4.2.1.1 Sites and mechanism of absorption

The proposed formulation of palbociclib for marketing takes the form of an IR capsule that is to be taken orally with food. Following administration of a single oral dose of 125 mg of the final Phase III free base palbociclib capsule to healthy males, the median T_{max} occurred 8.08 h following dosing and the mean C_{max} and AUC_{inf} were 59.6 ng/mL and 1864 ng.h/mL, respectively. The mean $t_{1/2}$ was 22.05 h and the apparent volume of distribution (Vz/F) and apparent oral clearance (CL/F) values were 2114 L and 67.1 L/h.

4.2.2 Bioavailability

4.2.2.1 Absolute bioavailability

The absolute oral BA of a 125 mg IR capsule formulation of palbociclib, which contained the initial Phase III freebase, under fasted conditions relative to a 50 mg IV infusion was examined in 14 healthy males as part of Study A5481015. The results indicated that the estimated absolute oral BA of palbociclib was 45.69% (90% CI: 39.25%, 53.19%). In addition, following oral administration, palbociclib geometric mean (GM) CL/F and Vz/F were 86.3 L/h and 3017 L, respectively, whereas, following IV infusion, palbociclib GM CL and Vss were 39.5 L/h and 1008 L, respectively.

4.2.2.2 Bioavailability relative to an oral solution or micronised suspension

Study A5481009 compared the BA of a 50 mg dose of an oral solution of palbociclib to a 125 mg dose of the isethionate hard capsule IR formulation in 24 healthy males. The dose-normalised GMRs (solution/capsule) for AUC_{inf} and C_{max} were 92.78% (90% CI: 85.65%, 100.50%) and 85.68% (90% CI: 75.42%, 97.34%), respectively. Although the dose normalised AUC ratio fell within the bioequivalence (BE) limits (80%, 125%), the lower bound of 90% CI for dose-normalised C_{max} was below the lower bound of the BE limit. The median T_{max} values were 8 h for the solution and 6 h for isethionate hard capsule, whereas, the mean $t_{1/2}$ was similar for both treatments and ranged from 22.4 h to 22.7 h.

4.2.2.3 Bioequivalence of clinical trial and market formulations

A number of studies examined the BE of the various clinical trial and the to-be-marketed formulations. Possibly the most relevant of these, Study A5481020, examined the BE between a single 125 mg dose of the final Phase III commercial free base capsule and a 125 mg dose of either the initial Phase III free base capsule or the isethionate salt form of palbociclib (as a 25-mg capsule and a 100-mg hard capsules), which was used in the Phase 1/2 studies in subjects with cancer, under fasted conditions. The ratios (90% CIs) of the adjusted GMs (final Phase III/initial Phase3) of palbociclib AUC_{inf} and C_{max} were 103.44% (98.14%, 109.03%) and 101.24% (91.19%, 112.39%), respectively and as the 90% CIs for the ratios fell entirely within the BE limits (80%, 125%) the two formulations can be considered bioequivalent. In addition, the median T_{max} values were 6.00 h for both treatments and the mean $t_{1/2}$ was similar for the 2 treatments with mean values of 22.2 h and 22.7 h for the final and initial Phase III forms, respectively. For the second comparison, the ratios of the adjusted GMs (final Phase III/isethionate salt) of palbociclib AUC_{inf} and C_{max} were 94.80% (89.97%, 99.90%) and 84.78% (76.36%, 94.12%), respectively. Although the 90% CIs for the AUC_{inf} ratio fell entirely within the BE limits, the lower bound of 90% CIs for C_{max} was below the lower bound of the BE limit. The median T_{max} values were 6.00 h following both treatments and the mean $t_{1/2}$ values were 22.2 h and 22.4 h for the final Phase III and the isethionate salt forms, respectively.

Two studies, A5481022 and A5481040 examined the effects of particle size (standard and larger) and different levels of lubrication (Levels 1 – 3) on the PKs of the final Phase III capsules. In general, the PK parameters were similar between the different formulations with the AUC_{inf} ranging from 1138 – 1245 ng.h/mL, C_{max} from 28.0 – 36.7 ng/mL, $t_{1/2}$ from 25.3 h – 25.9 h, Vz/F from 3597 – 3992 L and CL/F 100.4 – 109.8 L/h. However, the median T_{max} appeared to occurr slightly later following administration of formulations with lubrication levels of 2 or 3 (6.00 h cf. 8.00). Statistical comparisons of the ratios of adjusted GMs (90% CI) for palbociclib AUC_{inf} indicated that in terms of AUC the different formulations were bioequivalent to final Phase III formulation with the standard particle size and lubrication level 1 as the 90% CIs for AUC were contained within the 80% to 125% equivalence limits. By contrast, the ratio of adjusted GMs (90% CI) of palbociclib C_{max} were 111.29% (91.48%, 135.41%) for API Level 1, 96.51% (79.32%, 117.42%) for API Level 2, 83.77% (68.90%, 101.86%) for API Level 3, relative to palbociclib API Level 1 formulation, indicating that in terms of C_{max} none of the formulations were bioequivalent to the palbociclib API Level 1 formulation.

One other study, A5481009, which has been previously described, compared the BA of two formulations of the initial Phase III capsules, formulated using palbociclib particle sizes of and , to capsules containing the isethionate salt. For the comparison of the freebase small particle capsule and the isethionate capsule, although the 90%CIs for palbociclib AUC_{inf} fell wholly within the BE limits (80%, 125%), the 90% CIs for C_{max} did not. By contrast, the isethionate capsule and the freebase large particle capsule were bioequivalent in regards to both the AUC and C_{max} values.

4.2.2.4 Bioequivalence of different dosage forms and strengths

No studies provided.

Comment: The current application is for the registration of 3 dosage strengths of IR capsules, which contain 75 mg, 100 mg or 125 mg of the final Phase III formulation of palbociclib. Although Study A5481032 examined dose proportionality between 4 single dose levels of palbociclib (75mg, 100 mg, 125 mg or 150 – 200 mg final Phase III capsule), no studies have been provided that examine the BE of these 3 dosage strengths nor has the Sponsor applied for a waiver of the requisite studies.

4.2.2.5 Bioequivalence to relevant registered products

Not applicable.

4.2.2.6 Influence of food

Two studies, A5481021 and A5481036, examined the influence of food on palbociclib PKs. The first of these studies, A5481021 estimated the BA of a single dose of palbociclib 125 mg (final Phase III form) administered 30 min after either a high-fat, high-calorie meal, a low-fat, low-calorie meal or a moderate-fat, standard calorie meal relative to that seen following a single dose of palbociclib 125 mg given under fasted conditions in 28 healthy males. The results indicated that following a high fat, low fat or moderate fat meal compared to fasted conditions the ratios (90% CIs) of adjusted GMs of palbociclib AUC_{inf} were 120.59% (112.61%, 129.14%), 111.81% (104.29%, 119.87%) and 113.13% (105.60%, 121.19%), respectively. Accordingly, the corresponding 90% CIs for the ratios of the adjusted GMs for AUC_{inf} were contained within the 80% to 125% BE limits when palbociclib was administered under fed low-fat (C) and fed moderate-fat (D) conditions but not under high-fat conditions. For C_{max}, the ratios (90% CIs) of adjusted GMs were 137.78% (120.55%, 157.47%), 127.08% (110.92%, 145.60%) and 124.04% (108.43%, 141.88%) for the high fat, low fat and moderate fat conditions, respectively, and the 90% CIs for the ratios of adjusted GMs for C_{max} fell outside the BE limits for the upper bound.

Study A5481036 compared the BA of a single oral dose of 125 mg palbociclib, formulated as the final Phase III capsule, 25 min after a moderate-fat, standard calorie meal relative to a 125 mg dose of the isethionate salt form following an overnight fast in 36 healthy males. Under these conditions, the ratios (90% CIs) of the adjusted GMs (fed/fasted) of palbociclib AUC_{inf} and C_{max} were 110.93% (106.65%, 115.38%) and 105.20% (100.54%, 110.07%), respectively. As the 90% CIs for the GMRs were completely contained within the (80%, 125%) BE limits the two formulations were bioequivalent.

Comment: It's interesting to note that the influence of food is not consistent between formulations. For instance, when the final Phase III and the isethionate forms were administered under fasted conditions they were not strictly bioequivalent as the 90% CIs for the GMR of C_{max} were not contained within the BE limits, whereas, when the final Phase III form was administered after a moderate-fat, standard calorie meal and the isethionate salt was administered under fasted conditions, as in Study A5481036, the two formulations could be considered bioequivalent in regards to both AUC and C_{max}.

4.2.2.7 Dose proportionality

The dose proportionality of 4 single oral dose levels of palbociclib (75mg, 100 mg, 125 mg or 150 – 200 mg final Phase III capsule) was examined in healthy Japanese volunteers in the fed state (Study A5481032). The results indicated that palbociclib AUC_{inf} and C_{max} increased with increasing dose from 75 mg to 150 mg with the increases appearing to be dose-proportional. Further evidence, which provided support for dose-proportionality, was presented in the form of the superimposition of dose normalised concentration-time profiles and box-plots of the individual C_{max}(dn) and AUC_{inf}(dn) demonstrating the relative consistency in the central tendency and range of the observed parameters across doses.

4.2.2.8 Bioavailability during multiple-dosing

No studies examined multiple dosing in healthy subjects.

4.2.2.9 Effect of administration timing

Not examined.

4.2.3 Distribution

4.2.3.1 Volume of distribution

Following administration of a single oral dose of 125 mg of the final Phase III capsule with a high fat, high-calorie breakfast in healthy subjects, the Vz/F (%CV) was 2114 L (17).

4.2.3.2 Plasma protein binding

Two *in vitro* studies, RR764-04174 and PF-05089326_17Dec12_104347, examined the binding of palbociclib to human plasma proteins. The results indicated that palbociclib is moderately bound to plasma proteins with an average protein binding of 85% as measured *in vitro* using equilibrium dialysis. By contrast, binding of palbociclib (500-5000 ng/mL) to human serum albumin and α1-acid glycoprotein was low, with mean values of 37.8% and 35.4%, respectively.

4.2.3.3 Erythrocyte distribution

The human blood-to-plasma concentration ratio for palbociclib was 1.63, suggesting a modest preferential distribution into blood cells relative to the plasma compartments. In addition, the Mass Balance study, (Study A5481011), identified low levels of radioactivity in red blood cells, compared with those in plasma and whole blood, indicating that the amount of radioactive moieties partitioning into erythrocytes was relatively small.

4.2.3.4 Tissue distribution

Based on the volume of distribution in can be assumed that palbociclib is highly distributed to the tissues.

4.2.4 Metabolism

4.2.4.1 Interconversion between enantiomers

Not applicable.

4.2.4.2 Sites of metabolism and mechanisms / enzyme systems involved

Three *in vitro* studies, PD-0332991_05Mar13_095443, PD-0332991_18Sep13_170350 and PD-332991_10Sep13_193503 examined the primary metabolic pathways of palbociclib. In human hepatocytes, palbociclib was primarily metabolised via oxidation, sulphonation, glucuronidation, and reduction. Experiments with human hepatocytes, liver cytosolic and S9 fractions, and recombinant sulfotransferase (SULT) enzymes indicated that metabolism of palbociclib was mediated mainly by CYP3A and SULT family 2A member 1 (SULT2A1) enzymes.

4.2.4.3 Non-renal clearance

In the Mass Balance study, three metabolites were responsible for 45% of the dose excreted in faeces. The sulphamic acid of palbociclib (M11, PF-06754233), was the major metabolite in all subjects accounting for 25.8% of the dose. One subject showed M11 as the only dominant faecal metabolite at 46% of dose. A carboxylic acid, M16, derived from sequential oxidative metabolism of the piperazine ring, was the next most abundant metabolite at 14.2% of dose, and M20, a cyclopentyl ring-hydroxylated metabolite of the lactam (M17), accounted for 5.0% of the dose. Palbociclib was present in faeces of 5 of the 6 subjects at levels ranging from 0.5% to 5.1% (with a mean of 2.3%) of dose. The formyl- and acetyl- derivatives of palbociclib, M26 and M12, respectively, were each present at 1.3% of dose.

4.2.4.4 Metabolites identified in humans: active and other

The Mass Balance study, (Study A5481011) that following a single dose of [^{14}C] palbociclib to healthy subjects, palbociclib was the primary drug-related material in circulation, accounting for 23.3% of the plasma radioactivity. M22 was the most abundant metabolite at 14.8% of circulating radioactivity. The other primary clearance metabolites M11, M26, and M12, were present at low levels (1.3%, 1.5%, and 1.0%, respectively). M16, a major faecal metabolite, was present in plasma at 2.6%, whereas M20 was not detected. Three minor radiochemical peaks characterised were 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. A single radiochemical peak (U) accounting for 6.2% of the circulating radioactivity did not yield an assignable mass spectrum.

Question: As M22 is the most abundant circulating metabolite (responsible for 14.8% of circulating radioactivity), does the Sponsor have information regarding its activity?

Active metabolite

The pharmacological activity of and systemic exposure to the circulating oxidative metabolite of palbociclib, PF-05089326, was investigated using *in vitro* techniques and as part of Studies A5481009 and A5481011. PF-05089326 was shown to have comparable potency with that of palbociclib for inhibiting CDK 4 (IC50=5.4 nM or 2.4 ng/mL) and CDK 6 (IC50=16.2 nM or 7.3 ng/mL) (Studies REG-RR 700-00180 and 75760087).

4.2.4.5 Pharmacokinetics of metabolites

Following a 125 mg dose of the initial Phase III, free base capsule with a particle size of to healthy males the C_{max} and AUC_{inf} values for PF-05089326 were 7.03 ng/mL and 110.8 ng.h/mL, respectively. PF-05089326 T_{max} was 4.00 h, representing metabolite formation and the mean $t_{1/2}$ value was 20.4 h. The metabolite to parent ratio, as reflected in MRAUC_{inf} value, was approximately 0.08.

4.2.4.6 Consequences of genetic polymorphism

Not examined.

4.2.5 Excretion

4.2.5.1 Routes and mechanisms of excretion

Following administration of [^{14}C]-palbociclib (125 mg containing approximately 100 µCi) to 6 healthy males, approximately 74% of the dose was excreted in faeces and 18% in urine. The amount of palbociclib excreted unchanged in the urine over the 192 h collection period was 6.9% indicating that urinary excretion was only a minor route for palbociclib elimination and the mean CLr was 5.9 L/h.

4.2.5.2 Mass balance studies

During Study A5481011, excreta samples were collected to at least 216 h post-dose for all six participating subjects. Excreta collection was continued for 2 subjects for up to 360 h post-dose. At the end of the collection period, the overall median mass balance of the radioactive dose excreted was 91.6%, with a median of 17.5% recovered in urine and a median of 74.1% recovered in faeces.

4.2.5.3 Renal clearance

The Mass Balance study identified that palbociclib and 2 isomeric mono-hydroxylated metabolites of palbociclib (M23a, M23b) were the major urinary components at 3.7% and 3.5%, respectively, of dose. The glucuronide of palbociclib (M22) was present in urine at 1.5% of dose. Two (2) radiochemical peaks (U) at retention times of 30.2 and 45.5 min representing 1.1% of dose, were not characterised by mass spectrometry.

4.2.5.4 Intra and inter individual variability of pharmacokinetics

The 2-compartment model population PK (popPK) model, which is described in PMAR-EQDD-A548b-DP4-269 and was developed based on a dataset that comprised 2208 PK observations from 184 cancer patients treated with palbociclib provided estimates for the inter-subject variability on CL/F, V2/F, inter-compartmental clearance (Q/F) and absorption rate constant (Ka) of approximately 36.2%, 30.2%, 126.1% and 83.6%, respectively. The intra-subject variability was estimated to be 0.317.

4.2.6 Pharmacokinetics in the target population

4.2.6.1 Breast cancer

Part of **Study A5481003** examined the PKs of palbociclib (125 mg QD isethionate capsules) when administered to steady-state in 12 postmenopausal women with ER-positive, HER2-negative advanced breast cancer. Results indicated that palbociclib appeared to reach steady-state exposures on or before Day 8, based on similar trough (pre-dose) concentrations on Day 8 through Day 14 in Cycle 1. When administered to steady state, the geometric mean CL/F and Vz/F of palbociclib were 63.08 L/h and 2583 L, respectively. In this population, the mean palbociclib C_{max}, AUC_{24}, $t_{1/2}$ and T_{max} values were 115.8 ng/mL 1982 ng.h/mL, 28.8 h and 7.9 h, respectively.

4.2.6.2 Other cancers

Two further studies, A5481001 and A5481010 examined the PKs of palbociclib in patients with advanced solid tumours, including some subjects with breast cancer. For instance, in Study A5481001 of the 74, predominantly White (n = 69), subjects who received at least 1 dose of palbociclib, six had breast cancer. The primary objectives of this study were to identify dose limiting toxicities (DLT) and maximum tolerated dose (MTD) following doses of 25 to 225 mg palbociclib QD for 14 to 21 days. Unfortunately, as some plasma samples were not obtained as per protocol, the planned PK analyses could not be performed. However, in 13 subjects who received either multiple doses of 125 mg or 200 mg palbociclib QD, plasma PK parameters could be determined (with the results for the 200 mg dose being corrected to the 125 mg dose level for reporting purposes) and indicated that the median T_{max}, mean $t_{1/2}$, Vz/F and CL/F values were 4 h, 26.5 h, 3103 L and 86.1 L/h, respectively; the accumulation ratio following multiple dosing was 2.4. Renal excretion of unchanged palbociclib was a minor route of elimination with approximately 1.7% of the drug excreted unchanged in urine over the 10 h collection period in the 125 mg and 200 mg dose group patients combined (CLR = 6.59 L/h). Study A5481001 also examined the effect of a high fat meal on the PKs of palbociclib and the results indicated that the adjusted GM palbociclib $AUC_{(0-10)}$ and C_{max} were higher in the fed state than in the fasted state ($AUC_{(0-10)}$: 370.5 vs. 290.5 ng.h/mL, respectively; C_{max}: 59.7 vs. 42.8 ng/mL, respectively). In terms of T_{max}, $t_{1/2}$, Vz/F and CL/F the results of this study were similar to the results of Study

A5481003.

4.2.7 Pharmacokinetics in special populations

Comment: The number of clinical trials that specifically examined the PKs of palbociclib in special populations was somewhat limited; therefore, the following discussion is primarily based on the results of the PopPK analysis PMAR-EQDD-A548b-DP4-269.

4.2.7.1 Pharmacokinetics in subjects with impaired hepatic function

Although **Study A5481013** examined the PKs of palbociclib in patients with hepatic impairment all that is provided in the evaluation materials in regards to this study is a SUSPECT ADVERSE REACTION REPORT.

Therefore, based on the PopPK analysis, which included 142 patients with normal liver function, 40 patients with mild hepatic impairment and 1 patient with moderate hepatic impairment, the liver enzymes including baseline alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and total bilirubin values were not significant covariates of palbociclib CL/F. Therefore the sponsor recommends that no dose adjustment is necessary for patients with mild hepatic impairment as defined based on the National Cancer Institute (NCI) scale.

Question: Can the sponsor please provide the complete clinical trial report for Study A5481013, which examined the effects of hepatic impairment on palbociclib PKs?

4.2.7.2 Pharmacokinetics in subjects with impaired renal function

No clinical studies specifically examined the effects of renal impairment on palbociclib PKs. However, given that renal clearance is responsible for approximately 6.9% of palbociclib excretion over a 192 h period after dosing, renal impairment is unlikely to significantly affect palbociclib PKs. This was confirmed in the PopPK analyses, which included 81 patients with normal renal function, 73 patients with mild renal impairment and 29 patients with moderate renal impairment and identified that creatinine clearance (range: 29-185 mL/min) was not a significant covariate on CL/F of palbociclib.

4.2.7.3 Pharmacokinetics according to age

Not examined.

4.2.7.4 Pharmacokinetics related to genetic factors

Not examined.

4.2.7.5 Pharmacokinetics in other special population/with other population characteristic

Race

Two studies examined the PKs of palbociclib in Japanese subjects. The first of these, **Study 5481032,** investigated the effect of ethnicity on the PK of a single oral dose of palbociclib 125 mg given under fed conditions to healthy Japanese subjects and demographic-matched healthy non-Asian subjects. The results indicated that although median T_{max} (6.05 h and 6.02 h) and mean $t_{1/2}$ values (22.8 h and 23.9 h) were similar in healthy Japanese and non-Asian subjects, palbociclib GM AUC_{inf} and C_{max} values were 30% and 35% higher, respectively, in Japanese subjects than in matched non-Asian subjects. Variability in palbociclib PK parameters was also similar between cohorts as the inter-subject variability (%CV) values for AUC_{inf} and C_{max} in Japanese subjects were 24% and 33%, respectively, and 26% and 39%, respectively, for the non-Asian population.

Study A5481010 examined palbociclib PKs following doses of 100 mg or 125 mg in a population of 12 Japanese patients with advanced solid tumours, including 3 patients with breast cancer. Following a single oral dose of 100 mg or 125 mg palbociclib, the median T_{max} occurred at 4-5 h

post-dosing. Mean $t_{1/2}$ values for the two doses were 25.7 and 23.9 h, respectively, and GM CL/F values were 96.4 and 50.3 L/h, and GM Vz/F were 3514 and 1730 L, respectively. After multiple oral doses of 100 mg or 125 mg palbociclib QD, the median T_{max} was generally achieved by 4 h post-dosing and the mean $t_{1/2}$ values were 23.8 h and 23.2 h, respectively, whereas, the accumulation ratios were 2.1 and 1.9 for the 100 mg and 125 mg dose groups, respectively.

Body weight

The PopPK analyses indicated that although baseline body weight (range: 37.9-123 kg) and age (range: 22-89 years) were significant covariates on CL/F, and baseline body weight was a significant covariate on apparent volume of distribution in the central compartment (V2/F), these covariates were not considered clinically significant.

4.2.8 Population pharmacokinetics

4.2.8.1 PopPK analysis ID

As previously described, Study PMAR-EQDD-A548b-DP4-269 outlined the development of a popPK model, which described the PKs of palbociclib in patients with cancer. Palbociclib PK was reasonably well characterised by a 2-compartment model and a typical cancer patient (i.e. body weight of 73.7 kg at age of 61 years old) was estimated to have a CL/F and V2/F of 60.2 L/h and 2710 L, respectively.

4.2.9 Pharmacokinetic interactions

4.2.9.1 Itraconazole – CYP3A4 inhibitor

Study A5481016 investigated the effect of multiple 200 mg QD doses of the CYP3A4 inhibitor, itraconazole on the PK of a single oral 125 mg dose of palbociclib in healthy subjects. The results indicated that although there was little change in median T_{max} values when palbociclib was administered alone (8.1 h) compared to when it was co-administered with itraconazole (7.4 h), mean palbociclib $t_{1/2}$ values increased from 22.1 h to 33.9 h following co-administration with itraconazole. In addition, the adjusted GM palbociclib AUC_{inf} and C_{max} values following co-administration of itraconazole were approximately 87% and 34% higher, respectively, compared to when palbociclib was administered alone. The apparent oral clearance of palbociclib decreased from 67.09 L/h when palbociclib was administered alone to 36.18 L/h when palbociclib was co-administered with itraconazole.

4.2.9.2 Rifampin – potent CYP3A4 inducer

Study 5481017 investigated the effect of multiple doses of 600 mg rifampin QD, a potent CYP3A4 inducer, on the PK, of a single oral dose of palbociclib 125 mg given under fasted conditions. The results indicated that following co-administration with rifampin, median palbociclib T_{max} decreased from 8.0 h to 3.0 h compared to when palbociclib was administered alone and mean $t_{1/2}$ decreased from 22.6 h to 7.8 h. In addition, palbociclib CL/F was approximately 6.3-fold higher following co-administration with rifampin compared to when palbociclib was administered alone and the ratios (90% CIs) of the adjusted GMs for palbociclib AUC_{inf} and C_{max} were 15.47% (12.03%, 19.88%) and 30.17% (23.51%, 38.72%), respectively.

4.2.9.3 Modafinil and pioglitazone - CYP3A inducers

Study A5481039 examined the effect of multiple 400 mg doses of the moderate CYP3A inducer modafinil on the PK of a single oral 125 mg dose of palbociclib administered in the fed state. This study also proposed to investigate the effect of multiple doses of the weak CYP3A inducer pioglitazone on the PK of a single oral 125 mg dose of palbociclib. Median palbociclib T_{max} occurred slightly later (approximately 2 h later) in the presence of steady-state modafinil compared to when it was administered alone and mean $t_{1/2}$ for palbociclib decreased from

approximately 22.8 h to 19.4 h in the presence of steady-state modafinil. By contrast, the GM apparent oral clearance of palbociclib increased from 69.48 L/h when palbociclib was administered alone to 102.5 L/h when co-administered with steady-state modafinil; the ratios of the adjusted GMs for palbociclib AUC_{inf} and C_{max} (90% CI) were 68.21% (61.62%, 75.51%) and 88.51% (80.55%, 97.25%), respectively, when palbociclib was co-administered with steady-state modafinil (Test) as compared to its administration alone. As the Sponsors considered that the effects of modafinil on palbociclib exposure were marginal, the study phases, which were to examine the effects of pioglitazone on palbociclib PKs, were not undertaken.

4.2.9.4 Midazolam – CYP3A4 substrate

Study A5481012 examined the effect of multiple doses of 125 mg palbociclib QD on the PKs of a single, 2mg, oral dose of midazolam in healthy women of non-childbearing potential. When midazolam was co-administered with palbociclib at steady-state, GM C_{max} and AUC_{inf} values for midazolam increased by 37.5% and 61.1%, respectively compared to when it was administered alone. By contrast, the median T_{max} values (0.5 h) for midazolam were the same whether midazolam was administered alone or with palbociclib, whereas, the mean $t_{1/2}$ value for midazolam was slightly longer with mean values of 7.2 and 8.2 h for midazolam alone and when co-administered with palbociclib, respectively.

Comment: Study A5481012 did not evaluate the effect of midazolam on palbociclib PKs.

4.2.9.5 Tamoxifen - CYP2D6 and CYP3A4 substrate

Study A5481026 evaluated the effect of multiple doses of 20 mg tamoxifen, which is used as a treatment for breast cancer and is a CYP2D6 and CYP3A4 substrate, on the PK of a single oral dose of 125 mg palbociclib in healthy males. For the full analysis set, the geometric mean ratios (GMRs) for C_{max} and AUC_{inf} were 1.20- and 1.13-fold, respectively, when palbociclib was co-administered with steady-state tamoxifen compared to when it was administered alone and the median T_{max} was 7.98 h and 6.10 h, respectively. As substantially lower exposure was observed in some subjects (low-liers), a second PK analysis was undertaken that excluded this group and for the population excluding low-liers, the GMR for C_{max} and AUC_{inf} were 1.16- and 1.08-fold, respectively, when palbociclib was co-administered with steady-state tamoxifen compared to when it was administration alone. A further PK analysis was conducted following the removal of 2 subjects who had been identified as poor metabolisers of CYP2D6 PMs; however, the exclusion of these subjects did not alter the interpretation of these results.

Comment: Study A5481026 did not evaluate the effect of palbociclib on tamoxifen PKs.

4.2.9.6 Letrozole – CYP2A6 and CYP3A4 substrate

Study A5481003 examined the PKs of palbociclib and letrozole, a substrate of CYP2A6 and CYP3A4, following co-administration of 125 mg and 2.5 mg QD, respectively, to postmenopausal women with ER-positive, HER2-negative advanced breast cancer. Co-administration of palbociclib with letrozole had no effect on the PKs of palbociclib at steady-state, compared to when palbociclib was administered alone; the GMRs for palbociclib AUC_{24} and C_{max} (90% CI) were 97.54% (90.16%-105.52%) and 93.60 % (84.24%-104.00%), respectively. Similarly, co-administration of letrozole with palbociclib had no effect on letrozole AUC_{24} (GMR [90% CI] = 89.84% [84.54%-95.47%]) or C_{max} (91.30% [85.21%-97.83%]), compared to when letrozole was administered alone.

4.2.9.7 H2-antagonists, PPI and antacids

Study A5481038 investigated the effect of: 20 mg famotidine (an H2-receptor antagonist) given 10 h before and 2 h after palbociclib; the protein pump inhibitor (PPI) rabeprazole sodium given 40 mg QD for 6 days before and 4 h prior to palbociclib; or 30 mL of the antacid Mi-Acid Maximum Strength Liquid given 2 h before or after palbociclib administration in healthy males. The results indicated that the GMRs for palbociclib AUC_{inf} and C_{max} (90% CI) were 96.02%

(87.90%, 104.89%) and 95.00% (79.23%, 113.90%), respectively following administration of palbociclib with famotidine relative to palbociclib administered alone. By contrast, following administration with the PPI, the GMRs for palbociclib AUC_{inf} and C_{max} (90% CI) were 86.85% (79.50%, 94.87%) and 59.18% (49.36%, 70.95%), relative to when palbociclib was administered alone. When antacid was administered either 2 h before or 2 h after palbociclib under fed conditions, the median T_{max} values for palbociclib increased slightly with values of 6.0 h, 8.0 h and 8.00 h for palbociclib alone, antacid 2 h before and 2 h after, respectively, whereas, there was little change in the AUC_{inf} and C_{max} values of palbociclib under either of these conditions as the 90% CIs for the GMR were contained within the (80%, 125%) BE limits.

Study A5481018 investigated the potential effect of increased gastric pH resulting from treatment with the PPI rabeprazole sodium 40 mg QD, on the PK of a single oral 125-mg dose of palbociclib given under fasted conditions. For the full analysis set population, co-administration of palbociclib plus QD rabeprazole decreased palbociclib exposures as measured by AUC_{inf} and C_{max} by approximately 56% and 75%, respectively and the median T_{max} was delayed (7.00 h cf. 24.0 h). By contrast, the mean $t_{1/2}$ was similar with values of 21.97 h when palbociclib was administered alone and 22.45 h when it was co-administered with rabeprazole.

The PopPK analysis, PMAR-EQDD-A548b-DP4-269, also examined the effects of co-administration of acid reducing agents, including proton pump inhibitors, H2 receptor antagonist and other types of antacids on the PKs of the palbociclib isethionate salt capsules and concluded that co-administration of these drugs with palbociclib did not significantly affect the relative BA or absorption of palbociclib.

4.2.9.8 Clinical implications of in vitro findings

Studies of human liver microsomes identified that palbociclib and its circulating metabolite, PF-05089326, demonstrated time-dependent inhibition of CYP3A enzyme(s). By contrast, further studies indicated that clinically relevant interactions were unlikely to occur with drug substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. In addition, palbociclib displayed low potential to inhibit CYP2A6 in human liver microsomes and it did not cause induction of CYP1A2, CYP2B6, CYP2C8, or CYP3A4 in human hepatocytes at concentrations exceeding the unbound palbociclib steady-state C_{max} at therapeutic doses in humans by greater than 50-fold. Palbociclib also showed low potential for inhibiting the activities of selected UGT enzymes (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) and transporters (P-gp, BCRP, OATP1B1, OATP1B3, BSEP, OAT1, OAT3, and OCT2) at clinically relevant concentrations.

4.3 Evaluator's overall conclusions on pharmacokinetics

4.3.1 ADME

- It is proposed that a single oral IR capsule dose of 125 mg dose of palbociclib be taken QD with food.
- Following a single oral dose of 125 mg of the formulation proposed for marketing to healthy males the T_{max}, C_{max}, AUC_{inf}, $t_{1/2}$, Vz/F and CL/F values of palbociclib were 8.1 h, 59.6 ng/mL, 1864 ng.h/mL, 22.1 h, 2114 L and 67.1 L/h.
- The absolute oral BA of a 125 mg IR capsule, which contained the initial Phase III freebase, under fasted conditions relative to a 50 mg IV infusion was 45.69% (90% CI: 39.25%, 53.19%).
- The dose-normalised GMRs (50 mg dose of an oral solution/125 mg dose of the isethionate hard capsule) for AUC_{inf} and C_{max} were 92.78% (90% CI: 85.65%, 100.50%) and 85.68% (90% CI: 75.42%, 97.34%), respectively.

- The final Phase III formulation of palbociclib 125 mg IR capsule, which is the formulation proposed for marketing, is bioequivalent to the initial Phase III formulation 125 mg IR capsule.
- Although the final Phase III formulation of palbociclib was bioequivalent in regards to AUC_{inf} to the isethionate salt, the lower bound of 90% CIs for C_{max} was below the lower bound of the BE limit (i.e. 80%, 125%).
- Following administration of 125 mg palbociclib (final Phase III form) with a high fat, low fat or moderate fat meal compared to fasted conditions, the GMRs (90% CIs) of palbociclib AUC_{inf} were 120.59% (112.61%, 129.14%), 111.81% (104.29%, 119.87%) and 113.13% (105.60%, 121.19%), respectively. For C_{max}, the GMRs (90% CIs) were 137.78% (120.55%, 157.47%), 127.08% (110.92%, 145.60%) and 124.04% (108.43%, 141.88%) for the high fat, low fat and moderate fat conditions, respectively.
- Following doses of 75mg, 100 mg, 125 mg or 150 – 200 mg of the final Phase III capsule palbociclib AUC_{inf} and C_{max} increased with increasing dose from 75 mg to 150 mg with the increases appearing to be dose-proportional.
- Following administration of a single oral dose of 125 mg of the final Phase III capsule with a high fat, high-calorie breakfast in healthy subjects the Vz/F (%CV) was 2114 L (17) indicating that that palbociclib is highly distributed to the tissues.
- Palbociclib is moderately bound to plasma proteins with an average protein binding of 85%. By contrast, binding of palbociclib to human serum albumin and α1-acid glycoprotein was low, with mean values of 37.8% and 35.4%, respectively.
- The human blood-to-plasma concentration ratio for palbociclib was 1.63, suggesting a modest preferential distribution into blood cells relative to the plasma compartments.
- In human hepatocytes, palbociclib was primarily metabolised via oxidation, sulphonation, glucuronidation, and reduction mediated by CYP3A and SULT2A1.
- The major metabolite in faeces was M11 (PF-06754233), which accounted for 25.8% of the radioactive dose. Other relatively abundant metabolites (≥ 5%) in the faeces included M16 and M20. Unchanged parent was also present in the faeces of 5 of 6 subjects at levels ranging from 0.5% to 5.1% (with a mean of 2.3%).
- Palbociclib was the primary drug-related material in circulation, accounting for 23.3% of the plasma radioactivity, whereas, the most abundant metabolite (M22) was responsible for 14.8% of radioactivity. Other metabolites identified in the circulation at levels of <5% of circulating radioactivity included M11, M26, M12, M16, PF-05089326, M24 and M25.
- PF-05089326 was shown to have comparable potency with that of palbociclib for inhibiting CDK 4 (IC50=5.4 nM or 2.4 ng/mL) and CDK 6 (IC50=16.2 nM or 7.3 ng/mL).
- Following a 125 mg dose of the initial Phase III, to healthy males, the C_{max} and AUC_{inf} values for PF-05089326 were 7.03 ng/mL and 110.8 ng.h/mL, respectively.
- The overall median mass balance of the radioactive dose excreted was 91.6%, with 17.5% recovered in urine and 74.1% recovered in faeces.
- Palbociclib, 2 isomeric mono-hydroxylated metabolites of palbociclib (M23a, M23b), the glucuronide of palbociclib (M22) and two other unidentified radiochemical peaks were identified in the urine at levels of < 5% of radioactive dose.
- The inter-subject variability on CL/F, V2/F, Q/F and Ka were estimated to be approximately 36.2%, 30.2%, 126.1% and 83.6%, respectively, whereas, intra-subject variability was estimated to be 0.317.

4.3.2 Pharmacokinetics in the target population

- Following QD dosing with 125 mg isethionate capsules in postmenopausal women with ER-positive, HER2-negative advanced breast cancer, palbociclib appeared to reach steady-state exposure on or before Day 8 and the steady-state GM CL/F and Vz/F of palbociclib were 63.08 L/h and 2583 L, respectively. The mean palbociclib C_{max}, AUC_{24}, $t_{1/2}$ and T_{max} values were 115.8 ng/mL 1982 ng.h/mL, 28.8 h and 7.9 h, respectively.
- In patients with advanced solid tumours, including some with breast cancer, the median T_{max} , mean $t_{1/2}$, Vz/F and CL/F values were 4 h, 26.5 h, 3103 L and 86.1 L/h, respectively and the accumulation ratio following multiple dosing was 2.4.

4.3.3 Pharmacokinetics in special populations

- Based on the PopPK analysis, liver enzymes including baseline alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and total bilirubin values were not significant covariates of palbociclib CL/F. Therefore the sponsor recommends that no dose adjustment is necessary for patients with mild hepatic impairment as defined based on the NCI scale.
- Given that renal clearance is responsible for approximately 6.9% of palbociclib excretion over a 192 h period and PopPK analysis identified that creatinine clearance (range: 29-185 mL/min) was not a significant covariate on palbociclib CL/F, mild or moderate renal impairment is not likely affect the PKs of palbociclib.
- In healthy Japanese and matched healthy non-Asians administered 125 mg palbociclib under fed conditions, the median T_{max} (6.05 h and 6.02 h) and mean $t_{1/2}$ values (22.8 h and 23.9 h) were similar. By contrast, palbociclib GM AUC_{inf} and C_{max} values were 30% and 35% higher, respectively, in Japanese.
- The PopPK analysis indicated that although baseline body weight (range: 37.9-123 kg) and age (range: 22-89 years) were significant covariates on CL/F, and baseline body weight was a significant covariate on V2/F, these covariates were not considered clinically significant.
- The popPK analysis identified that in patients with cancer, palbociclib PK was reasonably well characterised by a 2-compartment model and for a typical patient (i.e. body weight of 73.7 kg at age of 61 years old) CL/F and V2/F were estimated to be 60.2 L/h and 2710 L, respectively.

4.3.4 Pharmacokinetic interactions

- Compared to administration of 125 mg palbociclib alone, co-administration with steady-state itraconazole, a CYP3A4 inhibitor, resulted in increases in palbociclib $t_{1/2}$ (from 22.1 h to 33.9 h), AUC_{inf} (+87%) and C_{max} (+34%), whereas, palbociclib CL/F decreased from 67.09 L/h to 36.18 L/h.
- Compared to administration of 125 mg palbociclib alone, co-administration with steady-state rifampin, a potent CYP3A4 inducer, resulted in decreases in palbociclib T_{max} (8.0 h to 3.0 h), $t_{1/2}$ (22.6 h to 7.8 h), AUC_{inf} (-84.5%) and C_{max} (-69.8%), whereas, palbociclib CL/F was approximately 6.3-fold higher.
- Compared to administration of 125 mg palbociclib alone, co-administration with steady-state modafinil, a moderate CYP3A inducer, resulted in decreases in palbociclib $t_{1/2}$ (22.8 h to 19.4 h), AUC_{inf} (-31.8%) and C_{max} (-11.5%), whereas, palbociclib CL/F increased from 69.48 L/h to 102.5 L/h.
- Compared to administration of 2 mg midazolam, a CYP3A4 substrate, alone, co-administration with steady-state palbociclib (125 mg QD), resulted in increases in

midazolam C_{max} and AUC_{inf} of 37.5% and 61.1%, respectively.

- Co-administration of palbociclib with steady-state tamoxifen, a CYP2D6 and CYP3A4 substrate, had little effect on palbociclib exposure.
- Co-administration of palbociclib with letrozole had no effect on the PKs of palbociclib at steady-state, compared to when palbociclib was administered alone. Similarly, co-administration of letrozole with palbociclib had no effect on letrozole exposure.
- Under fed conditions, co-administration of palbociclib with famotidine, an H2-receptor antagonist, or the antacid Mi-Acid Maximum Strength Liquid did not affect palbociclib exposure, whereas, co-administration with multiple doses of the PPI, rabeprazole sodium, decreased palbociclib AUC_{inf} and C_{max} by 13.1% and 40.8%, respectively. Under fasted conditions, the PPI decreased palbociclib AUC_{inf} and C_{max} by approximately 56% and 75%, respectively.

Clinical implications of in vitro findings

- In vitro studies identified that palbociclib and PF-05089326 time-dependently inhibited CYP3A, whereas, clinically relevant interactions were unlikely to occur with drug substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2A6. Additionally, palbociclib did not induce CYP1A2, CYP2B6, CYP2C8, or CYP3A4 in human hepatocytes and also displayed low potential for inhibiting the activities of selected UGT enzymes (UGT1A1, UGT1A4, UGT1A6, UGT1A9 and UGT2B7) and transporters (P-gp, BCRP, OATP1B1, OATP1B3, BSEP, OAT1, OAT3 and OCT2).

4.3.5 Limitations of the clinical pharmacology studies

- The current application is for the registration of 3 dosage strengths of IR capsules, which contain 75 mg, 100 mg or 125 mg of the final Phase III formulation of palbociclib. No studies have been provided that examine the BE of these 3 dosage strengths nor has the Sponsor applied for a waiver of the requisite studies.
- No study data, other than the PopPK analysis, has been provided regarding effects of hepatic or renal impairment on the PKs of palbociclib.
- Although **Study A5481012** examined the effect of palbociclib on midazolam PKs, it did not evaluate the effect of midazolam on palbociclib PKs.
- Although **Study A5481026** examined the effect of tamoxifen on palbociclib PKs, it did not evaluate the effect of palbociclib on tamoxifen PKs.
- Many of the PK studies were undertaken in predominantly Black males. As palbociclib is indicated for the treatment of breast cancer and the Australian population is predominantly white it could be argued that the PK study population group is not representative of the target population in Australia.

4.3.6 Questions related to the PK studies

- Although Study A5481032 examined dose proportionality between 4 single dose levels of palbociclib (75mg, 100 mg, 125 mg or 150 – 200 mg final Phase III capsule), no studies have been provided that examine the BE of these 3 dosage strengths nor has the sponsor applied for a waiver for the required studies. Can the Sponsor please comment?
- As M22 is the most abundant circulating metabolite (responsible for 14.8% of circulating radioactivity), does the Sponsor have information regarding its activity?
- Can the sponsor please provide the complete clinical trial report for Study A5481013, which examined the effects of hepatic impairment on palbociclib PKs?

4.3.7 General Comments on the PK

Although, in general, the studies providing information regarding the PKs of palbociclib appear to have been undertaken according to TGA guidelines there were a number of notable shortcomings in the methodology or the populations examined. Most notably in 11 of the 21 PK studies provided the populations were solely Black or predominantly Black and very few if any female subjects were enrolled. As stated previously, as palbociclib is indicated for the treatment of breast cancer and the Australian population is predominantly white it could be argued that the PK study populations examined in these 11 trials are not representative of the drug's target population in Australia. In addition, the relative BE of the three proposed dose strengths of palbociclib have not been examined and no Biowaiver has been provided by the sponsor. Moreover, the summary report and results for the study which examined the PKs of palbociclib in hepatically impaired subjects have not been provided and crossover drug-drug interaction studies examining the effect of the midazolam on palbociclib PKs and palbociclib on tamoxifen PKs have not been undertaken.

5 Pharmacodynamics

5.1 Studies providing pharmacodynamic information

Note: Only the studies that have not been previously described in Table 4 (included PK data) have been summarised in Table 5.

Table5: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on biomarkers	A5481002	Compare biomarkers of CDKs 4/6 inhibition in tumour biopsies
Population PD and PK-PD analyses	Patients with advanced cancers	PMAR-EQDD-A548b-DP4-387	To explore the relationship between PFS and palbociclib exposure and attempted to identify potential prognostic factors
		PMAR-EQDD-A548b-DP4-271	To describe the effect of palbociclib on absolute neutrophil count
		PMAR-EQDD-A548b-DP4-286	To describe the effect of palbociclib on absolute thrombocyte count
		PMAR-EQDD-A548b-DP4-287	To characterise the effects of palbociclib exposure on the QT interval

*Indicates the primary PD aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

5.2 Summary of pharmacodynamics

5.2.1 Mechanism of action

Palbociclib is a highly selective inhibitor of cyclin-dependent kinase (CDK) 4/cyclin D1 (CCND1) kinase activity as well as the redundant CDK 6/cyclin D1 kinase. 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 D-type cyclins in early G1 phase. The only known natural substrate for CDK 4 and CDK 6 activity is retinoblastoma susceptibility gene product (Rb), which mediates G1 arrest through sequestration of transcriptional factors of the heterodimeric transcription factor (E2F-DP) family. 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 requisite genes for S-phase entry. Therefore, inhibition of CDK 4 and CDK 6 activation prevents cellular DNA synthesis and thus inhibits cell division. Non-clinical data has also indicated that palbociclib may be expected to cause both growth arrest as well as a potential secondary cytoreductive effect.

5.2.1.1 Assays for primary PD effects

Immunohistochemical identification of biomarkers in tumour biopsies

In order to assess the extent to which palbociclib is pharmacologically active against molecular targets in tumour cells, immunohistochemistry analysis of paired serial tumour biopsy specimens was performed to measure changes in intra-cellular biomarkers associated with cellular growth and division. These biomarkers included: the phosphorylation status of Rb protein, levels of the proliferation marker Ki-67 and levels of the cell cycle associated protein cyclin D1.

The percent reduction in phospho-Rb between the screening and Day 21 tumour biopsies was calculated for each subject and was an endpoint for proof of mechanism. If ≥ 50% reduction in phospho-Rb at the serine-780 site in >30% of the evaluable subjects was seen, proof of mechanism was considered to be achieved. The percentage of subjects with ≥ 60%, ≥ 50%, ≥ 40% and ≥ 30% reduction in phospho-Rb was provided. In addition, the mean change from baseline to Day 21 in percent of cells expressing phospho-Rb was analysed using a paired-differences t-test.

The mean change from baseline to Day 21 in the composite score (sum of each intensity category x percent of cells in that category) for Ki-67 and cyclin D1 were analysed using a paired-differences t-test. If other tumour biopsy biomarkers were collected, they were summarised appropriately (mean change, percent change, etc.).

Identification of biomarkers in in situ lesions using positron emission tomography (PET)

A screening PET was used to determine evaluable index lesions for each subject. Tumour background ratios (TBR) and development of new sites of abnormality were recorded. Whenever possible, both FLT-PET and FDG-PET scanning were performed within the same timeframe, and both assessments were done at screening and then during the first treatment cycle.

FDG-PET can be used to identify hotspots of cellular metabolism, which provides information about possible cellular proliferation and cell death; however, FDG does not convey an actual measurement of cancer cell proliferation. In regards to FLT-PET, the primary mechanism for its specificity for cell proliferation is in its relationship to thymidine kinase 1, which sequesters FLT for phosphorylation and is hyper-expressed in multiplying cells. This relationship has been demonstrated in studies involving brain, breast and lung tumours.

The repeated measures hierarchical model was used to analyse the mean change from baseline

to Cycle 1 Day 21 in the natural log of the maximum standard uptake value (SUVmax) for [^{18}F]-FDG-PET and [^{18}F]-FLT-PET. If, for either parameter, the upper end of individual 60% CIs were below 0 and at least 30% of the CIs achieved this criteria, the primary endpoint for proof of mechanism using PET was considered to be achieved. All paired baseline and Cycle 1 Day 21 SUVmax measurements were used where baseline FLT-PET SUVmax ≥ 2.0, and FDG-PET SUVmax ≥ 5.0 for liver lesions and ≥ 3.5 for other lesions.

Efficacy - Response Evaluation Criteria In Solid Tumours (RECIST)

Disease and response assessments were defined by RECIST, which is a set of guidelines that define when tumours in cancer patients improve ('respond'), stay the same ('stabilize'), or worsen ('progress') during treatment. Changes in tumour size were categorised as complete response (CR), partial response (PR), stable disease (StD) or progressive disease (PrD); the latter incorporating the appearance of new lesions. Confirmation of responses was to be done no less than 4 weeks after the response was initially documented. Bone marrow assessments were to be completed to confirm CRs in NHL patients.

5.3 Pharmacodynamic effects

5.3.1 Primary pharmacodynamic effects

Comment: No dedicated PD studies examined the primary PD effects of palbociclib in the target population of patients with HR-positive, HER2-negative advanced or metastatic breast cancer.

5.3.1.1 Biomarker analysis of tumour biopsies

Study A5481002 evaluated and compared biomarkers of CDKs 4/6 inhibition in tumour biopsies with [^{18}F]-FDG-PET, [^{18}F]-FLT-PET, and anti-tumour activity following 125 mg palbociclib QD in subjects with mantle cell lymphoma (MCL). The results indicated that all 10 subjects who had percent phospho-Rb positive measurements available at baseline and following 21 days treatment with palbociclib (Cycle 1) had ≥ 50% change from baseline, while 9 (90%) of these subjects had ≥ 60% change from baseline and mean (SD) percent change from baseline was -89.49 (14.80). There was also a reduction in mean total Rb percent positive cells between baseline (87.8%) and Cycle 1 Day 21 (75.5%). The small magnitude of change, while statistically significant (p=0.0142), does not account for the large and significant decrease seen in the mean phospho-Rb percent positive cells seen at baseline versus Cycle 1 Day 21. Paired t-test results for phospho-Rb percent positive cells, Ki-67 composite score, and cyclin D1 composite score (baseline versus Cycle 1 Day 21) indicated that there were clinically significant decreases in mean phospho-Rb percent positive cells and Ki-67 composite score at baseline versus Cycle 1 Day 21, but not cyclin D1.

5.3.1.2 PET screening of lesions

As part of Study A5481002, PET studies were undertaken to determine levels of tumour biomarkers prior to and after 21 days treatment with palbociclib. The results indicated that FLT-PET and FDG-PET SUVmax were correlated at both baseline and Cycle 1 Day 21, with r=0.615 and 0.766, respectively (p≤0.0001 for both). The correlation between FLT-PET and FDG-PET SUVmax percent change from baseline to Cycle 1 Day 21 was 0.406 (p=<0.0001).

For FLT-PET, 15/17 (88.2%) had a 60% CI below 0. For FDG-PET, 14/17 (82.4%) had a 60% CI below 0. In terms of PET response for FLT, 15 patients were considered partial responders to treatment, 2 patients had stable disease and no patients had disease progression. For FDG, 7 patients were considered partial responders, 10 patients had stable disease and as for FLT no patients had progressive disease.

PET response determined at Cycle 1 Day 21 showed a trend towards decreased uptake post treatment with anti-tumour activity. However, the relationship between PET response on Cycle 1 Day 21 and objective response at the end of the study was not significant (Kappa=0.0638 and 0.1864 for FLT-PET and FDG-PET, respectively).

The correlations between mean change from baseline to Cycle 1 Day 21 in FLT-PET and FDG-PET SUVmax versus mean change from baseline to Cycle 1 Day 21 in phospho-Rb percent positive cells were -0.250 and 0.136, respectively (p=0.4854 and p=0.7090, respectively). The correlations between mean change from baseline to Cycle 1 Day 21 in FLT-PET and FDG-PET SUVmax versus mean change from baseline to Cycle 1 Day 21 in Ki-67 composite score were 0.562 and -0.265, respectively (p=0.2454 and p=0.6112, respectively). The correlations between mean change from baseline to Cycle 1 Day 21 in FLT-PET and FDG-PET SUVmax versus mean change from baseline to Cycle 1 Day 21 in cyclin D1 composite score were -0.083 and 0.435, respectively (p=0.8756 and p=0.3891, respectively).

5.3.1.3 Efficacy - RECIST

In terms of RECIST, Study A5481002 indicated that a total of 3 subjects achieved a best response of PR (2 subjects [12.5%]) or CR (1 subject [6.3%]). The overall ORR was 18.8% (95% CI: 4.0% to 45.6%). Seven subjects (43.8%) had a best response of stable disease/no response. Both median TTP and PFS were 5.5 months (95% CI: 2.0 to 18.6 months). The probability of being event-free at Month 12 was 36.4% (95% CI: 11.1 to 61.6%).

Following treatment with QD doses of 25 mg to 225 mg palbociclib (Study A5481001) in 74 patients with advanced solid tumours, including six diagnosed with breast cancer, one patient (who had testicular cancer and was on the 14/21 day dosing schedule) had a confirmed 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 StD 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 StD 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 StD for 10 or more cycles. At the time of data cut off for this report, 5 patients (2 on the 21/28 day schedule and 3 on the 14/21 day schedule) had StD (having received between 20 and 39 cycles of treatment) and were continuing to receive study drug. No patient achieved a complete response. There were no notable differences in response between the 14/21 day and 21/28 day dosing schedules. The numbers of patients in the different tumour-type subgroups are too small to comment on any potential differences in efficacy.

Following 3 weeks of QD dosing with 100 mg or 125 mg palbociclib (Study A5481010) in 12 Japanese patients with advanced solid tumours, including 3 patients with breast cancer, no objective responses (CR/PR) were reported. The best overall tumour response was stable disease in 3 patients in the palbociclib 100 mg group and 1 patient in the palbociclib 125 mg group. Among them, StD ≥ 24 weeks was observed in 1 patient with rectal cancer in the palbociclib 100 mg group and 1 patient with oesophageal carcinoma in the palbociclib 125 mg group. The best overall tumour response was indeterminate (discontinued the study for the reasons other than disease progression) in 1 patient in the palbociclib 100 mg group.

5.3.1.4 Progression free survival (PFS)

PopPK-PD analysis PMAR-EQDD-A548b-DP4-387 explored the relationship between PFS and palbociclib exposure and attempted to identify potential prognostic factors (covariates) for PFS. The dataset for this analysis was taken from Study A5481003 which examined the PKs and efficacy of palbociclib when given alone and in combination with letrozole in postmenopausal women with ER-positive, HER2-negative advanced breast cancer. The subsequent exposure response analyses were conducted using 2 datasets: one included the data from both the letrozole alone (control arm) and the palbociclib plus letrozole arm (test arm) and one included data from only the palbociclib plus letrozole arm (test arm). A stronger ER relationship was found when data from both arms (control and test arms) were used, while a weaker

relationship was found when the data from only the test arm were used. It should be pointed out that by using the data from only the palbociclib plus letrozole arm, the effect of drug exposure on PFS could not be adequately characterized due to the issues of the confounding effects of other prognostic factors and the small sample size.

Subject data were then divided into two groups according to low and high palbociclib exposure with the high exposure group receiving ~18.5% higher daily doses than the low exposure group. CL/F was also ~34.5% lower in the high exposure group compared to the low exposure group, whereas, the mean (SD) C_{avg} values in the low and the high groups were 47.7 (9.71) and 85.2 (30.0) ng/mL, respectively. As a result of both the higher dose intensity and a lower CL/F in the high exposure group, the mean C_{avg} in the high exposure group was 78.7% higher than that in the low exposure group.

Overall, the baseline demographic and other clinical characteristics (laboratory values, tumour size, etc.) were similar between the two exposure groups; however, the baseline tumour size was higher and the lymphocyte counts were lower in patients within the low exposure group and it should be noted that these differences may influence estimation of the drug exposure effect on PFS.

The median survival time obtained from Kaplan Meier analysis in the letrozole alone, the low, and the high palbociclib exposure group was 10.2, 17.3, and 24.4 months, respectively, which not only suggested that PFS improved as palbociclib exposure increased, but also that PFS was improved in both the low- and high-exposure groups compared to the group receiving letrozole alone.

In order to evaluate the impacts of the confounding factors of tumour size and lymphocyte count on the estimate of palbociclib exposure effect on PFS, the hazard ratios between the high and the low exposure groups were compared by the univariate and the multivariate analyses. After excluding the patients who had missing baseline tumour size values, the estimated hazard ratios of the high exposure to the low exposure group were 0.698 and 0.796 by the univariate and the multivariate analyses, respectively. These results suggest that after accounting for the prognostic factors, a positive trend between palbociclib exposure and PFS was still observed, as evidenced by the fact that the hazard ratio between the high and the low exposure group was less than 1 in the multivariate analysis.

When time-varying C_{avg} was used in the multivariate analysis, the estimated slopes of the C_{avg}, the baseline lymphocyte count, the baseline AST value, and the baseline tumour size value were -0.0157 ng/mL, -0.704 10^6/mL, 0.0152 U/L, and 0.00409 mm, respectively. In addition, the estimate of the palbociclib exposure effect on PFS was slightly stronger (C_{avg} coefficient -0.0157 vs. -0.0149 ng/mL) when a time-varying C_{avg} was used rather than when a constant C_{avg} over treatment duration was used.

Based on the Akaike information criteria (AIC), a log-normal distribution best described the PFS event time and was used for the parametric analysis. The parametric analyses confirmed that C_{avg}, baseline lymphocyte count, baseline AST value, and baseline tumour size value were significantly associated with the PFS. The intercept, the coefficients for C_{avg}, baseline lymphocyte count, baseline AST value, and baseline tumour size value were 1.699, 0.0146 ng/mL, 0.613 10^6/mL, -0.0113 U/L, and -0.00287 mm, respectively.

5.3.2 Secondary pharmacodynamic effects

5.3.2.1 Effect on white blood cells

PopPK-PD analysis PMAR-EQDD-A548b-DP4-271 was undertaken to establish a popPK-PD model that described the longitudinal observations of absolute neutrophil count (ANC) in patients with advanced cancer on treatment of palbociclib based on pooled data from Studies A5481001, A5481002 and A5481003. The results indicated that longitudinal ANC observations

were well described by a sequential linked PK-PD model. In combination with the previously described popPK model, PMAR-EQDD-A548b-DP4-269, it was estimated that the drug concentration required to produce 50% of the maximum effect (EC50) was 37.7 ng/mL which was much lower than the mean average concentration at steady state with 125 mg daily dosing, 86.5 ng/mL, derived from the population typical value of CL/F 60.2 L/h in patients. Following administration of 125 mg palbociclib once daily in 3/1 schedule, the population mean of ANC nadir was estimated to be approximately 1.18×109/L for a female patient with BALB value of 3.90 g/dL, and the nadir occurred on Day 22 in Cycle 1. Due to the repeated pattern, the nadir in each cycle happened around the same time with the similar nadir value. The analysis also provided estimates that the baseline ANC value of a typical male patient was 34.9% higher than that of a typical female patient and that baseline albumin levels (BALB) appeared to be inversely correlated with ANC values. For instance, relative to the baseline ANC for a patient with median value 3.90 g/dL of BALB in the study population, the baseline ANC is increased by 68.1% if the BALB value is decreased to 2.4 g/dL.

5.3.2.2 Effect on platelets

PopPK-PD analysis PMAR- EQDD-A548b-DP4-286 was undertaken to establish a popPK-PD model that described the observed absolute thrombocyte count (ATC) in patients with advanced cancer over the duration of palbociclib treatment in data pooled from Studies A5481001, A5481002 and A5481003. Given the known anti-proliferative action of palbociclib as a cell cycle inhibitor, the model assumed that palbociclib suppressed the proliferation rate of stem cells. Therefore, a semi-mechanistic myelo-suppression model was developed using a linear function that successfully described the thrombocyte time-course following palbociclib therapy. Thrombocytopenia profiles were also well characterised when several treatment cycles were modelled continuously in time, and they were applicable to different schedules of administration. A relationship between plasma palbociclib concentration and thrombocyte levels in plasma was identified with higher doses of palbociclib being associated with lower ATC time profiles. Baseline albumin value (range: 2.4-4.89 g/dL) was a statistically significant covariate on $CIRC_0$ with higher baseline albumin concentration associated with lower $CIRC_0$ value. According to the model parameter estimates based on the current analysis data, the lowest thrombocyte counts on Cycle 1 were achieved on Day 21 (167.1 x 10^9/L) for a patient with baseline albumin concentration value of 3.95 g/dL, whereas nadir was reached on Day 24 of Cycle 2 (161.9 x 10^9/L) for a patient with the same baseline albumin following administration of 125 mg palbociclib once daily with a schedule of 3 weeks on treatment and 1 week off treatment.

5.3.2.3 QT

Study PMAR-EQDD-A548b-DP4-287 was undertaken in an attempt to characterise the effects of palbociclib exposure on the QT interval (QTc or heart rate-corrected QT) based upon 3593 individual QT records and 1904 concentrations obtained from 185 cancer patients and to assess whether palbociclib exposure affects heart rate (via effect on RR). The analysis identified that individual QT and RR values were strongly correlated, suggesting that RR is a confounding factor on QT change. Therefore, in order to adequately evaluate the drug effect on QT, the correlation between QT and RR needed to be corrected and among the correction factors tested, QTcS was found to be the best in minimising this correlation. PK results from Study A5481003 were then used to determine the maximum palbociclib concentrations at steady state (c) in patients receiving a therapeutic regimen of 125 mg palbociclib QD for 3 weeks on/1 week off and in combination with 2.5 mg letrozole QD. In this study, the median and mean c values were 107 and 112 ng/mL, respectively. Further analysis identified a slightly positive linear relationship between palbociclib concentration and QTcS and following therapeutic doses (125 mg QD) in cancer patients the mean (90% CI) QTcS increase as compared with baseline at the mean and median palbociclib c were 5.60 (2.48-8.72) msec and 5.88 (2.61-9.16) msec, respectively. However, as the upper bound of the one-sided 95% confidence interval for the

increase in QTcS did not exceed the threshold of 10 msec; therefore, QT prolongation is not a major safety concern for palbociclib at the recommended therapeutic dose. A similar palbociclib concentration dependent QTc effect was also observed when QTcF was used in the analysis.

Question: Given that at the mean and median c following QD dosing with 125 mg palbociclib the upper bounds of the 90%CIs for QTcS range from +8.72 to +9.16 msec and therefore are relatively close to the 10 msec threshold, is it possible that co-administered drugs that increase palbociclib exposure even by as little as 20% to 30% will possibly result in major safety concerns?

5.3.3 Time course of pharmacodynamic effects

Please see the preceding PD sections of this report.

5.3.4 Relationship between drug concentration and pharmacodynamic effects

5.3.4.1 Plasma concentration and PFS

As stated previously in this report there was some evidence to suggest that PFS was improved in patients with higher levels of palbociclib exposure.

5.3.4.2 Plasma concentration and biomarker expression

Study A5481002, described previously, examined the relationships between palbociclib plasma concentrations and the change from baseline in biomarkers including Ki-67 composite score, cyclin D1 composite score and the number of phospho-Rb positive cells following 21 days of treatment. Although, for phospho-Rb there appeared to be a trend towards larger changes from baseline at higher plasma concentrations (n=10), no clinically significant correlations were identified and the correlation coefficients were 0.277, -0.691 and -0.555 for Ki-67, cyclin D1 and phospho-Rb changes, respectively. Similarly, there was no correlation observed between the palbociclib plasma concentrations on Cycle 1 Day 21 and the mean percent change in FLT-PET SUVmax or FDG-PET SUVmax; the correlation coefficients were 0.288 and -0.185, respectively.

5.3.5 Genetic, gender and age related differences in pharmacodynamic response

Gender was examined as a covariate of baseline QTc as part of Study PMAR-EQDD-A548b-DP4-287 but it was not included in the popPK-PD model based on ANOVA analysis. This Sponsor states that this may have resulted from the unequal number of females and males (136 cf. 48) contained in the dataset.

5.3.6 Pharmacodynamic interactions

Study A5481010 examined the efficacy of palbociclib when given alone and when co-administered with 2.5 mg letrozole QD to 12 Japanese patients with advanced solid tumours, including 3 patients with breast cancer. As stated previously, when 125 mg palbociclib was administered alone QD for 3 weeks no objective response (CR/PR) was reported. By contrast, following administration with letrozole, objective response was reported in 2 (33.3%) patients; both were PR. Two patients had a best overall tumour response of StD ≥ 24 weeks and 2 patients had a best response of indeterminate who discontinued the study for the reasons other than disease progression. At the data cut-off date, PFS was 505 days and duration of response was 421 days in one of the patients with PR, PFS was 582 days and duration of response was 498 days in the other patient with PR. PFS were 582 days and 592 days, respectively in the 2 patients with StD.

Comment: Based on the information provided it is difficult to ascertain whether the improvement in objective response seen in this study results from the co-

administration of letrozole and palbociclib or from letrozole alone.

5.4 Evaluator's overall conclusions on pharmacodynamics

5.4.1 Mechanism of action

Palbociclib selectively inhibits CDK 4/CCND1, which are important components of the cell cycle.

5.4.1.1 Primary pharmacodynamic effects

- Following 125 mg palbociclib QD for 21 days to patients with MCL, all subjects who had percent phospho-Rb positive measurements available had ≥ 50% change from baseline in phospho-Rb percent positive cells, while 90% of these subjects had ≥ 60% change from baseline and the mean (SD) percent change from baseline was -89.49 (14.80). Paired t-test results for phospho-Rb percent positive cells, Ki-67 composite score, and cyclin D1 composite score (baseline versus Day 21) indicated that there were clinically significant decreases in mean phospho-Rb percent positive cells and Ki-67 composite score at baseline versus Cycle 1 Day 21, but not for cyclin D1.
- In terms of PET response for FLT, 15 patients were considered partial responders to treatment, 2 patients had stable disease and no patients had disease progression, whereas, for FDG, 7 patients were considered partial responders, 10 patients had stable disease and as for FLT no patients had progressive disease.
- PET response determined at Cycle 1 Day 21 showed a trend towards decreased uptake post treatment with anti-tumour activity. However, the relationship between PET response on Day 21 and objective response at the end of the study was not significant.
- There was correlation between the PET SUVmax values and phospho-Rb percent positive cells, Ki-67 composite score or cyclin D1 composite score.
- In terms of RECIST, 3 subjects achieved a best response of PR (2 subjects [12.5%]) or CR (1 subject [6.3%]). The overall ORR was 18.8% (95% CI: 4.0% to 45.6%). Seven subjects (43.8%) had a best response of stable disease/no response. Both median TTP and PFS were 5.5 months (95% CI: 2.0 to 18.6 months). The probability of being event-free at Month 12 was 36.4% (95% CI: 11.1 to 61.6%).
- Following treatment with QD doses of 25 mg to 225 mg palbociclib in patients with advanced solid tumours, included six diagnosed with breast cancer, one patient (who had testicular cancer and was on the 14/21 day dosing schedule) had a confirmed 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 StD 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 StD 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 StD for 10 or more cycles.
- There were no notable differences in response between the 14/21 day and 21/28 day dosing schedules.
- Following 3 weeks of QD dosing with 100 mg or 125 mg palbociclib in 12 Japanese patients with advanced solid tumours, including 3 patients with breast cancer, no objective responses (CR/PR) were reported.

5.4.1.2 Secondary pharmacodynamic effects

- The estimated EC50 for the inhibition of ANC count was 37.7 ng/mL, which was much lower

than the mean average concentration at steady state with 125 mg daily dosing, 86.5 ng/mL, derived from the population typical value of CL/F 60.2 L/h in patients.

- A relationship between plasma palbociclib concentration and thrombocyte levels in plasma was identified with higher doses of palbociclib being associated with lower ATC time profiles. Baseline albumin value (range: 2.4-4.89 g/dL) was a statistically significant covariate on CIRC0 with higher baseline albumin concentration associated with lower CIRC0 value.
- A slightly positive linear relationship was identified between palbociclib concentration and increased QTcS and following therapeutic doses (125 mg QD) in cancer patients the mean (90% CI) QTcS increase as compared with baseline at the mean and median palbociclib c were 5.60 (2.48-8.72) msec and 5.88 (2.61-9.16) msec, respectively.

5.4.1.3 Relationship between drug concentration and pharmacodynamic effects

- There is some evidence to suggest that PFS was improved in patients with higher levels of palbociclib exposure.
- Although, for phospho-Rb there appeared to be a trend towards larger changes from baseline at higher plasma concentrations, no clinically significant correlations were identified between palbociclib plasma concentration and the following biomarkers of cell proliferation: Ki-67; cyclin D1; phospho-Rb; FLT-PET SUVmax; or FDG-PET SUVmax.

5.4.1.4 Genetic, gender and age related differences in pharmacodynamic response

Gender was not identified as a covariate of baseline QTc.

5.4.1.5 Pharmacodynamic interactions

When palbociclib was co-administered with letrozole QD in Japanese patients with advanced solid tumours, improvements in objective response were identified, which were not seen when palbociclib was administered alone.

5.4.1.6 Limitations of the PD studies

No dedicated PD studies examined the primary PD effects of palbociclib in the target population of patients with HR-positive, HER2-negative advanced or metastatic breast cancer.

5.4.1.7 Questions regarding the PD studies

- Given that at the mean and median c following QD dosing with 125 mg palbociclib the upper bounds of the 90%CIs for QTcS range from +8.72 to +9.16 msec and therefore are relatively close to the 10 msec threshold, is it possible that co-administered drugs that increase palbociclib exposure even by as little as 20% to 30% will possibly result in major safety concerns?

5.5 Clinical Pharmacology questions

5.5.1 Pharmacokinetics

1. Although Study A5481032 examined dose proportionality between 4 single dose levels of palbociclib (75 mg, 100 mg, 125 mg or 150 – 200 mg final Phase III capsule), no studies have been provided that examine the BE of these 3 dosage strengths nor has the sponsor applied for a waiver for the required studies. Can the sponsor please comment?
2. As M22 is the most abundant circulating metabolite (responsible for 14.8% of circulating radioactivity), does the sponsor have information regarding its activity?
3. Can the sponsor please provide the complete clinical trial report for Study A5481013,

which examined the effects of hepatic impairment on palbociclib PKs?

5.5.2 Pharmacodynamics

4. Given that at the mean and median c following QD dosing with 125 mg palbociclib the upper bounds of the 90%CIs for QTcS range from +8.72 to +9.16 msec and therefore are relatively close to the 10 msec threshold, is it possible that co-administered drugs that increase palbociclib exposure even by as little as 20% to 30% will possibly result in major safety concerns?

Second round evaluator comment:

It is noted that palbociclib was initially investigated for the treatment of other malignancies and that as such, initial investigation of the PK/PD may have been in men as well as women. Given this is now solely being indicated for use in women, it is recommended that appropriate consideration is given to whether adequate characterisation has occurred in women, and also that reference to male subjects be removed from the PI as there are no proposed usages in men at this time. This is particularly important given:

1. breast cancer in men is seldom ER-negative or HER2-positivethat is, almost always ER-positive
2. no data are presented on the safety and efficacy in men and registration is not being sought
3. the safety and efficacy of aromatase inhibitors and fulvestrant is unproven in men with breast cancer, therefore the addition of palbociclib to either of these adds further uncertainties

6 Dosage selection for the pivotal studies

6.1 Pharmacokinetics and pharmacodynamics: dose finding studies

Comment: This has not been formally evaluated and is presented to explain the dosing rationale for the proposed usage.

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 (Study 1001 CSR, Section 3.3). Schedule 3/1 was intended to allow the maximum duration of dosing. It was thought that Schedule 3/1 might not permit as high a daily dose to be achieved, as a shorter Schedule 2/1. Schedule 2/1 is expected to permit incorporation of palbociclib dosing with other chemotherapy agents later in clinical development. The predicted toxicity of reversible myelosuppression observed nonclinically in rats and dogs prompted the inclusion in each schedule of a 1-week treatment interruption in each cycle to allow recovery of hematologic parameters.

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

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 antitumour activity observed on Schedule 3/1, led to the selection of this treatment schedule for the advanced breast cancer study.

6.2 Phase II dose finding studies

The combination of letrozole was evaluated for safety and drug interactions in the Phase I part of Study 1003. The final proposed dose for palbociclib was Schedule 3/1 (3 weeks on and 1 week off) in combination with the standard daily dose of letrozole (2.5 mg) given continuously.

Comment: This dose schedule is satisfactory and is used in both Study 1003 and 1008.

6.3 Phase III pivotal studies investigating more than one dose regimen

None provided.

7 Clinical efficacy

7.1 Studies providing evaluable efficacy data

7.1.1 Ibrance in combination with letrozole

Study A5481003 (Study 1003) was a Phase I/II, open-label, randomised trial assessing the safety, efficacy and pharmacokinetics of palbociclib and letrozole compared with letrozole alone in postmenopausal women who did not receive previous systemic treatment for their ER positive, HER2-negative advanced breast cancer.

This study included a Phase I portion to confirm safety and tolerability and exclude a drug-drug interaction with the combination (N = 12), followed by a randomised Phase II portion (N = 165) in patients who had no prior or current brain metastases and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Study A5481008 (Study 1008) is an ongoing international, double-blind, placebo-controlled, multi centre Phase III trial that randomised 666 postmenopausal women 2:1. The purpose of Study 1008 was to confirm the efficacy and safety results from the Phase I/II Study 1003. The full CSR is not available but the data submitted include some information on the study design (unfinalised version of the SAP), information on the patient population, primary and 4/11 secondary efficacy results, limited biomarker analyses, safety analyses (all-causality adverse events [AEs], treatment related AEs, serious AEs, treatment discontinuations and deaths) and supporting data tables.

No data are provided for the blinded review of the primary and secondary efficacy outcomes. All CIOMS or narratives are blinded with respect to treatment allocation.

7.1.2 Ibrance in combination with fulvestrant

Study A5481023 (Study 1023) was a Phase III, multi centre, double-blind, placebo-controlled study in 521 pre/postmenopausal women assessing the safety and efficacy of palbociclib plus fulvestrant or placebo plus fulvestrant in women with HR-positive, HER2-negative advanced breast cancer, whose disease progressed after prior endocrine therapy regardless of their menopausal status. The study was still blinded as of the 23-0ct-15 and updated PFS analyses reports for the 16-Mar-15 and 23-0ct-15 data cut-offs were provided.

Some additional efficacy data supportive of efficacy in solid tumours comes from the dose-finding Phase I Study A5481001 in solid tumours.

7.2 Pivotal or main efficacy studies

In support of the proposed indication *in combination with letrozole* data comes from the dose-finding and proof of concept Phase I/II trial Study 1003 with top line summary results from the ongoing Phase III study, 1008.

Data in support of the proposed indication in combination with fulvestrant comes from the pivotal Study 1023.

7.2.1 A5481003 ('PALOMA-1') hereafter referred to as Study 1003

7.2.1.1 Study design, objectives, locations and dates

This was a randomised, open-label, multi centre, international Phase I/II Study A5481003 (PALOMA-1; Study 1003) to assess the safety, efficacy, and pharmacokinetics of palbociclib (isethionate salt formulation) plus letrozole and letrozole alone administered as initial endocrine-based therapy for ER-positive, HER2-negative advanced breast cancer in postmenopausal women.

Comment: The formulation used in this study was not that now proposed for registration. Inter and intra-patient variability was noted in the absorption.

There were 7 amendments to the study plan (dated 27 March 2008) and there were 3 amendments to the original SAP (dated 19 May 2008). These changes are considered key and were summarised by the sponsor. The study design followed an adaptive course and in the final design (see Figure 2) there were 2 Phases and Phase II consisted of 2 parts:

Phase I: to assess the safety and tolerability of the combination and to exclude a drug-drug interaction (DDI) with the combination.

Randomised, open label Phase II in 2 parts:

Part 1 to assess the efficacy and safety of palbociclib in combination with letrozole and of letrozole alone in the first-line treatment

Part 2: had the same objective but enrolled a prospectively defined population of ER-positive, HER2-negative postmenopausal patients with tumors additionally demonstrating:

1. CCND1 gene amplification (CCND1/CEP11 ratio ≥ 1.5, from this point forward CCND1 ≥ 1.5 will be used in the text and tables)
2. and/or loss of CDKN2A/ p16INK4A gene (CDKN2A/CEP9 ratio <0.8, from this point forward CDKN2A <0.8 will be used in the text and tables) by fluorescence in situ hybridization (FISH) analysis

The initial Phase II study design included 150 patients randomised in a 1:1 fashion to receive palbociclib plus letrozole (Arm A) or letrozole alone (Arm B). When preclinical data suggested that the tumours with CCND1 amplification and/or loss of CDKN2A were particularly sensitive to palbociclib, the Phase II portion of the trial was subsequently modified to comprise 2 parts; the Phase II Part 1 (Ph2P1) Cohort was to include 60 patients randomised in a 1:1 fashion to receive palbociclib plus letrozole or letrozole alone, without biomarker selection; and the Phase II Part 2 portion (Ph2P2) was to include approximately 150 similar patients who also expressed biomarker-positive disease (defined as CCND1 gene amplification and/or loss of CDKN2A) and were randomised in the same fashion (1:1) as in Ph2P1. (Amendment #3 July 2010).

An interim analysis of Ph2P1 data was performed and showed that clinical activity of palbociclib in combination with letrozole for the first-line treatment of ER-positive, HER2-negative advanced breast cancer in postmenopausal women was independent of patients' biomarker (CCND1/CDKN2A) status. Therefore, accrual to Ph2P2 was terminated (99 patients had accrued to Part 2), and the protocol was amended to determine the clinical benefit of the combination in

patients randomised in both Ph2P1 and Ph2P2 (Amendment #5, June 2012) combined with secondary subgroup analysis in Ph2P1 and Ph2P2 separately. Additionally, Blinded Independent Central Review (BICR) evaluation was incorporated as a secondary analysis for multiple efficacy endpoints prior to the final analysis (Amendment #6).

All patients were randomised with 2 stratification factors:

1. Site of disease (visceral[1] vs. bone only vs. other [2])
2. Disease free interval (>12 months from the end of adjuvant treatment to disease recurrence vs. ≤12 months from the end of adjuvant treatment to disease recurrence or de novo advanced disease)
3. 1 'Visceral' refers to lung and/or liver + any other site.
4. 2 'Other' refers to bone with other non-visceral disease site or other disease site alone.

The SAP also states: since the primary analysis of PFS contains patients from both Part 1 and Part 2, that were randomised separately and were enrolled under different selection criteria, the Cohort (Part 1 vs. Part 2) should also be considered as a stratification factor in the stratified analysis.

Comment: This biomarker-selected status was not a prespecified stratification factor and is being applied post hoc; in doing this, the SAP does recognize that there were different selection criteria and therefore potential differences between the two groups. The meaningfulness of any statistical outcomes and treatment effect when the two groups are combined for primary efficacy analysis is uncertain and outcomes require confirmation in a well-designed randomised double-blind trial.

The following is taken from the supplemental SAP: 'As Phase II Part 1 was originally intended as a pre-proof-of-concept study (pre-POC), the study team had full access to the data, as the study was ongoing, and summary analyses were performed for the first interim analysis. Conversely, Part 2 was originally intended as the POC study for this indication, thus, although open-label, the study-team did not have access to aggregate analyses or summaries by treatment arm. With the most recent amendment to the protocol, the primary analysis set is now all patients randomised in Phase II (Part1 and Part 2). As such, the study team is not to be provided aggregate analyses or summaries by treatment arm for both Part 1 and part 2, outside of the scope of pre-specified interim analyses.'

Patients continued with the assigned study treatment until progression of disease, unacceptable toxicity, or consent withdrawal and underwent study-related safety and efficacy assessments. (Amendment #6, dated November 2012 required that post-study patient survival status will be collected for all patients randomised in the Phase II portion of the study every 2 months until death).

Comments:

1. The initial open label, proof of concept study design was modified at several points based on investigator assessments and interim data analyses, and to accommodate emerging data about a potential biomarker, resulting in a new eligibility criterion. When an interim analysis indicated that a palbociclib treatment effect was independent of that biomarker status, accrual to the biomarker-positive Phase II Part 2 arm was terminated early (when 99/planned 150 patients were recruited) and the two groups from Part 1 and 2 amalgamated for the final data analysis. Separate analyses were also planned post hoc. This last amalgamation appears to contradict the SAP to treat the 2 as separate cohorts.
2. The SAP states that the study was originally intended as a pre-proof of concept (Part 1) and Proof of concept (Part 2), and the alterations to the study design, protocol and SAP were driven both by looks at the data, and emerging preclinical results – therefore, it cannot be considered a 'pivotal trial' for the purposes of establishing safety and efficacy as required

for TGA regulatory approval. As such, it is suitable for generating hypotheses and demonstrating the promise of palbociclib but this requires data from a confirmatory, well-designed Phase III study to be presented for evaluation. The CSR for Study 1008 data is not available for a full evaluation by the TGA at this time.

The clinical trial design has multiple potential sources of bias and limitations:

1. The open label nature of this study.
2. The study design was proof of concept, and pre-proof of concept in design with an alpha to reflect this.
3. The analyses and amendments were based on investigator-reported results.
4. The ITT population for efficacy is comprised of two groups recruited with differing eligibility criteria – the impact of this is uncertain.
5. This raises uncertainties about the generalizability of the findings when the majority of patients have a particular profile.
6. Multiple looks at the data and data-driven amendments, especially in the open label setting
7. A BICR was only introduced as a secondary analysis for multiple efficacy endpoints prior to the final analysis. In the absence of blinding in the trial design, all trial amendments were made based on investigator assessments.
8. There were no per protocol analysis sets for those in the Phase II part of the study (v4, 31 July 2013).

Patients in the Phase II part of the study received palbociclib 125 mg daily on Schedule 3/1 (3 weeks on/1week off) in combination with letrozole administered continuously versus letrozole administered continuously.

Figure2: The final study design of A5481003

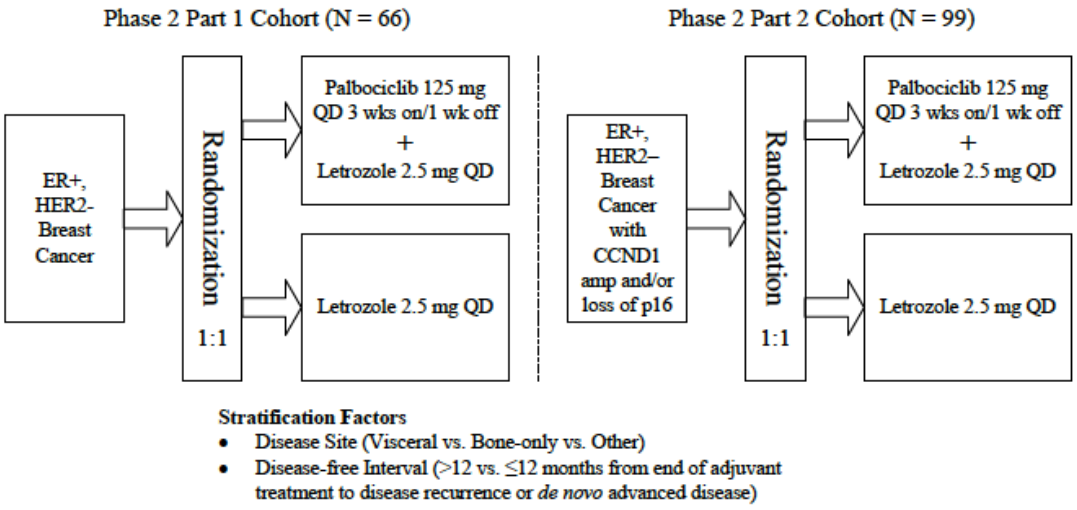
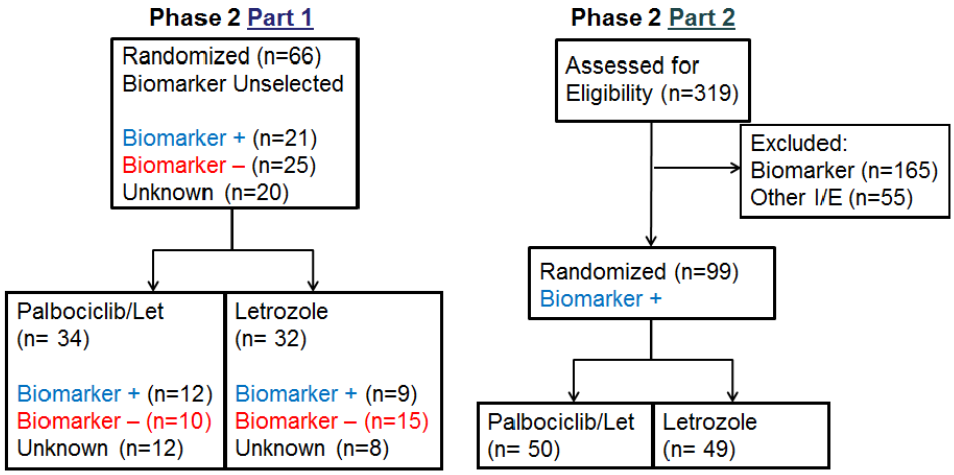


Figure 3: Biomarker status of Study A5481003 by Part 1 and 2



I/E: inclusion/exclusion criteria; Let: Letrozole

7.2.1.2 Study dates

Date of First Enrollment: 15 September 2008

Data Cutoff Date: 29 November 2013

Date of Report 28 July 2015

7.2.1.3 Study locations

Phase I: 3 sites in 1 country (United States);

Phase II portion: 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], South Korea [2 sites], Spain [5 sites], Ukraine [4 sites], and the United States [10 sites]).

7.2.1.4 Study Endpoints

Phase I Primary Endpoint

- To assess the safety and tolerability of palbociclib in combination with letrozole in postmenopausal women with ER-positive, HER2-negative advanced breast cancer.

Secondary Endpoints

- Plasma pharmacokinetic parameters of PD 0332991 and letrozole.
- QTc interval.
- Objective tumour response (OR).
- Clinical benefit response (CBR).
- Tumour tissue levels including but not limited to Rb, p16/INK4A, CCND1, CDK4, CDK6, and Ki67.
- Germline polymorphism in CYP19A1 and CCND1 genes.

Comment: as the Phase I was a PK/safety study, the efficacy endpoints will be summarised at the end of the efficacy data for the Phase II efficacy data.

Phase II Primary Endpoint

- progression-free survival (PFS)

Secondary endpoints

- OR.
- CBR. (defined as CR or PR or SD ≥24 weeks as per RECIST v. 1.0)
- Time to tumour progression (TTP)
- Duration of response (DR).
- Overall survival (OS).
- Overall safety profile.
- Patient Reported Outcome (PRO) of pain using the modified Brief Pain Inventory – short form (mBPI-sf).
- Tumour tissue levels including but not limited to Rb, p16/INK4A, CCND1, CDK4, CDK6, and Ki67 and copy number of CCND1 and p16.

7.2.1.5 Inclusion and exclusion criteria

Inclusion Criteria:

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

- 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.
- ER-positive tumour: defined either as ≥ 10 fmol of H3 -oestrogen binding per mg of cytosol protein for dextran-coated charcoal and sucrose density methods, or ≥ 0.10 fmol of H3 -oestrogen binding per mg of DNA for IF/EIA technique. In case of use of immunohistochemistry, the report should mention positive receptor status according to the standards of the laboratory.
- HER2-negative breast cancer by FISH or IHC.
- Paraffin-embedded tumour block(s) available for centralized assessment of Rb and other cell cycle-related proteins. Phase II Part 2 only: CCND1 amplification and/or loss of p16 as determined by the central laboratory.
- Measurable disease according to RECIST or bone-only disease (Phase II only).
- Previously irradiated lesions are deemed measurable only if progression is documented at the site after completion of radiation.
- Females, 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 FSH and oestradiol in the postmenopausal ranges.
- Eastern Cooperative Oncology Group (ECOG) Performance status 0 or 1
- Resolution of all acute toxic effects of prior therapy or surgical procedures to CTCAE grade <1 (except alopecia or other toxicities not considered a safety risk for the patient).
- Adequate organ function as defined by the following criteria:

  - Absolute neutrophil count (ANC) ≥ 1500/μL;
  - Platelets ≥ 100,000/μL;
  - Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤3 x upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy;
  - Total serum bilirubin ≤1.5 x ULN regardless of liver involvement secondary to tumor. Inclusion of patients with increased serum indirect bilirubin due to Gilbert's syndrome is permitted;
  - Serum creatinine ≤1.5 x ULN;
  - QTc ≤470 msec (based on the mean value of the triplicate ECGs).
- Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.
- Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Comment: This study did not allow enrolment of premenopausal women who were proven to be biochemically postmenopausal after treatment with an LHRH analogue. A protocol amendment allowed women to have received neoadjuvant letrozole as long as their relapse did not occur within 12 months.

Exclusion criteria

Patients presenting with any of the following were not to be included in the study:

- Brain metastases (even if treated and stable), spinal cord compression (history or presence of), carcinomatous meningitis, or leptomeningeal disease.
- Major surgery within 3 weeks of first study treatment.
- Prior treatment with:
  - o Any anti-cancer 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 II only);
  - Any CDK inhibitor.
- Current treatment with:
  - Any anti-cancer therapies for advanced disease;
  - Any experimental treatment on another clinical trial;
  - Therapeutic doses of anticoagulant. Low dose anticoagulants for deep vein thrombosis prophylaxis are allowed. Low molecular weight heparin is allowed. Aspirin is permitted.
- Current use or anticipated need for:
  - food or drugs that are known strong CYP3A4 inhibitors (that is, 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 (that is, carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine, and St. John's Wort) – for Phase I only.

- 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.
- 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.
- Active inflammatory bowel disease or chronic diarrhea, Short bowel syndrome, Upper gastrointestinal surgery including gastric resection.
- Known hypersensitivity to letrozole or to any of its excipients.
- Known human immunodeficiency virus infection.
- 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 subject inappropriate for entry into this study.

Comment: The exclusion criteria are standard for a clinical trial for a new chemical entity.

7.2.1.6 Study treatments

Patients were randomised 1:1, and those in the experimental arm received: palbociclib (PD 0332991) 125 mg/d (dose confirmed at the end of the Phase I portion, based upon the safety profile and lack of a clinically relevant DDI with letrozole) orally for 3 weeks followed by 1 week off treatment, and letrozole 2.5 mg/d orally in a continuous regimen.

Patients randomised to the control arm received letrozole 2.5 mg/d orally in a continuous regimen.

Letrozole dose interruptions but dose modifications were not allowed, while palbociclib dose modifications for toxicities were as below:

Table 6: Dose levels

Dose Level	Palbociclib for 3 out of 4 weeks (3/1 schedule)	Letrozole on a continuous daily dosing regimen
1	125 mg QD	2.5 mg QD
-1	100 mg QD	2.5 mg QD
-2	75 mg QD	2.5 mg QD

Palbociclib dose de-escalation below 75 mg QD was not allowed.
Abbreviation: QD=Once daily.

Table 7: Recommended palbociclib dose modifications based on worst treatment-related toxicity in the previous cycle

Worst Toxicity During Previous Cycle	New Cycle
Grade 4 neutropenia	Reduce by 1 dose level
Grade 4 thrombocytopenia	Reduce by 1 dose level
Grade 3 neutropenia associated with a documented infection or fever ≥38.5°C	Reduce by 1 dose level
Grade ≥3 nonhematologic toxicity (includes nausea, vomiting, diarrhea, and hypertension only if persisting despite maximal medical treatment)	Reduce by 1 dose level

Doses could be withheld as needed for toxicity resolution during a cycle. Doses omitted for

toxicity were not replaced or restored within the same cycle. Patients were instead supposed to resume palbociclib at the next planned treatment cycle. If the patient had not recovered after 2 weeks (including the scheduled 1-week off treatment period within a cycle), treatment with palbociclib could have been permanently discontinued if the toxicity was considered treatment-related after discussion with the sponsor.

The following concomitant medications were not permitted: strong CYP3A inhibitors, primary prophylaxis with granulocyte-colony stimulating factors (GCSFs) although secondary treatment with GCSF for neutropenia was permitted; bisphosphonates or RANK-ligand inhibitors could not be introduced without the permission of the sponsor.

Patients were scheduled to continue with the assigned study treatment until progression of disease, unacceptable toxicity or consent withdrawal.

Comment: Patients were required to fast for 1 hour prior and 2 hours after, which is now known to result in high inter and intra-patient variability in exposure and 'low liers'. Administration with food was reported to increase exposure among the low liers without increasing the exposure significantly in others, and is recommended in the PI.

7.2.1.7 Efficacy variables and outcomes

The efficacy variables for the Phase I part are not presented here as they do not form part of the analysis of efficacy for this study.

Disease assessment at screening included computed tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis, X-rays for bone lesions (if applicable), and clinical assessment of superficial disease. Post-baseline tumour assessments were performed every 8 weeks (also whenever disease progression was suspected), until disease progression was documented or the patient began a subsequent anticancer therapy, regardless of study treatment discontinuation. Progression had to be determined objectively as defined by RECIST v1.0 and using the same method and technique as at baseline, during the study treatment period and during follow-up.

Bone scans were carried out at baseline and every 12 weeks thereafter, or when new metastases were suspected, in order to detect bony sites of disease. Baseline bone lesions were followed up with the most appropriate imaging technique. A bone scan was required at the time of confirmation of CR for patients who had bone metastases. Every effort was to be made to perform a last tumour assessment before starting a new anticancer therapy.

All imaging studies (including photographs for superficial disease, if applicable) from patients randomised in Ph2P1 and Ph2P2 were submitted to an independent core imaging laboratory for review. The sponsor has indicated that this requirement was implemented in September 2012 in Amendment #6 for all Phase II patients, thus some scans were reviewed retrospectively. PFS, TTP, OR, DOR, and CBR) were based on investigator assessments of disease response and progression. Analyses based on the BICR were considered as secondary and supportive.

Comment: In an open label trial, investigator assessment is a significant potential source of bias. The sponsor is requested to provide a breakdown for both the control and experimental arms of the numbers and percentage where BICR was performed prospectively versus retrospectively. The sponsor is requested to provide concordance rates between the investigator and BICR by imaging modality eg bone scan, CT, MRI and lesion type (bone lesions, visceral, other) (Clinical Question).

Primary efficacy endpoint

PFS was defined as the time from randomisation (Phase II)/date of first dose (Phase I) to the date of first documentation of objective progression or death due to any cause, whichever occurred first.

Secondary efficacy endpoints

Objective tumour response (CR or PR) for all patients with responding tumours (CR or PR); the response had to be confirmed no sooner than 4 weeks after the initial documentation of response. CBR was defined as the occurrence of CR, PR or SD ≥ 24 weeks; Overall survival (OS) was defined as the time from randomisation date to date of death due to any cause; TTP was defined as the time from randomisation date to the date of first documentation of objective progression; Duration of response (DOR) was defined as the time from first documentation of CR or PR to date of first documentation of objective progression or death.

7.2.1.8 Randomisation and blinding methods

There was no blinding (open label trial) and randomisation occurred in the Phase II portion only using interactive web response system (IWRS).

Stratification factors were:

disease site (visceral versus bone only versus other)

disease-free interval from the end of adjuvant treatment to disease recurrence: >12 months versus ≤ 12 months from the end of adjuvant treatment to disease recurrence or de novo advanced disease

Comment: Those presenting with de novo disease are treatment-naïve and historically have better clinical outcomes than those relapsing rapidly within 12 months of completion of adjuvant therapy. Thus this groups together those likely to respond (de novo) with those least likely to respond (early relapse) to endocrine therapy in this setting.

7.2.1.9 Analysis populations

Full analysis sets

- Phase I All Enrolled Set: All enrolled patients
- Phase II
- 3 ITT analysis sets are proposed:

1. Primary Analysis Set (ITT): All Randomized As Randomized Set (Phase II Part 1 and Part 2): This represents the Intent to Treat (ITT) population: all randomised patients where patients are classified according to the randomised treatment regardless of what treatment, if any, was received.
2. All Randomized As Randomized Set - Phase II Part 1 (ITT): all randomised patients from Part 1 (who did not prospectively have tumours identified with CCND1 amplification and/or loss of p16) where patients are classified according to the randomised treatment regardless of what treatment, if any, was received.
3. All Randomized As Randomized Set - Phase II Part 2 (ITT): all randomised patients where patients (who did prospectively have tumours identified with CCND1 amplification and/or loss of p16) are classified according to the randomised treatment regardless of what treatment, if any, was received.

There was no 'Per Protocol' analysis set.

Comment: There was no per protocol analysis set to provide support to determine whether any treatment effect was seen in those who received the treatment as planned. The SAP (July 31, 2013) indicates that in the Phase II part, 'Major deviation is defined as having been treated according to the other treatment arm. Patients not treated with one of the protocol treatments are excluded from safety analyses. Otherwise patients are not excluded from analyses due to post-randomisation deviations.' This

is consistent with this trial being designed as a proof of concept rather than to gain registration, and supportive evidence from a more rigorously designed trial is required.

7.2.1.10 Sample size

The planned sample size was changed after two separate interim analyses of efficacy (2), a protocol amendment to recruit according to an emerging biomarker, and again following the demonstration that a palbociclib treatment effect was independent of that biomarker status.

At the time of enrollment termination, a total of 165 patients had been randomised to the Phase II portion of the study (66 patients in Part 1 and 99 patients in Part 2). Thus the final sample size for analysis of the primary endpoint was 165 patients: 84 received the investigational treatment (125-mg palbociclib QD on Schedule 3/1 + 2.5-mg letrozole QD continuously) and 81 received 2.5mg letrozole QD continuously.

7.2.1.11 Statistical methods

The Phase II primary endpoint was progression-free survival (PFS). Assuming a median PFS of 9 months for the control treatment arm and a 50% improvement in the combination arm, 114 PFS events were anticipated to be observed with a minimum follow-up time of approximately 17 months, for total trial duration of approximately 30 months. With a 1-sided alpha = 0.10, there is approximately 80% power to detect a hazard ratio of 0.67 (letrozole plus PD 0332991: letrozole alone) under the alternative hypothesis, assuming one futility interim analysis.

An interim analysis of Phase II Part 1 data was performed and supported that clinical activity of PD 0332991 in combination with letrozole for the first-line treatment of ER-positive/HER2 negative advanced breast cancer in postmenopausal women is independent of patients' biomarker (CCND1/p16) status. In addition, the analysis suggested that the combination of PD 0332991 plus letrozole may demonstrate substantially better efficacy than previously hypothesized as described above. As such, the accrual to the Phase II Part 2 portion has been terminated, and the protocol is being amended to determine the clinical benefit of the combination in patients randomised in both Part 1 and Part 2 and includes additional interim analyses. At the time of enrollment termination, a total of 165 patients had been randomised to the Phase II portion of the study (66 patients in Part 1 and 99 patients in Part 2). This sample size will support, under the same assumptions as above, the statistical analysis plan changes that will include up to 3 efficacy interim analyses.

The primary analysis population will be all randomised patients from Part 1 and Part 2 and analyzed in a group-sequential manner (Lan-DeMets α-spending function with an O'Brien-Fleming efficacy boundary to control the overall Type I error rate) with 2 interim analyses. The first interim analysis was performed as mentioned above at 28% of information (31 PFS events). The second interim analysis was planned at approximately 50% of information (approximately 57 PFS events).

Based on the event rate evaluation and the observed effect size from the two interim analyses, events are being observed at a slower pace than anticipated, and the determination of 114 PFS events for the final analysis may not be accumulated in a practical timeframe.

Therefore, the final analysis of the primary endpoint of PFS will be performed when approximately 95 PFS events have accumulated. The critical value that will be used to declare statistical significance at the time of the final analysis will be based on the actual number of events observed and the alpha already spent at the interim analyses.

Comment: The power of 80% and alpha of 0.1 in Study 1003 is consistent with an early exploratory study, designed to generate hypotheses. The multiple data-driven amendments to the study design make it difficult to establish statistical significance of the resulting findings.

The following is taken from the Health Canada summary basis of decision: 'No statistical methods can take into account clinical and operational aspects of these amendments, therefore the reported p-values and 95% confidence intervals are not meaningful or reliable.'

A confirmatory study is ongoing (Study 1008) and the evaluation of the data from this trial are required from this to establish whether there is a statistically significant difference with adding palbociclib to letrozole. It is noted that Study 1008 has been designed (without significant amendments) to have 90% power to detect a hazard ratio of 0.69 in favour of palbociclib plus letrozole arm using a 1-sided, unstratified log-rank test at a significance level of 0.025.

7.2.1.12 Participant flow

The number of patients screened could not be located in the data but between 22 December 2009 and 12 May 2012, 165 women were randomised 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]).

In Phase II (Ph2P1+Ph2P2), 84 and 81 patients were randomised 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 randomised but not treated (See Table 8 below).

At the time of data cutoff for the CSR (29 November 2013), in the palbociclib and letrozole versus letrozole alone arms respectively:

- 19 patients (22.6%) and 8 patients (9.9%) were ongoing.
- 51.2% versus 70.4% discontinued the study due to objective progression or relapse or death
- 13.1% versus 2.5% discontinued due to an AE

Table 8: Study A5481003 Patient disposition at the end of treatment – Phase II: ITT population

A5481003

Table 11: Patient Disposition at End of Treatment - Phase 2: Intent-To-Treat Population

	Phase 2 (Ph2P1+Ph2P2)		Ph2P1		Ph2P2	
Number (%) of Patients	Palbociclib + Letrozole	Letrozole	Palbociclib + Letrozole	Letrozole	Palbociclib + Letrozole	Letrozole
Randomized to study treatment	84	81	34	32	50	49
Randomized and not treated	1 (1.2)	4 (4.9)	1 (2.9)	3 (9.4)	0	1 (2.0)
Treated	83	77	33	29	50	48
Ongoing at data cutoff	19 (22.6)	8 (9.9)	7 (20.6)	1 (3.1)	12 (24.0)	7 (14.3)
Discontinued	64 (76.2)	69 (85.2)	26 (76.5)	28 (87.5)	38 (76.0)	41 (83.7)
AE	11 (13.1)	2 (2.5)	8 (23.5)	1 (3.1)	3 (6.0)	1 (2.0)
Global Deterioration of Health Status	5 (6.0)	3 (3.7)	0	1 (3.1)	5 (10.0)	2 (4.1)
Objective Progression or Relapse	42 (50.0)	57 (70.4)	16 (47.1)	22 (68.8)	26 (52.0)	35 (71.4)
Patient Died	1 (1.2)	0	0	0	1 (2.0)	0
Patient No Longer Willing to Continue Treatment for Reason Other Than AE	5 (6.0)	6 (7.4)	2 (5.9)	2 (6.3)	3 (6.0)	4 (8.2)
Other[a]	1 (1.2)	5 (6.2)	1 (2.9)	5 (15.6)	0	0

Source: Table 14.1.1.1.b and Table 14.1.1.2.2.b.
The number of patients who completed, discontinued and ongoing is as per the Patient Summary EOT CRF page.
The percentage is based on the number of patients randomized to study treatment.
[a] Includes some patients that were randomized and not treated (Listing 16.2.1.2.b, Listing 16.2.1.4.1.b, and Listing 16.2.1.4.2.b).
Abbreviations: AE=Adverse event; CRF=Case report form; EOT=End of Treatment; Ph2P1=Phase 2 Part 1; Ph2P2=Phase 2 Part 2; Ph2P1+Ph2P2=Phase 2 combined.

Comment: The evaluator is in agreement with the sponsor that increased clinical experience of the investigators in managing the toxicity of the combination may be reflected in the relative decrease in number and proportion of patients in Ph2P2 who discontinued due to AEs although this could also be a chance finding in such a small study (see Table 8)

7.2.1.13 Major protocol violations/deviations

Major deviation was defined as having been treated according to the other treatment arm. Patients not receiving 1 of the protocol treatments were excluded from safety analyses. Otherwise, patients were not excluded from analyses due to post-randomisation deviations.

The reported rates of any protocol deviations were high (93.9%) in both parts of the Phase II study, with 10.6% in Part 1 and 10.1% in the control considered 'clinically significant' deviations; most of these were breaches of the inclusion/exclusion criteria such as the menopausal status of 4 patients not being confirmed. Incorrect stratification factors being used at the time of randomisation led to some small imbalances in prognostic factors eg higher rates of visceral disease in the letrozole alone arm.

Comment: The impact of the frequent and wide-ranging nature of these protocol deviations (including inclusion/exclusion criteria, randomisation, deviations from the conduct of the study and study assessments) on the outcome is difficult to assess, especially when not provided by treatment allocation and the definition of the sponsor's phrase 'clinically significant' could not be found. However, following a detailed review of protocol deviations, it is noted that the FDA clinical reviewers of Study 1003 concluded that these were unlikely to affect the efficacy outcomes significantly (FDA clinical review report, Study 1003 NDA).

7.2.1.14 Baseline data

Baseline demographics

The median age was 62.5 years (range: 41 to 89 years) and 64.0 years (range: 38 to 84 years) in the palbociclib plus letrozole arm and the letrozole alone arm, respectively (see Table 9).

Comment: The baseline demographics were reasonably balanced between the arms, particularly given the small size of the study. The study population was mostly White and no men were included. Of relevance to the Australian population, is noted that studies in Asian patients are underway which will likely determine whether there are any clinically significant differences.

Table 9: Study A5481003 Demographic characteristics for Phase II ITT population

	Phase 2 (Ph2P1+Ph2P2)		Ph2P1		Ph2P2	
	Palbociclib + Letrozole (N=84)	Letrozole (N=81)	Palbociclib + Letrozole (N=34)	Letrozole (N=32)	Palbociclib + Letrozole (N=50)	Letrozole (N=49)
Age (years), n (%)						
18-44	2 (2.4)	4 (4.9)	2 (5.9)	2 (6.3)	0	2 (4.1)
45-64	45 (53.6)	38 (46.9)	15 (44.1)	15 (46.9)	30 (60.0)	23 (46.9)
≥65	37 (44.0)	39 (48.1)	17 (50.0)	15 (46.9)	20 (40.0)	24 (49.0)
Mean (Std Dev)	62.7 (10.19)	63.0 (9.16)	64.1 (11.05)	62.9 (8.55)	61.7 (9.56)	63.0 (9.62)
Median (Range)	62.5 (41 to 89)	64.0 (38 to 84)	65.5 (41 to 89)	64.0 (42 to 75)	62.0 (46 to 83)	63.0 (38 to 84)
Race, n (%)						
White	76 (90.5)	72 (88.9)	31 (91.2)	26 (81.3)	45 (90.0)	46 (93.9)
Black	1 (1.2)	1 (1.2)	1 (2.9)	1 (3.1)	0	0
Asian	6 (7.1)	4 (4.9)	2 (5.9)	1 (3.1)	4 (8.0)	3 (6.1)
Other[a]	1 (1.2)	4 (4.9)	0	4 (12.5)	1 (2.0)	0
Weight (kg)						
Mean (Std Dev)	71.0 (15.68)	68.1 (13.34)	70.1 (15.11)	67.3 (12.43)	71.6 (16.17)	68.5 (14.01)
Median (Range)	70.0 (42.2 to 123.0)	65.4 (46.0 to 106.0)	67.5 (45.0 to 102.0)	63.7 (48.1 to 101.5)	70.5 (42.2 to 123.0)	67.0 (46.0 to 106.0)

Source: Table 14.1.2.1.b.
[a] The 1 patient in the palbociclib plus letrozole arm and 4 patients in the letrozole alone arm classified as 'Other race' were of Hispanic ethnicity (Listing 16.2.4.1.b).
Abbreviations: Ph2P1=Phase 2 Part 1; Ph2P2=Phase 2 Part 2; Ph2P1+Ph2P2=Phase 2 combined; Std Dev=Standard deviation.

7.2.1.15 Baseline disease characteristics and prior treatments (Table 10)

The following imbalances are noted in the Phase II combined P1+P2 populations:

- Shorter median time to diagnosis in the combination arm (1.3 versus 2.4 years) – this was in part due to the larger number of *de novo* patients in combination arm;
- Fewer patients with visceral disease in the palbociclib plus letrozole arm (44.1%) than in the letrozole alone arm (53.1%);
- More patients in the combination arm had bone-only disease (20.2% versus 14.8%) due to incorrect stratification at randomisation and discovered subsequently;
- There was a large discrepancy between the PR-negative status with 13.1% in the combination versus 28.4% in the letrozole alone arm;
- More patients with Grade 3 disease in combination arm (36.9% versus 22.2%);
- More patients had ductal carcinoma in the combination arm overall (75% versus 66.7%);

The majority had metastatic disease with only 3 patients with locally advanced disease enrolled.

Comment:

1. Discrepancies between the CRF data and that used for randomisation identified errors with incorrect stratification factors being used to randomize patients, resulting in fewer patients with visceral disease and more with bone-only disease being randomised to the palbociclib and letrozole arms - both of these would favour a better outcome in this arm. Sensitivity analyses have not demonstrated a significant impact of these errors.
2. The first four imbalances in baseline disease factors would be likely to favour a better outcome in the palbociclib and letrozole arm, while the 5th would favour the letrozole alone arm – the 6th is of uncertain significance.

Table 10: Study A5481003 Baseline disease characteristics – Intention-to-Treat population

	Phase 2 (Ph2P1+Ph2P2)		Ph2P1		Ph2P2	
	Palbociclib + Letrozole (N=84)	Letrozole (N=81)	Palbociclib + Letrozole (N=34)	Letrozole (N=32)	Palbociclib + Letrozole (N=50)	Letrozole (N=49)
Duration Since Histopathological Diagnosis of Breast Cancer (years)						
Mean	4.5	6.1	5.1	7.2	4.2	5.5
Median	1.3	2.4	0.9	3.4	1.5	2.1
Range	0.0 to 27.0	0.0 to 40.0	0.0 to 27.0	0.0 to 33.9	0.0 to 25.0	0.0 to 40.0
Current Disease Stage, n (%)						
IIIB	2 (2.4)	1 (1.2)	2 (5.9)	0	0	1 (2.0)
IV	82 (97.6)	80 (98.8)	32 (94.1)	32 (100.0)	50 (100.0)	48 (98.0)
Histopathological Classification, n (%)						
Ductal	63 (75.0)	54 (66.7)	28 (82.4)	21 (65.6)	35 (70.0)	33 (67.3)
Lobular	18 (21.4)	19 (23.5)	5 (14.7)	9 (28.1)	13 (26.0)	10 (20.4)
Other	3 (3.6)	8 (9.9)	1 (2.9)	2 (6.3)	2 (4.0)	6 (12.2)
Histopathological Grade, n (%)						
1	8 (9.5)	10 (12.3)	6 (17.6)	7 (21.9)	2 (4.0)	3 (6.1)
2	31 (36.9)	38 (46.9)	9 (26.5)	16 (50.0)	22 (44.0)	22 (44.9)
3	31 (36.9)	18 (22.2)	14 (41.2)	3 (9.4)	17 (34.0)	15 (30.6)
Not Done	5 (6.0)	6 (7.4)	2 (5.9)	4 (12.5)	3 (6.0)	2 (4.1)
Unknown	9 (10.7)	9 (11.1)	3 (8.8)	2 (6.3)	6 (12.0)	7 (14.3)
Progesterone Receptor, n (%)						
Positive	65 (77.4)	53 (65.4)	23 (67.6)	18 (56.3)	42 (84.0)	35 (71.4)
Negative	11 (13.1)	23 (28.4)	5 (14.7)	10 (31.3)	6 (12.0)	13 (26.5)
Unknown	1 (1.2)	0	1 (2.9)	0	0	0
Not Done	7 (8.3)	5 (6.2)	5 (14.7)	4 (12.5)	2 (4.0)	1 (2.0)

Table 10 continued: Study A5481003 Baseline disease characteristics – Intention-to-Treat population

	Phase 2 (Ph2P1+Ph2P2)		Ph2P1		Ph2P2	
	Palbociclib + Letrozole (N=84)	Letrozole (N=81)	Palbociclib + Letrozole (N=34)	Letrozole (N=32)	Palbociclib + Letrozole (N=50)	Letrozole (N=49)
Measurable Disease Present[a], n (%)						
Yes	65 (77.4)	66 (81.5)	27 (79.4)	23 (71.9)	38 (76.0)	43 (87.8)
No	19 (22.6)	15 (18.5)	7 (20.6)	9 (28.1)	12 (24.0)	6 (12.2)
Adequate Baseline Assessment[b], n (%)						
Yes	84 (100.0)	81 (100.0)	34 (100.0)	32 (100.0)	50 (100.0)	49 (100.0)
ECOG Performance Status, n (%)						
0	46 (54.8)	45 (55.6)	23 (67.6)	20 (62.5)	23 (46.0)	25 (51.0)
1	38 (45.2)	36 (44.4)	11 (32.4)	12 (37.5)	27 (54.0)	24 (49.0)

Source: Table 14.1.2.2.b, Table 14.1.2.5.b and Table 14.1.3.b.
Duration (years) from first diagnosis to the screening date.
Per Protocol, patient's ECOG performance status must have been 0 or 1 to be eligible for enrollment into the study.
[a] At least 1 target lesion ≥20 mm by conventional techniques or ≥10 mm for spiral CT.
[b] Assessments within 35 days prior to first dose. Patients either had measurable disease or bone-only disease.
Abbreviations: CT=Computed tomography; ECOG=Eastern Cooperative Oncology Group; Ph2P1=Phase 2 Part 1; Ph2P2=Phase 2 Part 2; Ph2P1+Ph2P2=Phase 2 combined.

Prior treatments

- *De novo* metastatic disease was reported in 49.1% and a higher number of these (44) were in the treatment arm versus 37 in the letrozole alone arm;
- In Study 1003 there were 57 patients (67.9%) in the palbociclib plus letrozole arm and 53 (65.4%) patients inthe letrozole arm who received no prior endocrine therapy.
- More patients in the combination arm compared with the letrozole alone arm had received no prior systemic therapy (52 vs. 46% in the full Phase II population, 50 vs. 41% in Part 2 cohort).
- 66.7% of patients presented within 12 months of any treatment or with de novo disease

Comment:

- 49.1% of patients had de novo metastatic disease which is a much higher figure than the 5-10% that would be expected with Stage IV disease at presentation in Australia.
- 66.7% had either relapsed within 12 months of completion of adjuvant treatment or had de novo disease, and these two groups have been put together for stratification purposes. The latter (49.1%) would be expected to have a better prognosis than those relapsing after treatment, which makes this stratification factor likely to lead to prognostic factor imbalances; indeed this did happen with more patients with de novo disease in the palbociclib and letrozole arm;
- The rates of prior antihormonal therapy indicate that 110/165 patients (67%) in the Phase II study received no prior hormonal therapy that is, 17.9% did not receive endocrine therapy following a diagnosis of ER-positive breast cancer; it is standard practice in Australia to offer endocrine therapy to women with ER-positive breast cancer, and may influence baseline response rates to any endocrine therapy commenced in the metastatic setting;
- the 'prior surgeries' rate is 81% in both arms, although it is not clear whether this is breast surgery; it would not be usual practice in Australia to perform breast surgery on a woman presenting with metastatic disease and this rate appears very high for palliative procedures. Similarly rates of radiation are 54.8% which may have been adjuvant or palliative.

7.2.1.16 Question for the sponsor:

1. Please provide the breakdown of the operations as to whether they were breast versus non-breast surgery for each treatment arm. For those who underwent breast surgery, please state the number and percentage going on to receive adjuvant therapy, by treatment arm.
2. Please provide a breakdown of the numbers of the 17.9 % patients for each arm who received no endocrine therapy following an earlier ER-positive breast cancer diagnosis.

ER-positive status was required and therefore no patients with ER-negative/PR-positive status have been recruited. The proposed population in the indication needs to be modified to reflect this that is, change from 'hormone-receptor positive' to 'oestrogen receptor-positive'.

The imbalance in bone-only disease resulted from incorrect stratification at the time of randomisation, discovered subsequently. While sensitivity analyses suggest this had no impact on the study outcomes, this adds to uncertainties about the trial outcomes overall and underscores the importance of evaluating data from a more robust Phase III study (that is, Study 1008).

The low numbers of locally advanced disease is not unexpected. The wording of the indication needs to state 'locally advanced'.

Overall, there are factors that could favour the experimental arm (higher rates of no prior treatment, less visceral disease, lower rates of PR-negative) but there are also negative prognostic factors including more patients with Grade 3 disease.

Post-study treatments

In the palbociclib+letrozole arm, 57.1% received follow-up systemic therapy for their breast cancer compared with the letrozole alone arm (76.5%) which was most commonly further endocrine therapy, but also included chemotherapy.

7.2.1.17 Results for the primary efficacy outcome

The Phase I efficacy outcomes will be discussed at the end as they are non-randomised and essentially descriptive.

Phase II PFS (investigator-assessed) ITT population

By investigator assessment:

- there were 100/165 (60.6%) PFS events (41 events [48.8%] and 59 events [72.8%] in the palbociclib plus letrozole arm and the letrozole alone arm, respectively;
- HR 0.488 (95% CI: 0.319-0.748; stratified 1-sided p=0.0004) in favour of the combination arm;
- median PFS was 20.2 months (95% CI: 13.8-27.5) in the palbociclib plus letrozole arm and 10.2 months (95% CI: 5.7-12.6) in the letrozole alone arm.

Censoring

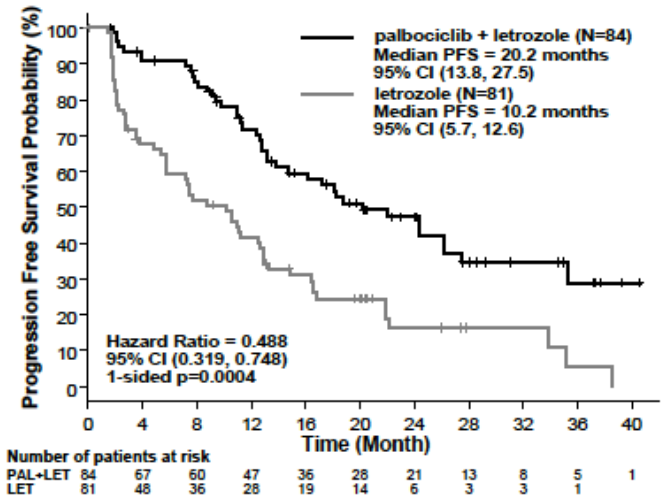
- 43 and 22 patients in the palbociclib plus letrozole arm and the letrozole alone arm, respectively, were censored in the PFS analysis;
- 19 patients and 6 patients, respectively, were still in follow-up for disease progression and had not had disease progression at the time of the final analysis
- The most common reason for censoring in each treatment arm was due to treatment being permanently discontinued without a PFS event. There was a higher percentage of patients censored for discontinuing treatment due to AEs in the palbociclib plus letrozole arm (8 patients, 9.5%) than in the letrozole alone arm (1 patient, 1.2%), and this difference in treatment discontinuation due to AEs was observed in the Ph2P1 Cohort only.

Comment: FDA report for Investigator censoring for Study A5481003. The sponsor is requested to provide an explanation for the differences in these data, noting that this FDA table was compiled following an FDA query, 28 Feb 2014 (Clinical Question).

As previously stated, this discontinuation due to AEs in the earlier part of the study may reflect clinician experience but may also be due to the vagaries of a small sample size.

Figure 4: Study A5481003 Kaplan-Meier plot of progression-free survival Investigator assessment (ITT population)

Phase 2 (Ph2P1+Ph2P2)



Phase II Part 1 and Part 2 PFS (investigator-assessed) ITT population

Part 1

By investigator assessment:

- HR 0.299 (95% CI: 0.156, 0.572; stratified 1-sided p<0.0001) in favour of the combination arm;
- median PFS was 26.1 months (95% CI: 11.2, NR) in the palbociclib plus letrozole arm and 5.7 months (95% CI: 2.6, 10.5) in the letrozole alone arm.

Part 2

By investigator assessment:

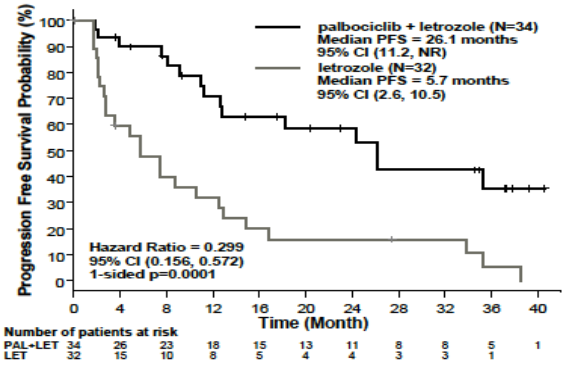
- HR 0.508 (95% CI: 0.303, 0.853; stratified 1-sided p=0.0046) in favour of the combination arm;
- median PFS was 18.1 months (95% CI: 13.1, 27.5) in the palbociclib plus letrozole arm and 11.1 months (95% CI: 7.1, 16.4) in the letrozole alone arm.

Comments:

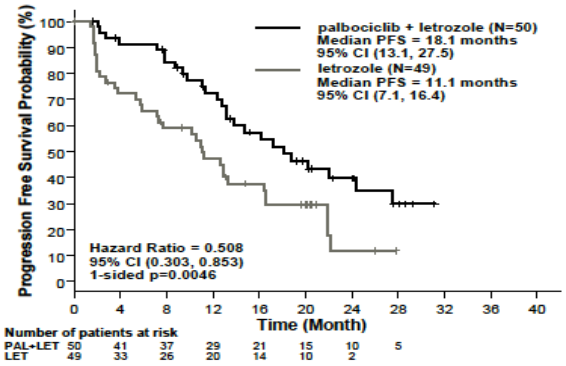
1. the median PFS for the letrozole alone arm in Part 1 is nearly half that of the same arm in the second cohort, and the median PFS for the palbociclib arm is much longer in the Part 1 compared with the same arm in Part 2 of the study.
2. Thus the Part 1 results suggest a treatment effect (with non-overlapping confidence intervals) and influences the statistical significance attributed to the treatment effect for the whole population (see Figure 5).
3. Any influence of the biomarkers used for selection of the Part 2 cohort on PFS in either arm remains unclear.
4. It is difficult when there have been so many data-driven protocol amendments to be confident in the value of statistical analyses performed under such conditions and their ability to demonstrate a true treatment effect.

Figure 5: Study A5481003 Kaplan-Meier plot of progression-free survival in the Part 1 and Part 2 cohorts of the Phase II study by Investigator assessment (ITT population)

Ph2P1 Cohort



Ph2P2 Cohort



Source: Figure 14.2.7.1.b , Table 14.2.1.1.b; and Listing 16.2.6.2.3.b.

Secondary analysis of PFS based on blinded independent central review (BICR)

Comment: Although this retrospective BICR requested by the FDA was not prespecified and was a secondary analysis, for reasons of flow it is included here.

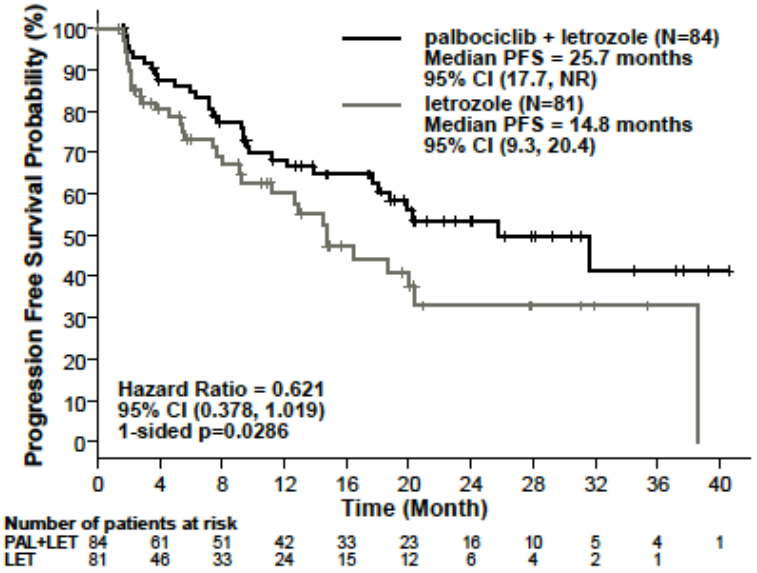
A blinded independent central review (BICR) was undertaken at the request of the FDA of radiographic images for 161/165 patients (97.6%) obtained retrospectively and read by the independent third party - missing scans for 4 patients were equally distributed across the 2 treatment arms.

By BICR analysis:

- there were 64 PFS events (31 and 33 in the palbociclib plus letrozole arm and the letrozole alone arm, respectively)
- median PFS in the palbociclib plus letrozole arm was 25.7 months (95% CI: 17.7-NR) and in the letrozole alone arm was 14.8 months (95% CI: 9.3-20.4)
- observed HR was 0.621 (95% CI: 0.378-1.019; stratified 1-sided p=0.0286)

Figure 6: A5481003 Kaplan-Meier plot of progression-free survival by blinded independent central review in the combined Phase II study (ITT population)

Phase 2 (Ph2P1+Ph2P2)



Comment: Compared with investigators, this represents 8 PFS events fewer than reported for the palbociclib and letrozole arm and 26 fewer PFS events in the letrozole alone arm. This independent analysis also indicates a 10-month improvement in median PFS, but the lower number of progression events identified in the control arm have resulted in the 95% confidence intervals overlapping between the two arms, and the HR now crosses 1, indicating a loss of reported statistical significance reported from the investigator-assessed progression. While it is possible for clinical progression without radiological confirmation to result in censoring, the large number and particularly the imbalance affecting the control arm, in an open label trial mean investigator bias cannot be excluded.

The PFS assessment supports that the use of this combination is promising in the proposed population, but requires confirmation from a well-designed, randomised, double-blind controlled trial.

BICR censoring

53 and 48 patients in the palbociclib plus letrozole arm and the letrozole alone arm, respectively, were censored in the BICR PFS analysis. Of these, 14 and 4 patients, respectively, were still in follow-up for disease progression. 24% of the Phase II population (29 and 21% in Part 1 and 2, respectively) were censored for PFS due to reasons other than still being on the study drug. The most common reason in each treatment arm was due to treatment being discontinued without a BICR PFS event. There was an imbalance in censoring rates between the 2 treatment arms, with fewer patients being censored for this reason in the palbociclib plus letrozole arm (26 patients, 31.0%) compared with the letrozole alone arm (33 patients, 40.7%).

Comment: The data presented in Table 28 [not in this document] differ from those data presented for the BICR censoring in Table 26 [not in this document] of the FDA report on the website for Study A5481003. The sponsor is requested to provide an explanation for all differences in the data presented in the dossier versus the FDA

report, including but not limited to, the higher AE rates, clinical progression, and withdrawal of consent; noting that the FDA table was generated in response to an FDA query on 28 Feb 2014. See Clinical Questions.

For the Ph2P1 Cohort:

- median PFS in the palbociclib plus letrozole arm was 31.6 months (95% CI: 11.2-NR) and in the letrozole alone arm was 38.6 months (95% CI: 7.5-38.6);
- observed HR was 0.731 (95% CI: 0.300-1.779; unstratified 1-sided p=0.2442).

For the Ph2P2 Cohort:

- median PFS in the palbociclib plus letrozole arm was 20.3 months (95% CI: 12.2-NR) and in the letrozole alone arm was 14.6 months (95% CI: 8.1-20.0);
- the observed HR was 0.576 (95% CI: 0.316-1.050; 1-sided p=0.0342).

Comment: While a large number of patients were censored in both the treatment and control arms, more were censored from analysis in the control arm, mostly due to discontinuation without evidence of disease progression. The Part 1 and Part 2 groups were not prespecified subgroups and the study is not powered to do subgroup analyses or assessments of HR, and together with the low number of PFS events, this precludes any conclusions being drawn. In the BICR, the Ph2P1 group, those receiving palbociclib were found to have an inferior median PFS which differs from the investigator findings. This raises two concerns:

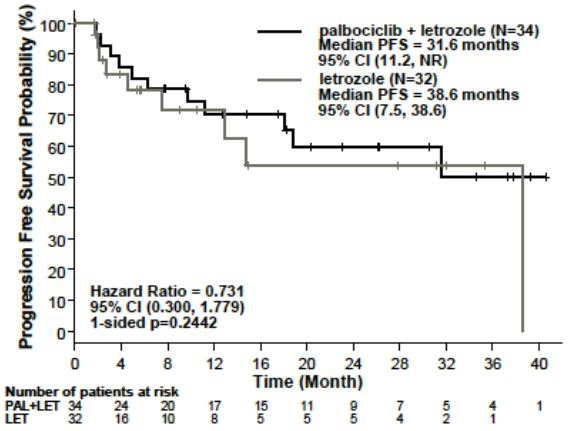
1. about including this population in an overall combined analysis
2. that protocol amendments were made based on these initial assessments

The findings in the Ph2P2 groups are encouraging, but not sufficient to provide adequate data to support registration for the proposed first line indication, particularly for such a common cancer.

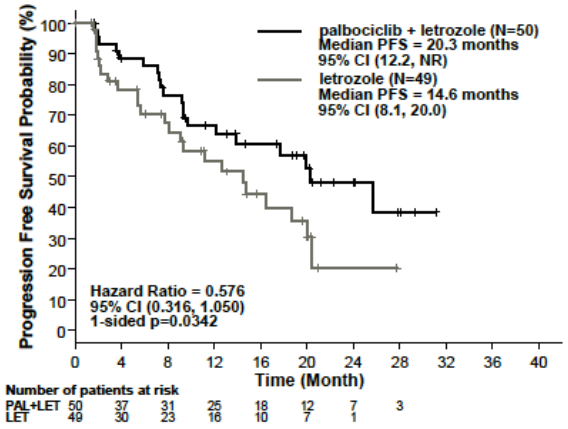
This supports that the use of this combination is promising in the proposed population, but requires confirmation from full evaluation of a well-designed, randomised, double-blind controlled trial, that is, Study 1003 is suitable as a supportive but not pivotal study for the proposed usage.

Figure 7: A5481003 Kaplan-Meier plot of progression-free survival by blinded independent central review for Part 1 and Part 2 cohorts of Phase II study (ITT population)

Ph2P1 Cohort



Ph2P2 Cohort



Discordance of Investigator Assessment and Blinded Independent Central Review of Progression-Free Survival (ITT Population)

The evaluation of the discordance of investigator and BICR assessment of PFS events is presented in Table 11.

Comment: Essentially, the greatest degree of discordance arose within the Ph2P1 group assessments, which is consistent with the different PFS outcomes reported by the two groups of assessors.

Table 11: Study A5481003 Discordance of Investigator assessment and BICR on progression-free survival: ITT population

	Palbociclib + Letrozole (N=84)			Letrozole (N=81)			Difference
	N	n	%	N	n	%	%
Total Event Disagreement Rate (c+b)/N							
Phase 2 (Ph2P1+Ph2P2)	84	28	33.33	81	28	34.57	-1.23
Ph2P1	34	10	29.41	32	16	50.00	-20.59
Ph2P2	50	18	36.00	49	12	24.49	11.51
Early Disagreement Rate (b+a3)/(a1+a2+a3+b)							
Phase 2 (Ph2P1+Ph2P2)	41	19	46.34	59	28	47.46	-1.12
Ph2P1	15	7	46.67	25	16	64.00	-17.33
Ph2P2	26	12	46.15	34	12	35.29	10.86
Late Disagreement Rate (c+a2)/(b+c+a2+a3)							
Phase 2 (Ph2P1+Ph2P2)	43	24	55.81	43	15	34.88	20.93
Ph2P1	15	8	53.33	18	2	11.11	42.22
Ph2P2	28	16	57.14	25	13	52.00	5.14
Overall Disagreement Rate (a2+a3+c+b)/N							
Phase 2 (Ph2P1+Ph2P2)	84	43	51.19	81	43	53.09	-1.90
Ph2P1	34	15	44.12	32	18	56.25	-12.13
Ph2P2	50	28	56.00	49	25	51.02	4.98

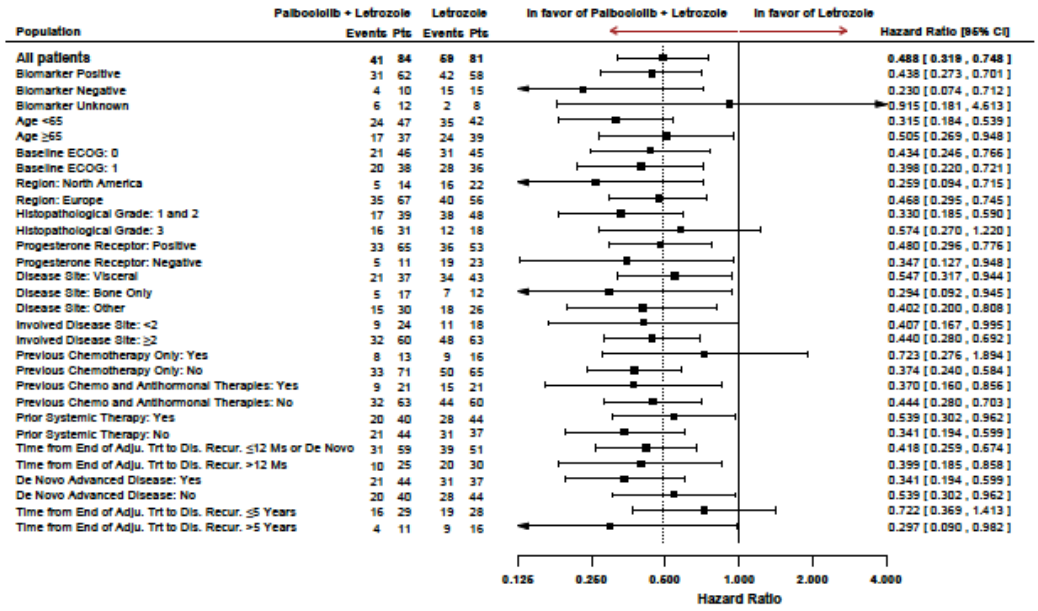
Source: Table 14.2.11.1.b.
Parameters defined as:
a1 was the number of agreements on timing and occurrence of PD by both BICR and investigator assessment.
a2 was the number of times investigator declares PD later than BICR (>7 days).
a3 was the number of times investigator declares PD earlier than BICR (>7 days).
b was the number of times investigator declares PD but BICR does not.
c was the number of times BICR declares PD but investigator does not.
Abbreviations: BICR=Blinded Independent Central Review; Ph2P1=Phase 2 Part 1; Ph2P2=Phase 2 Part 2; Ph2P1+Ph2P2=Phase 2 combined; PD=Progressive disease.

Sensitivity Analyses of Investigator-Assessed and BICR assessed Progression-Free Survival

The prospectively defined sensitivity analyses of investigator-assessed PFS in the Phase II (Ph2P1+Ph2P2) dataset are all reported with statistically significantly longer PFS in the palbociclib plus letrozole arm compared with the letrozole alone arm. Sensitivity analyses using the BICR assessments did not yield statistically significant differences between the treatment arms (HR all crossing 1).

Comment: The sensitivity analyses are consistent with the analyses of the PFS by each group. The lack of statistical significance underscores the need for an additional well-designed, larger, randomised, double blind controlled study. It also indicates the importance of a blinded central review, especially for an open label study – preferably prespecified.

Figure 8: A5481003 Subgroup analyses of Investigator-assessed PFS Phase II population (ITT)



Source: Table 14.2.13.2.b.
Abbreviations: Adju=Adjuvant; CI=Confidence interval; CRF=Case report form; Dis=Disease; ECOG=Eastern Cooperative Oncology Group; ITT=Intent-to-treat; Pts=Patients; Recur=Recurrence; Trt=Treatment.

Separate multivariate analyses of PFS (ITT population) were performed controlling for each of the baseline factors individually using investigator and BICR assessments, and identified that age≥65 and non-visceral disease site had a better prognosis.

Comment: These are known prognostic factors for ER-positive disease.

7.2.1.18 Results for other efficacy outcomes

Secondary efficacy outcomes

Overall survival (OS)

After 61 deaths and a median of 29.6 months in the treatment arm and 27.9 months in the control arm, the estimated median OS in the palbociclib plus letrozole arm was not statistically significant: 37.5 months (95% CI: 28.4-NR) and in the letrozole alone arm was 33.3 months (95% CI: 26.4-NR).

Comment: These data are immature and the study was not powered to demonstrate OS. In addition, there will also be extensive treatment switching effects after progression to therapies known to influence OS, given this study was examining first line therapy in the metastatic setting.

Overall Confirmed Objective Response by Investigator Assessment (ITT Population)

Investigator-assessed

- ORR was 42.9% [95% CI: 32.1-54.1] and 33.3% [95% CI: 23.2-44.7] in the palbociclib plus letrozole arm compared with the letrozole arm, respectively);
- odds ratio of 1.50 [95% CI: 0.76-2.97; stratified 1-sided p-value of 0.1347]);
- There was one CR in each arm, and PR was reported in 41.7% in the combination arm versus 32.1% for the control arm.

By BICR, there was no statistically significant difference between the 2 treatment arms for:

- ORR 25 (29.8%)in the palbociclib plus letrozole arm compared with 17 (21.0%) in the letrozole alone arm with an odds ratio of 1.59 (95% CI: 0.74-3.48; stratified 1-sided p=0.1314);

Overall tumour response in those with measurable disease ITT population (75% of patients)

Investigator assessed:

- ORR was numerically but not statistically significantly higher at 55.4% in the palbociclib plus letrozole arm compared with 39.4% in the letrozole alone arm;
- odds ratio of 1.93 (95% CI: 0.91-4.08; stratified 1-sided p=0.0471).

By BICR:

- ORR was 49.0% in the palbociclib plus letrozole arm compared with 32.7% in the letrozole alone arm with an odds ratio of 1.96 (95% CI: 0.82-4.70; stratified 1-sided p=0.0728);
- 10 of 35 patients with investigator-assessed PR were classified as SD by BICR in the palbociclib plus letrozole arm; 14 of 26 patients with investigator-assessed PR were classified as SD in the letrozole arm;

Comment: 25% of patients did not have measurable disease which is most likely to be due to the difficulty of assessing bone-only disease responses by currently available methods. Assessing benefit in such patients is difficult and relies upon measures of quality of life such as improvement in pain, reduced skeletal event rates etc.

Duration of response

By investigator assessment:

- median DOR was longer in the palbociclib and letrozole arm (20.3 months; 95% CI: 13.4-25.8) compared with the letrozole alone arm (11.1 months; 95% CI: 9.3-31.6)

By BICR assessment

- median DOR was NR (95% CI: 13.1-NR) in the palbociclib plus letrozole arm and 14.8 months (95% CI: 5.8-NR) in the letrozole alone arm

Comment: these results need to be interpreted with caution given the lower CR and PR rates and the small numbers of patients in the BICR assessment (25 and 17 for the treatment and control arms, respectively) as well as the overlapping confidence intervals in the investigator assessment.

Clinical benefit response

Both the investigator and retrospective BICR-assessed CBR rates were statistically significant.

Investigator assessed:

- 81.0% in the palbociclib and letrozole arm and 58.0% in the letrozole alone arm with an odds ratio of 3.18 (95% CI: 1.48-6.98; stratified 1-sided p-value=0.0009) in favour of treatment with palbociclib and letrozole.

BICR assessed:

- 71.4% in the palbociclib and letrozole arm and 50.6% in the letrozole alone arm; odds ratio was 2.47 (95% CI: 1.23-4.93; stratified 1-sided p=0.0046) in favour of treatment with palbociclib and letrozole.

Time-To-Progression

Investigator assessed:

- Median TTP was reported as statistically significant: 20.2 months in the palbociclib and

letrozole arm compared with 10.2 months in the letrozole alone arm with an HR of 0.399 (95% CI: 0.265-0.601; stratified log-rank p<0.0001)

BICR assessed:

- Median TTP was 25.7 months in the palbociclib and letrozole arm compared with 14.8 months in the letrozole alone arm with an HR of 0.621 (95% CI: 0.378-1.019; stratified log-rank p=0.0286); When analysed by cohort, there was a shorter TTP in the Ph2P1 set

Comment: The differences in statistical significance between the two assessments reflect the discordance between the rates of progression in the PFS analysis. Uncertainty remains about the benefit on time to progression, requiring confirmation in a larger, randomised double blind, controlled trial. The importance of evaluating fully both the independent and investigator reported measurements is underscored and would need to be available for Study A5481008.

Patient-reported outcomes

Modified Brief Pain Inventory Questionnaire

This was undertaken to determine whether palbociclib and letrozole increased the pain compared with letrozole, particularly for arthralgias and myalgias. Completion rates of those eligible were satisfactory.

Comment: The trial was open label and subject to potential bias, making assessments difficult to interpret. It is unclear whether this tool would be sufficiently sensitive to detect a significant change in symptoms and whether, in the metastatic setting, that could be attributed to a clinical benefit versus an adverse event related to the treatment.

This requires confirmation in a randomised, double blind, placebo-controlled clinical trial using a wider range of patient reported outcome tools.

Cell Cycle Biomarkers

There distribution of biomarkers within the biomarker positive populations was:

Part 1 (determined retrospectively)

- 21 biomarker- positive patients all of which had CCND1 amplification;
- 2 patients (9%) met criteria for CDKN2A loss (both in the letrozole alone arm).

Part 2 (biomarker selected population for CCND1 amplification and/or CDKN2A loss)

- 31 patients from the palbociclib plus letrozole arm had CCND1 amplification alone, 11 had CDKN2A loss alone and 8 had a combination of CCND1 amplification and CDKN2Aloss;
- 36 patients in the Part 2 letrozole alone arm had CCND1 amplification alone, 4patients had CDKN2A loss alone and 8 patients had a combination of CCND1 amplification and CDKN2A loss.

Based on investigator-assessed PFS, the median PFS in the palbociclib plus letrozole arm was 26.1 months for the biomarker-positive population and 35.3 months for the biomarker-negative population, respectively. Various exploratory subgroup and sensitivity analyses showed that there was an improvement in PFS with the combination treatment regardless of biomarker status.

Comment: These should be interpreted with caution due to:

- the retrospective determination of the biomarker status in the Part 1 cohort;
- the small numbers involved;
- the uncertainties about the statistical significance of the primary efficacy endpoint, PFS,

as outlined above when assessed by BIRC;

No statement is proposed in the PI and this is appropriate.

Other biomarkers

A range of exploratory biomarker analyses including CYP19A1 polymorphisms, CCDN1 genotypes, Ki67, Rb expression.

Comment: It is important to identify any populations that might or might not benefit, in a prospectively designed substudy within a larger randomised, controlled trials

Phase I efficacy summary

Additional minor support of a treatment effect comes from the non-randomised safety and PK part of this study (12 patients treated from cycle 2 onwards with palbociclib and letrozole as proposed, following completion of a dose-assessment in the first cycle).

- 7 out of 12 patients (58.3%) had a PFS event. Five patients were censored in the analysis: 2 were in follow-up for disease progression and had not had disease progression; 2 permanently discontinued due to global deterioration of health status; and 1 had permanently discontinued treatment for other reasons;
- median PFS was 24.8 months (95% CI: 6.1-not reached [NR]);
- No patients had a CR, 4 had a PR and 6 had SD>24 months and 2 SD< 24 months
- median DOR was 13.1 months (95% CI: 2.3-38.7)
- biomarker assessments were not correlated with clinical outcomes

7.2.1.19 Evaluator commentary

The Phase I/II Study A4581003 was designed as a pre-proof of concept (Phase I) and proof of concept study (Phase II) to test primarily whether adding palbociclib to letrozole in women not previously treated for their metastatic ER-positive, HER2-negativebreast cancer would improve PFS. The open label study design was amended on several occasions based on interim looks at the data which were available to the study team (Phase II Part 1). Based on preclinical data emerging about biomarkers, new eligibility criteria were introduced, requiring biomarker positivity for entry into the Phase II Part 2. This was followed subsequently by a termination in recruitment to that arm and amendment to the numbers required for a statistical analysis after better than expected results from another interim analysis of the Part 1 data, and also the finding that biomarker positivity was independent of that treatment effect. The two Parts of the Phase II study were then amalgamated to form the intention to treat population for analyses testing the hypothesis. The SAP was amended several times to accommodate changes in design during the course of the study.

The resulting design is thus more adaptive in nature, and acceptable for a proof of concept study and for hypothesis generation for future studies. However, there are significant limitations in demonstrating efficacy satisfactorily due to the multiple potential sources of bias (open label design, study team able to view Part 1 data and basing decisions upon interim analyses, errors in stratification factors (both in the design and those that emerged at the time of randomisation). These raise issues of both external and internal validity that prevent this from being a pivotal study and satisfactorily demonstrating efficacy and safety for registration purposes in Australia.

The final design of the randomised Phase II study after amendments included 165 patients, 66 in Part 1 and 99 in Part 2. The design and results of the randomised phase 2 part of Study 1003 raise significant issues about both external and internal validity.

1. Baseline and pretreatment

- 49.1% were enrolled with de novo metastatic disease whereas such patients would normally account for no more than 10% of patients with metastatic breast cancer in Australia. Evidence suggests that patients with de novo disease have a potentially better response rates than those who have relapsed following an earlier diagnosis and adjuvant therapy. However, for stratification, de novo disease was bracketed with those relapsing within 12 months of completion of adjuvant therapy for stratification where response rates are likely to be lower; this, together with errors at the time of randomisation, meant distribution across the arms for de novo disease was not even.
- In addition, it appears that 67% had received no prior systemic therapies suggesting possibly that an earlier diagnosis of breast cancer was not followed by endocrine therapy for 17.9% (clarification being sought in Clinical Questions); this would not be the standard of care in Australia if this were the case.

Internal validity issues arise from imbalances in baseline and prior treatment factors in the letrozole arm that could favour the experimental arm:

- more visceral disease in the letrozole alone arm
- a younger median age including more 18-44 yr old women
- fewer prior treatments and more patients with de novo metastatic disease compared with the palbociclib and letrozole arm.

Multivariate analyses identified the first two factors as being associated with a poorer outcome.

Non-measurable disease

- 25% had non-measurable metastatic disease at baseline (mostly due to bone-only disease), which makes objective response assessments difficult, and may have accounted in some part for the differences between the investigator and BICR assessments of rates of disease progression. In a study with small numbers, and a primary endpoint of progression-free survival, this raised significant issues in establishing, and in the independent assessment confirming, the primary endpoint.

2. Differences in selection criteria

During this trial, an amendment required those entering Part 2 to be positive for biomarkers while those in Phase I were not selected by their biomarker status. 165 patients were screened but not enrolled in the Part 2, and it is not clear what differences exist between the two groups. Thus the effect of combining them for an overall analysis and then analysing by Part 1 and by Part 2 results, a non pre-specified subgroup analysis, is unknown.

The decision to amalgamate this group with the uncertainties above, together with those from a second, biomarker-positive group (Part 2) raises concerns about the results obtained using the ITT dataset to prove the hypothesis and primary endpoint. Sensitivity analyses and subgroup analyses may to some extent provide some support for a treatment effect from palbociclib, but are not sufficient to overcome the internal validity issues and cannot provide satisfactory evidence for efficacy for registration.

3. Censoring

Clarification is being sought as to the exact figures (see Clinical Questions) but a large proportion of patients were censored for PFS for reasons not related to being still on study drug. The BICR censored more patients than the investigators, largely due to discontinuations not supported by objective measurements of assessment of progression. No post-treatment imaging was undertaken in those without objective evidence of relapse to allow independent and objective determination of the magnitude of this potential bias.

4. Independent review

The statistically significant results reported in the investigator-based analysis were not confirmed by statistically significant results in the BICR-based analyses. Clarification is being sought regarding censoring rates but there did not appear to be the same difference between the two assessments with respect to discontinued due to progression/relapse not confirmed by BICR as in Part 1. However, given the amalgamation of the two cohorts in a single efficacy analysis, this undermines the analyses of the dataset as a whole.

5. Patient-reported outcomes

Patient-reported outcomes assessments were hampered by the use of very general tools and didn't add clinically meaningful information. It is considered important that appropriate tools are used in future studies to provide data for evaluation, and information to patients regarding whether this treatment intervention improves patient wellbeing and functioning in what is a palliative treatment setting.

Conclusion

The results from Study A5481003 *suggest* that adding palbociclib to letrozole improves progression-free survival but do not establish efficacy satisfactorily for registration purposes as required in Australia. It is noted that this study formed the basis for accelerated approval in the United States and conditional registration in Canada. However, Australia does not have an option to provisionally approve medicines. It is considered important that full evaluation of the CSR from Study A5481008 (the sponsor has indicated this is expected to be available at the beginning of September 2016) is undertaken to determine whether this early promise of a potential improvement in PFS, together with an improvement in patient-reported outcomes, is confirmed, prior to any recommendation regarding registration. The differences between the investigator and independent assessments have been important in identifying uncertainties, and these should both be available for full evaluation by the TGA. It is noted that a top-line summary of the randomised, controlled, double blind, Phase III study is included in this submission (but does not include blinded review assessments of the data), but it is recommended that the full CSR be available for evaluation.

7.2.2 A5481023 'PALOMA-3' hereafter referred to as Study 1023

Pivotal study which provided efficacy supporting of the proposed indication of palbociclib in combination with fulvestrant.

7.2.2.1 Study design, objectives, locations and dates

Phase III Study A5481023 (PALOMA-3; Study 1023) is a randomised, double-blind, placebo-controlled study of the safety, efficacy, and pharmacokinetics of palbociclib plus fulvestrant or placebo plus fulvestrant administered following disease progression after prior endocrine therapy in women with hormone receptor-positive, HER2-negative advanced breast cancer.

The primary objective of the study was to determine the efficacy of palbociclib 125 mg QD on Schedule 3/1 in combination with fulvestrant with or without goserelin in this same population.

Between 26 September 2013 and 26 August 2014, 521 women were randomised, 347 patients to the palbociclib plus fulvestrant arm, and 174 patients to the placebo plus fulvestrant arm. Two (2) patients in the palbociclib plus fulvestrant arm and 2 patients in the placebo plus fulvestrant arm were randomised, but not treated.

144 sites in 17 countries enrolled patients including Australia, Belgium, Canada, Germany, Ireland, Italy, Japan, the Netherlands, Portugal, Romania, Russian Federation, Republic of South Korea, Taiwan, Turkey, Ukraine, the United Kingdom, and the United States).

2 PFS updates provided

- Study Initiation Date: 26 September 2013
- Data cut-off Date: 23 October 2015 for updated PFS and some other efficacy measures, limited safety update
- Report date: 14 April 2016
- Data Cutoff Date: 16 March 2015 for updated PFS and some other efficacy measures
- Report Date: 16 July 2015
- Data cutoff for main CSR including remaining data 5 December 2014
- Report date: 20 November 2015 (previous report dates 31 July 2015; 11 September 2015; 18 September 2015 – these have not been submitted to the TGA)

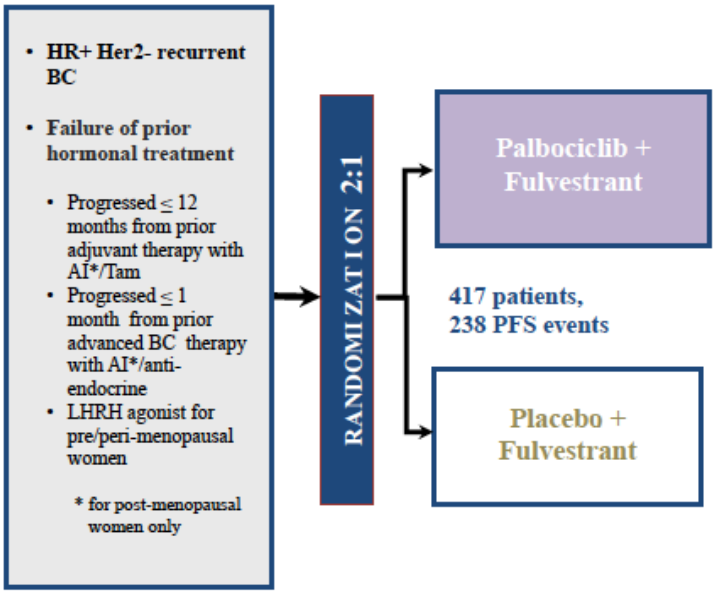
Primary Objective

- To demonstrate the superiority of palbociclib in combination with fulvestrant (with or without goserelin) over fulvestrant (with or without goserelin) alone in prolonging investigator-assessed PFS in women with HR-positive/HER2- negative metastatic breast cancer whose disease had progressed on prior endocrine therapy.

Secondary Objectives

- To compare measures of tumour control (including PFS, OR, duration of response [DR], CBR, 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.
- To compare fulvestrant and goserelin trough concentrations when given in combination with palbociclib to those when given without palbociclib.
- To explore correlations between palbociclib exposures and efficacy/safety findings in this patient population.
- To compare Patient-Reported Outcomes (PRO) measures between treatment arms.
- To characterize alterations in genes, proteins, and ribonucleic acids (RNAs) relevant to the cell cycle, drug targets, tumor sensitivity and/or resistance.
- To conduct subgroup analyses for primary, secondary endpoints in stratified groups.

Figure 9: A5481023 Study design



The following 2 amendments to the protocol were made, together with one change to the SAP:

Amendment 1, 04 April 2014

New ocular safety assessments based on preclinical data suggesting a risk of cataract formation; administration of palbociclib with food, and not concomitantly with proton-pump inhibitors (local antacids permitted and H2 receptor antagonists permitted) or with strong or moderate CYP3A inducers/inhibitors.

Amendment 2, 30 September 2014

Prospective HbA1c monitoring to characterize whether palbociclib affects glucose metabolism;

This amendment also included the following: 'In order to answer the many requests of clarifications from the clinical sites, the language related to cycle delay was further defined to clearly state that any new cycle may only start if blinded study treatment can be resumed.'

Comment: These amendments incorporated changes resulting from external trials and preclinical data and do not appear to have resulted in a significant change to the SAP and study conduct.

An external DMC was appointed and reviewed PK data after approximately 40 patients had been enrolled to determine safety of the study combination. When the protocol was amended to include ophthalmological assessments, a review of the number required for the sample size for a pre-specified analysis was only to be shared with the DMC before the interim analysis. The SAP states that there will be descriptive statistics, potentially pooled if there were insufficient numbers to analyse this variable.

Patients will continue to receive assigned treatment until objective Progressive Disease (PD), symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. Crossover between treatment arms will not be allowed.

7.2.2.2 Inclusion and exclusion criteria

Inclusion criteria

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 ≥ 12 consecutive months with no alternative pathological or physiological cause; and serum oestradiol 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, that is not meeting the criteria for being postmenopausal.
  - 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 randomisation. 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) utilising an assay consistent with local standards.
4. Documented HER2-negative tumour based on local testing on most recent tumour biopsy.
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 tumor 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 locoregional 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/mm^3 (1.5 x 10^9/L);
   - Platelets ≥ 100,000/mm^3 (100 x 10^9/L);
   - Haemoglobin ≥ 9 g/dL (90 g/L);
   - Serum creatinine ≤1.5 x upper limit of normal (ULN) or estimated CrCL ≥ 60 mL/min;
   - Total serum bilirubin ≤1.5 x ULN (<3ULN if Gilbert's disease);
   - AST and/or ALT ≤3 x ULN (≤5.0 x ULN if liver metastases present);
   - ALP ≤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.
12. Patients who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Comment:

1. One previous line of chemotherapy for advanced/metastatic disease was allowed in addition to endocrine therapy. This means a proportion of these patients would be enrolling having had at least 2 prior treatments for their metastatic disease. It is difficult to determine under what circumstances postmenopausal women with ER-positive disease would receive chemotherapy followed by endocrine therapy in the metastatic setting, other than for visceral crises. If so, such patients may represent a poorer prognostic group; both due to the presence of such metastases and more lines of prior therapy.
2. Postmenopausal women were only eligible if their disease had progressed on an aromatase inhibitor that is, they were not eligible if they had only received tamoxifen. Notably a premenopausal patient who had undergone bilateral oophorectomy but remained on tamoxifen (clinical practice would not necessarily be to change to an aromatase inhibitor in these circumstances) was considered to have been ineligible- such criteria are likely to lead to such protocol violations.

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 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 (for example, radiotherapy, stereotactic surgery) and were clinically stable off anticonvulsants and steroids for at least 4 weeks before randomisation.
4. Current use of food or drugs known to be potent CYP3A4 inhibitors, drugs known to be potent CYP3A4 inducers and drugs that are known to prolong the QT interval.

5. Major surgery, chemotherapy, radiotherapy, or other anti-cancer therapy within 2 weeks before randomisation. 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 randomisation, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.
7. QTc interval >480 ms, 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 randomisation: 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 diarrhea 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 randomisation in the current study.

Comment: The exclusion criterion of suicidal ideation or behaviour is again noted (it was also in the study protocol of Study 1008 but not for 1003). The sponsor is requested to explain the rationale behind this exclusion criterion and provide details of any details where palbociclib might have been implicated in causing patients to commit suicide or become suicidal that is, while taking or after recently stopping palbociclib (Clinical Questions).

7.2.2.3 Study treatments

Patients in Arm A (at least 278) received 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.

Patients in Arm B (at least 139) received 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.

In both arms, pre- and peri-menopausal women also received the LHRH agonist goserelin (Zoladex or generic) which must have been commenced at least 4 weeks prior to randomisation.

Patients were to continue to receive assigned treatment until objective progressive disease (PD), symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. Crossover between treatment arms will not be allowed.

Patients continued to receive assigned treatment until objective Progressive Disease (PD), symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first.

Dose reductions were permitted for the palbociclib/placebo but not fulvestrant, and fulvestrant was not to be delayed by more than 7 days. 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. Where palbociclib/placebo dose delays occurred, administration of fulvestrant and goserelin was scheduled to continue according to the pre-planned schedule.

7.2.2.4 Efficacy variables and outcomes

Baseline disease assessment for all patients (within 28 days of randomisation):

- CT or MRI scan of the chest, abdomen and pelvis.
- CT or MRI scan of any other sites of disease as clinically indicated.
- Clinical assessment of superficial disease which included photographs of all superficial metastatic lesions. All lesion measurements were recorded in the CRF.
- Bone scans; any suspicious abnormalities (that is, hotspots) identified on the bone scans at baseline were confirmed by X-ray, CT scan with bone windows or MRI. Bone lesions identified at baseline as the only site of disease followed the same assessment schedule as for measurable lesions that is, bonescan plus additional imaging modality used to confirm/characterise at baseline.

Disease assessments were performed:

- Every 8 weeks (±7 days) for the first year, then every 12 weeks (±7 days) until documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anticancer therapy, or discontinuation of patient from overall study participation (for example, death, patient's request, lost to follow-up).
- The same tumour assessment technique had to be used throughout the study for a given lesion/patient.
- Bone scans were not routinely performed in those with no bone lesions at baseline, unless clinically or biochemically indicated but were required to confirm a CR

Interpretation of PD for bone-only disease was if:

- The malignant nature of one or more new lesions identified with bone scan is
- confirmed with X-ray, or CT, or MRI scan;
- Flare observed in bone scan is followed by confirmation of progression with other imaging modalities;
- Clinical worsening of the disease is assessed by bone scan and disease progression (that is, new lesion(s)) is confirmed with other imaging modalities;

- Unequivocal progression of existing bone lesions is observed.

Interpretation will be SD if:

- The malignant nature of all the new lesions identified with bone scan is not confirmed.

If receiving a clinical benefit, patients can continue treatment with the study treatment beyond RECIST-proven PD; or in presence of toxicities, patients can continue to receive fulvestrant alone. Patients discontinuing the active treatment phase (that is, discontinuing both palbociclib/placebo and fulvestrant) entered a follow-up phase during which survival and new anti-cancer therapy information will be collected, initially every 3 months and then every 6 months.

In the following cases the patient were to be censored at the date of prior tumour assessment with no PD: 1) on-study fracture; 2) on-study management of pain (palliative radiation therapy, palliative surgery), 3) clinical worsening not objectively confirmed; 4) on-study change of therapy. In all the censored cases (no objectively documented PD) tumor assessment will be performed until PD. Also, it will be at the discretion of the investigator to discontinue the study treatment.

Patients who discontinued study treatment for reasons other than objectively documented disease progression as per RECIST definitions:

- were not to be recorded on the CRF as PD but as 'off treatment due to Global Deterioration of Health Status';
- continued to have tumour assessments performed during the follow-up visits every 8 weeks (±7 days) for the first year, and then every 12 weeks (±7 days) until
- documented disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (for example, death, patient's request, lost to follow-up).

Comment: The detail regarding bony progression and interpretation study is similar to that in the protocol for Study 1008 (see Study 1008 Efficacy Variables and Outcomes). Assessment of the BICR analyses will help determine whether this reduces some of the discordance observed between investigator assessments and BICR assessments in Study 1003.

The censoring rules for PFS determination were included to inform regarding definitions of PFS.

OS efficacy

Following the End of Treatment visit, survival status will be collected in all patients (telephone contact is acceptable) every 3 months (Month 3, 6, and 9, ±14 days) then every 6 months starting at Month 15 (±14 days) from the last dose of study treatment. Information on start, stop and type of subsequent anticancer therapy was also to be collected.

Comment: The collection of OS data in this study was more intensive than in Study 1008 (every 6 months following end of treatment) and accordingly, has potential to provide more accurate assessments of OS.

Efficacy analyses

Investigator assessments

All primary and secondary endpoints based on radiological (and photographical where applicable) assessments of tumour burden (that is, PFS, OR, DR, CBR) were derived using the local radiologist's/investigator's tumour assessments as primary data source.

Blinded independent central review (BICR)

BICR of radiographic and clinical data for a randomly selected subgroup of patients

(approximately 40%) was undertaken. The independent reviewers assessed tumour progression based on the review of scans, physical examination data and other data from the final data cut for this randomly selected subgroup of the study population. These were to verify investigators' findings and be used for supportive analyses.

Exploratory

Trough concentrations of palbociclib were collected from all patients for exposure/response analysis for safety and efficacy findings. The SAP describes these as exploratory.

Patient Reported Outcomes (PRO) will be collected in this trial using:

- the EuroQol-5D (EQ-5D);
- European Organisation for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ-C30);
- breast cancer (EORTC-QLQ-BR23).

Biomarker analyses

Under Secondary endpoints, the protocol states:

'Tumor tissue biomarkers, including genes (for example, copy numbers of CCND1 and CDKN2A, PIK3CA mutations), proteins (for example, Ki67, pRb, CCNE1), and RNA expression (for example, cdk4, cdk6)' (Study Protocol dated 30 September 2014; 2 page numbers listed on same page: 9 and 11).

Therefore, no specific biomarkers other than ER and HER2 were prespecified in the protocol.

Comment: These biomarker studies are important but essentially exploratory in nature from a statistical perspective.

Study Endpoints:

Primary Endpoint:

- Progression-Free Survival (PFS) as assessed by the Investigator.

Secondary Endpoints:

- Overall Survival (OS);
- 1-year, 2-year, and 3-year survival probabilities;
- Objective Response (OR): Complete Response (CR) or Partial Response (PR);
- Duration of Response (DR);
- Clinical Benefit Response (CBR): CR or PR or Stable Disease (SD) $\geq$24 weeks;
- Type, incidence, severity [NCI CTCAE] v4.0), seriousness and relationship to study medications of Adverse Events (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 review;
- PRO endpoints
- Tumour tissue biomarkers;

7.2.2.5 Randomisation and blinding methods

Patients deemed eligible by the sponsor on the basis of information provided in forms submitted from the trial site, were randomised into the study by interactive randomisation technology (IRT).

This form included the following information needed for patient stratification:

- documented sensitivity to prior hormonal therapy (yes vs. no);
- menopausal status at study entry (pre-/peri- vs. postmenopausal);
- presence of visceral metastases (yes vs. no).

Blinding codes could be broken in emergency situations for patient safety, or where on disease progression, it was deemed necessary to select the next therapy, after discussion with the sponsor. Wherever the blinding code was broken, site staff were to document the reasons and date but not communicate the results to sponsor personnel.

7.2.2.6 Analysis populations

Intent-to-Treat Population (Full Analysis Set)

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

As-Treated (AT) Population (Safety Analysis Set)

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.

Biomarker Analysis Set

A subset of AT patients, who have both baseline and at least one follow-up values for $\geq$ 1 biomarker.

Patient Reported Outcome (PRO) Evaluable Population (PRO Analysis Set)

The PRO –evaluable population is defined as a subset of ITT patients, who have completed a baseline and at least one post –baseline PRO assessment prior to end of study treatment.

Comment: The proportion of patients from the ITT completing the assessment will be evaluated when determining the relevance of the findings and the validity of this PRO analysis set. It is noted that 'prorating' was to be used for missing data for the QLQ-C30 and QLQ-BR23 if at least half of the scales had been answered. This introduces potential bias and makes assumptions about patients' highly personal, individual and subjective responses. If a substantial number of these are incomplete, then the appropriateness of the tool should be re-examined rather than extrapolations made.

7.2.2.7 Sample size

At least 417 patients were initially planned to be randomisation in a 2:1 ratio and stratified by documented sensitivity to prior hormonal therapy (yes vs. no), menopausal status at study entry (pre-/peri- vs. postmenopausal), and presence of visceral metastases (yes vs. no).

The sample size for this study was determined based on the median PFS for the control arm in this study being assumed to be 6.0 months. Therefore, an improvement of 56% to a median PFS of 9.38 months (corresponding to a HR=0.64) would be considered clinically meaningful. A total of 238 PFS events will be required in the two treatment arms for the study to have a 90% power to detect an increase in PFS assuming a true HR of 0.64 (representing a 56% increase in median PFS from 6 to 9.38 months), if tested at a 1-sided significance level of p=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 randomisation for final PFS analysis, and a non-uniform dropout with dropout rate of 25% at 18 months for PFS, a total sample size of 417 patients (278 in the fulvestrant plus palbociclib arm and 139 in the placebo plus fulvestrant arm) is required.

Comment: The anticipated dropout rate was high at 25% for those with metastatic disease and high degree of motivation to continue treatment if no disease progression. The sponsor is requested to provide a rationale for this. Was this to reflect anticipated side effects related to the use of fulvestrant, the administration of which is associated with significant discomfort?

The median OS for women with recurrent advanced or metastatic breast cancer treated with AI and fulvestrant monotherapy is assumed to be 24 months. With an overall one-sided p of 0.025 and one interim analysis of OS (at the time of final PFS analysis), the study will have approximately 80% power to detect a Hazard Ratio (HR) of 0.65 (representing a 54% increase in median OS from 24 months to 37 months) when 198 deaths have occurred.

7.2.2.8 Statistical methods

The study was designed to have one interim analysis 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 was also to be assessed at the interim analysis. The interim analysis of PFS will be performed after approximately 143 patients have documented PD or death (approximately 60% of the total events expected). The information fraction for the interim analysis may be adjusted if needed. The sample size of the study may also be adjusted as appropriate. Rules for determining PFS and censoring were included.

Only one interim analysis of OS was planned. This was to be hierarchically tested for significance at the time of PFS analyses, provided the primary PFS endpoint is statistically significant at the interim and/or final PFS analyses. At that point, it was estimated that 97 deaths would have occurred; if OS is not significant at the interim analysis, a final analysis will be performed after 198 deaths. With an overall one-sided α of 0.025 and one interim analysis of OS (at the time of PFS final analysis), the study will have approximately 80% to detect a HR of 0.65 (representing a 54% increase in median OS from 24 months to 37 months) when 198 deaths have occurred.

An external DMC was appointed to undertake the following:

- review PK data after approximately 40 patients had been enrolled to determine safety of the study combination;
- make recommendation as to whether or not the trial should continue based on ongoing reviews of safety data;
- evaluate interim efficacy data and make a recommendation regarding study continuation based on observed results of the study;
- When the protocol was amended to include ophthalmic assessments, a review of the number required for the sample size for a pre-specified analysis was only to be shared with the DMC before the interim analysis. The SAP states that there will be descriptive statistics and potentially pooled results if there were insufficient numbers to undertake comparative analyses.

A BICR was undertaken in 40% of the total population – assuming investigator assessment and BICR results are similar and the estimated log of investigator-based HR is -0.45 (HR=0.64), the audit size of 40% will ensure that the upper bound of a one-sided 95% CI for BICR-based treatment effect (log-hazard ratio) has 90% probability of being below zero if the correlation (ρ) between investigator assessment and BICR is 0.76 and the standard error is 0.39.

7.2.2.9 Participant flow

Between 26 Sep 2013 and 26 Aug 2014, 521 patients were randomised 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]).

Table 12: Study A5481023 Analysis populations

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)

Source: Section 14.1, Table 14.1.1.1, Table 14.2.3.2, Table 14.4.3.1
Abbreviations: BICR: blinded independent central review, ITT: intent-to-treat population, PK: pharmacokinetic, PRO: patient-reported outcome

1. Percent of patients refers to the Palbociclib Analysis population (denominator).
2. All patients who have PK blood samples collected for palbociclib and have at least 1 measured plasma drug concentration included in the analysis.

7.2.2.10 Major protocol violations/deviations

No protocol deviations were reported with the updated PFS from data cut-offs of 16 March 2015 and 23 October 2015, so the report for the data cut-off date is 5 December 2014 will be used.

Comment: The information provided at randomisation (Impala) and subsequent CRF data are very similar and any of the very minor discordances reported are unlikely to affect results of the study.

7.2.2.11 Baseline data

The demographic data were generally well-balanced as were the baseline disease data (see Table 13) except for:

- ECOG PS: 8.3% more had ECOG 0 performance status in the control arm
- Liver metastases: 10% more patients had liver metastases in the control arm
- From stage at initial diagnosis, 4.1% more had de novo metastatic disease in the treatment arm

Comment: Overall the two arms were reasonably balanced – the control arm had more patients with the poorer outlook due to having more liver metastases, and fewer with the better prognosis associated with de novo presentation but had more patients with a better ECOG PS 0.

Table 16 in the CSR includes data about the recurrence type. This includes 'newly diagnosed' as a significant category (17.7% of total population) amongst breakdown by anatomical site which makes it difficult to establish how many in the each arm of the study had locoregional disease only. The sponsor is requested to provide this information as this is a population identified in

the indication. (Clinical Question)

Table 13: Study A5481023 Summary of demographic and baseline characteristics by treatment (ITT population).

Parameter	Palbociclib Plus Fulvestrant N = 347	Placebo Plus Fulvestrant N = 174
Age (years)		
Median (min, max)	57 (30, 88)	56 (29, 80)
<65, n (%)	261 (75.2)	131 (75.3)
≥65, n (%)	86 (24.8)	43 (24.7)
Race, n (%)		
White	252 (72.6)	133 (76.4)
Black	12 (3.5)	8 (4.6)
Asian	74 (21.3)	31 (17.8)
Other	8 (2.3)	1 (0.6)
Unspecified	1 (0.3)	1 (0.6)
Region, n (%)		
North America	158 (45.5)	82 (47.1)
Europe	111 (32.0)	56 (32.2)
Asia/Pacific	78 (22.5)	36 (20.7)
ECOG performance status, n (%)		
0	206 (59.4)	116 (66.7)
1	141 (40.6)	58 (33.3)
Documented sensitivity to prior hormonal therapy[a], n (%)		
Yes	274 (79.0)	136 (78.2)
No	73 (21.0)	38 (21.8)
Visceral metastases[a], n (%)		
Yes	206 (59.4)	105 (60.3)
No	141 (40.6)	69 (39.7)
Menopausal status[a,b], n (%)		
Pre/peri	72 (20.7)	36 (20.7)
Post	275 (79.3)	138 (79.3)
Measurable disease present[c], n (%)		
Yes	268 (77.2)	138 (79.3)
No	79 (22.8)	36 (20.7)
Prior systemic therapies, n (%)		
No	0	0
Yes	347 (100)	174 (100)
Number of regimens		
1	85 (24.5)	45 (25.9)
2	126 (36.3)	66 (37.9)
3	84 (24.2)	40 (23.0)
>3	52 (15.0)	23 (13.2)

Prior treatments presented in the Table 14 and in more detail in Table 15.

Comment: The proposed indication is for those whose disease has progressed after prior endocrine therapy. This study enrolled patients who had progressed after a single line of therapy in the metastatic setting (but who may have been treated in an earlier setting), but also significant numbers who had been heavily pre-treated with 39.2% and 36.2% in the palbociclib and fulvestrant arm and placebo and fulvestrant arms respectively, having received ≥ 3 prior systemic treatments; and 75.5% and 74.1% having had ≥ 2 prior systemic therapies, respectively. 72.6% in the palbociclib and fulvestrant arm and 79.3% in the placebo and fulvestrant arm had received chemotherapy at the time of their primary diagnosis (although it is not clear whether this initial presentation was with local or metastatic disease), with

32.6% and 36.8% having had chemotherapy for metastatic disease, respectively.

This is considered representative of the target population identified in the proposed indication.

Table 14: Study A5481023 Summary of demographic and baseline characteristics by treatment (ITT population)

Parameter	Palbociclib Plus Fulvestrant N = 347	Placebo Plus Fulvestrant N = 174
Previous chemotherapy regimen for primary diagnosis		
No	95 (27.4)	36 (20.7)
Yes	252 (72.6)	138 (79.3)
Oncology treatment types		
Neoadjuvant	67 (19.3)	33 (19.0)
Adjuvant	151 (43.5)	89 (51.1)
Advanced/metastatic	113 (32.6)	64 (36.8)
Missing	1 (<1.0)	1 (<1.0)
Prior hormonal regimen for primary diagnosis		
1	134 (38.6)	77 (44.3)
>1	213 (61.4)	97 (55.7)
Prior antihormonal therapy		
Tamoxifen	210 (60.5)	104 (59.8)
Aromatase inhibitors	296 (85.3)	151 (86.8)
Involved disease site[a,d], n (%)		
Bone	264 (76.1)	130 (74.7)
Breast	60 (17.3)	18 (10.3)
Liver	127 (36.6)	81 (46.6)
Lung	100 (28.8)	45 (25.9)
Lymph node	138 (39.8)	63 (36.2)
Other	122 (35.2)	51 (29.3)
Disease stage at initial diagnosis, n (%)		
Stage I	23 (6.6)	11 (6.3)
Stage IB	3 (0.9)	2 (1.1)
Stage II	22 (6.3)	15 (8.6)
Stage IIA	59 (17.0)	20 (11.5)
Stage IIB	39 (11.2)	21 (12.1)
Stage III	42 (12.1)	29 (16.7)
Stage IIIB	13 (3.7)	7 (4.0)
Stage IIIC	14 (4.0)	11 (6.3)
Stage IV	86 (24.8)	36 (20.7)
Other	13 (3.7)	8 (4.6)
Unknown	33 (9.5)	14 (8.0)

Source: Table 1023.407.4, Table 1023.407.6, Table 1023.407.7, Table 1023.407.8, and Table 1023.407.11 (16 March 2015 data cutoff date).
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.
b. Postmenopausal defined by at least 1 of the following criteria: 1) ≥60 years of age; 2) <60 years of age 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; 3) documented bilateral oophorectomy; or 4) medically confirmed ovarian failure. Pre or perimenopausal defined as not meeting the criteria for being postmenopausal.
c. At least 1 target lesion ≥20 mm by conventional techniques or at least 1 target lesion >10 mm for spiral CT.
d. Involved sites included both target and non-target lesions. Sites with multiple lesions were counted once.

7.2.2.12 Results for the primary efficacy outcome

Primary efficacy endpoint Progression-free survival investigator assessment

Due to rapid accrual, a total of 195 events (82% of the total planned final PFS events expected (SAP specified 60%)) were included in the interim analysis. At the data cut-off date of 05 December 2014, 102 (29.4%) out of 347 patients in the palbociclib plus fulvestrant arm and 93

(53.4%) out of 174 patients in the placebo plus fulvestrant arm had experienced disease progression or had died.

- median PFS 9.2 months (95% CI: 7.5, not estimable) for palbociclib and fulvestrant arm 3.8 months (95% CI: 3.5, 5.5) for placebo plus fulvestrant;
- observed HR was 0.422 (95% CI: 0.318, 0.560; stratified 1-sided p-value <0.000001) in favour of palbociclib plus fulvestrant;

Of 70.6% of patients in the palbociclib plus fulvestrant arm and 46.6% in the placebo plus fulvestrant arm were censored in the investigator-assessed PFS analysis, the majority were still in follow-up for disease progression: (65.4%) patients in the palbociclib plus fulvestrant arm and 40.2% the placebo plus fulvestrant arm.

16 March 2015 cut-off data

As of the 16 March 2015 data cutoff date for the updated analysis, 259 patients with progression or death have been reported:

- 145 (41.8% of 347 patients) were from the palbociclib plus fulvestrant arm and 114 (65.5% of 174 patients) were from the fulvestrant arm, respectively.
- The median duration of follow-up for both arms was 8.9 months (95% CI: 8.7, 9.2 for the treatment arm; 8.3, 9.4 for the control).

Among the censored patients, 177 and 48 patients in the palbociclib plus fulvestrant arm and the placebo plus fulvestrant arm, respectively, were still in follow-up for disease progression.

- Median PFS was 9.5 months (95% CI: 9.2-11.0) in the palbociclib plus fulvestrant arm
- and 4.6 months (95% CI: 3.5, 5.6) in the placebo plus fulvestrant arm;
- HR was 0.461 (95% CI: 0.360, 0.591; 1-sided p<0.000001) in favour of palbociclib plus fulvestrant.

23 October 2015 cut-off data

As of the 23 October 2015 data cutoff date for this updated analysis, a total of 333 patients with objective progression or death have been reported:

- 200 (57.6% of 347 patients) were from the palbociclib plus fulvestrant arm and 133 (76.4% of 174 patients) were from the fulvestrant arm;
- median duration of follow-up was 15.8 months (95% CI: 15.5,16.2) for the palbociclib plus fulvestrant arm and 15.3 months (95% CI: 15.0, 15.9) for the placebo plus fulvestrant arm

Comment: A 95% CI has been provided for the duration of follow-up rather than a range. Given the short accrual time, presenting the range is unlikely to alter the outcomes or understanding of the data but it would normally be a range that is presented as follow up is an actual measurement not an estimate.

Table 15: Study A5481023 Investigator-assessed patient disposition as at the cut-off 23 October 2015

Patient Category	Number (%) of Patients (N=521)	
	Palbociclib + Fulvestrant (N=347)	Placebo + Fulvestrant (N=174)
Ongoing	111 (32.0)	29 (16.7)
Treated and discontinued	234 (67.4)	143 (82.2)
Randomized not treated	2 (0.6)	2 (1.1)
Reason for discontinuation[a]		
Adverse event	17 (4.9)	4 (2.3)
Global deterioration of health status	9 (2.6)	5 (2.9)
Lost to follow-up	0 (0)	0 (0)
Medication error without associated adverse event	0 (0)	0 (0)
Objective progression or relapse + progressive disease	195 (56.2)	127 (73.0)
Protocol violation	1 (0.3)	0 (0)
Study terminated by Sponsor	0 (0)	0 (0)
Patient died	1 (0.3)	1 (0.6)
Patient refused to continue treatment for reason other than adverse event	5 (1.4)	2 (1.1)
Patient started new treatment for disease under study	0 (0)	0 (0)
Withdrew consent	3 (0.9)	4 (2.3)
Other[b]	3 (0.9)	0 (0)

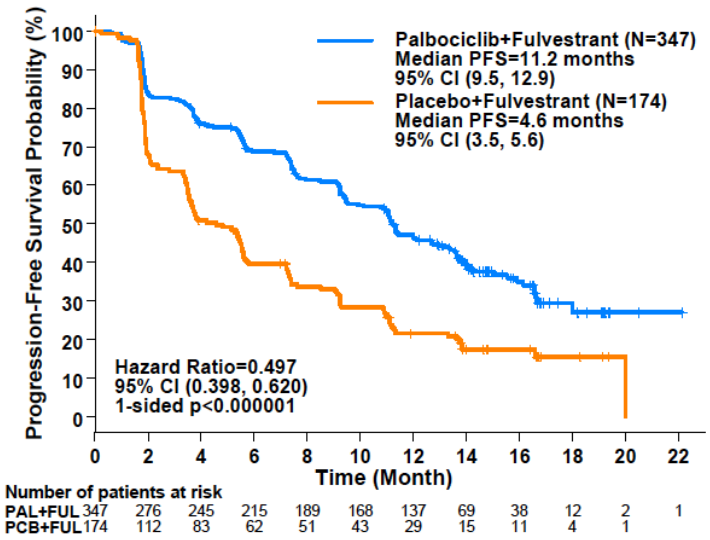
Data source: Table 1023.511.1.
Notes: 1) "Discontinued" or "ongoing" status was determined per the Conclusion-of-Treatment page in the CRF. 2) Doses of 0 mg have not been excluded from the algorithm determining patient status.
CA=cancer antigen; CRF=Case Report Form; N=total number of patients in population.
a. Includes patients who were discontinued from treatment because of disease progression or any other reason.
b. Other category is specified as "surgery on target lesion" or "subject received palliative radiation and exceeded the allowable amount of marrow exposure; physician's decision: slight bone progression with elevated CA15-3."

Among the censored patients in the palbociclib plus fulvestrant arm (2 patients were not treated), 109 (31.4%) and were still being followed up for disease progression as of 23 October 2015, while 25 patients (14.4%) were still in follow up in the comparator arm. Censoring for reasons other than progression was similar between the arms, with similar percentages of protocol deviations across the two arms:

- median PFS was 11.2 months (95% CI: 9.5-12.9) in the palbociclib plus fulvestrant arm and 4.6 months (95% CI: 3.5-5.6) in the placebo plus fulvestrant arm;
- HR (stratified analysis) was 0.497 (95% CI: 0.398-0.620; stratified 1-sided p<0.0001) in favour of palbociclib plus fulvestrant treatment.

Comment: These results demonstrate a clinically relevant and statistically significant improvement in progression-free survival. The statistically significant improvement in the PFS results are robustly demonstrated at all 3 time points for which data are presented.

Figure 10: Kaplan Meier plot for PFS (Investigator assessment, ITT population – Study A5481023 as of 23 October 2015)



Data source: Table 1023.560.1 and Figure 1023.560.12.
CI=confidence interval; FUL=fulvestrant; N=total number of patients in population; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

Sensitivity analyses

The following is taken from an evaluation of the data from the report dated 20 November 2015, data cut-off 5 December 2014, which included sensitivity analyses including BICR of approximately 40% of the data.

The preplanned sensitivity analyses 1-7 support the findings from the investigator-assessed analysis for the ITT population as at the data cut-off 5 December 2014; none are presented in support of the analyses of data from subsequent cut-off dates.

Sensitivity analysis 8, designed to test investigator bias (an issue in the earlier Phase I/II Study 1003 due to the open label nature and multiple data driven amendments) used data for the ITT population comprised of BICR-derived data if either the BICR declared an earlier PFS or if there was concordance with the investigator, and investigator data for all other patients (59.5%) in the study. There was an imbalance in the distribution of BICR reviews as this was selected randomly for 40.5% of the population (42.4% treatment arm and 36.8% control arm). This audit included 70 of the total 195 declarations of PD by the investigators: 42 in the palbociclib and fulvestrant arm and 28 in the control arm that is, the random sampling of 40.5% of the study population incorporated assessment of 35.9% of events assessed as PD by the investigators.

The discordance of investigator and BICR assessments were presented for the 40.5% of ITT randomly sampled. The following were calculated by the Clinical Evaluator:

- Total agreement on outcomes of timing of PD or no PD occurred in 170/211 (80.6%) results examined from the ITT population (123/147 or 83.7% for the palbociclib and fulvestrant arm compared with 47/64 (73.4%) for the placebo and fulvestrant arm;
- The percentage where the investigator recorded an 'early' PD, and the BICR did later or not at all was higher in the palbociclib and fulvestrant arm (18/42; 42.9%) than the placebo and fulvestrant arm (6/28; 25%);
- The percentage where the BICR recorded an 'early' PD, and the investigator did later or not at all was lower in the palbociclib and fulvestrant arm (6/24; 25%) than the placebo and fulvestrant arm (11/17 cases; 64.71%);

Comments:

1. A weakness of the audit was that the BICR was not conducted across the entire ITT population. Generating an estimated HR to support the sensitivity analysis from amalgamating predominantly (59.5%) investigator assessed data with the data amended following BICR assessments generates a population where the validity of the outcomes for more than half has not been confirmed; the results and value of such an analysis are limited (Sensitivity analysis 8). As an assessment of the value of the audit, of greater relevance is the lower HR observed when the analysis is confined to the 40.5% whose data were sampled: this was presented as 0.268 (95% CI: 0.158, 0.455; stratified 1-sided p-value <0.000001) in favour of palbociclib plus fulvestrant. However, this figure does not belong in the PI and should be removed – see Comment 7 below.
2. The total concordance rates are high based on the data.
3. Where discordance did occur, the BICR was more likely to record an earlier PD for the placebo and fulvestrant arm, and the investigator was more likely to identify an earlier PD for the palbociclib and fulvestrant arm; of note, the HR for the combined BICR/investigator PFS analysis was lower than for the investigator analysis indicating this had the greater effect on the results.
4. No information is provided on the censoring rates for the two differing groups of assessors. Therefore, the sponsor is requested to present for the 40.5% whose data was assessed by both groups:
    i. Two tables with the same information as in Table 14.2.1.1.1 [not in this document]: one for the BICR and then one for the investigator assessment data;
    ii. under the same headings as in Table 14.2.1.7 [not in this document] the results restricted to the 40.5% whose data was assessed by both groups to allow an assessment of the impact of the BICR on that subgroup.
5. However, as discordance has been established as being relatively low, the subsequent BICR secondary analyses are not as critical.
6. The PI statement in the Clinical Trials section needs to use the sponsor' description of the BICR and state that the currently presented PFS 'was supported by a random sample blinded independent committee review audit analysis conducted on 40.5%...' .
7. Given the clinical evaluator's conclusions, which are in agreement with the sponsor's own statement in the CSR: 'The objective of the random sample BICR audit approach was to corroborate the analysis results of the primary endpoint (that is, investigator assessed PFS) and to assist in the evaluation of potential bias. The BICR audit approach was not intended to provide an alternative means of definitive analysis' the HR for the BICR PFS analysis should be removed from the PI as it has no clinical relevance for prescribers.
8. Overall, within the limitations of the methodology, the data presented provided some reassurance that investigator bias is unlikely with respect to reporting of the PFS, which is important given the side effect profile of palbociclib (particularly neutropenia) would likely lead to an awareness by the investigator of the treatment allocation.
9. The sample size for the audit limits the ability of the BICR to provide support for analyses of endpoints that occurred less commonly, given there will be fewer outcomes available for direct comparisons of the declarations by the investigators. There is a lack of power to detect a difference between the arms or between the analyses for such events.
10. It is noted that the BICR for Study 1008 incorporated all ITT patients thereby avoiding these limitations.

Subgroup analyses

The sponsor included in addition to the CSR (cut-off date 5 December 214), two updated PFS analyses (16 March 2015, 23 October 2015), which also included updated OR, DoR and clinical benefit rate. Neither of these updated analyses was accompanied by BICR-derived analyses.

Comment: The PI does not include any of the updated data from the cut-off date of 23 October 2015, which means all of the results presented in the text, tables and figures in the Clinical Trials section have been superseded. There is a mixture of data from the original CSR (cut-off date 5 December 2014 and 16 March 2015. It is also noted that all the safety data and text in the PI from the cut-off date 5 December 2014 and not from the latest safety update (31 July 2015). The sponsor is requested to provide an updated PI for evaluation as part of the s31 response.

The clinical evaluator will evaluate the data but confine comments on the PI to the parts pertaining to this study that will not be changed by updated data.

The forest plot indicates that for most of the subgroups within the study, defined by stratification factors and baseline characteristics, there appeared to be a consistent treatment effect over time. Those where it was not statistically significant (that is, 95% confidence intervals cross 1) included those with:

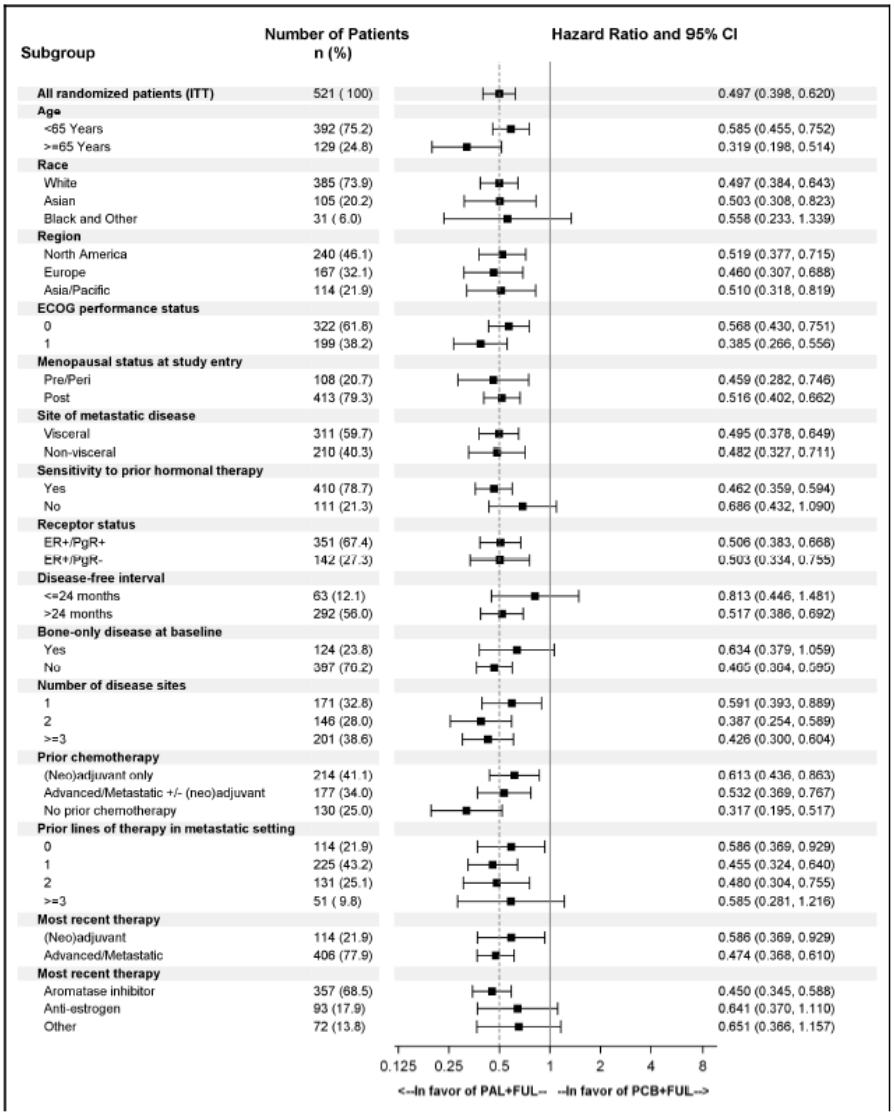
- Those of 'Black and other' or 'Asian' race
- Those from the Asia/Pacific region;
- a shorter disease-free interval;
- more $\geq$3 lines of prior therapy;
- most recently received: 'anti-estrogen' or 'other'

At the 3rd data cut-off (23 October 2015) compared with earlier subgroup analyses, the HR for the PFS analysis for those whose most recent therapy was defined as 'other' (defined as anything other than an aromatase inhibitor, tamoxifen or toremifene) now crosses 1 indicating uncertainty about a benefit in this population.

Comment:

1. Each of the first 3 of these groups are associated with a poorer prognosis, and the lack of a statistically significant treatment effect (hazard ratios all cross 1) is not unexpected. The non-significant subgroup analysis for those with $\geq$3 prior treatments may reflect the uncertain benefit of fulvestrant in more heavily pre-treated this population. However, the number of patients is small especially in the control arm so this subgroup analysis should be interpreted with caution.
2. The category of 'other' includes those no longer receiving an endocrine therapy as their most recent treatment and indicates from that treatment choice, it was likely that their disease was considered at that time to no longer be responsive to aromatase inhibitors or SERMs. Breast cancer is a heterogeneous disease and that there was some degree of response may indicate (albeit not statistically significant) following the last non-endocrine treatment, a degree of progression of the endocrine-sensitive residual disease as well as the known effect of fulvestrant in disease resistant to AIs and SERMs.
3. It is important that this latest updated forest plot is included in the PI, without truncation, to ensure prescribers are aware of the outcomes. Similarly, the accompanying PI text requires modification as outlined in the PI changes.

Figure 11: Study A5481023 Forest plot of subgroup analyses as of 23 October 2015



Data source: Table 1023.560.1, Table 1023.560.3, and Table 1023.560.11.

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.

Comments: The PI currently shows a truncated forest plot which introduces another race not identified in the study labeled in the PI as 'unspecified' and does not included 4 of those subgroups mentioned above. Specifically, the 'more ≥3 lines of prior therapy' has been left off the PI while the other prior treatment line breakdowns are included. The sponsor should include the comprehensive forest plot from the latest update (see PI changes) to ensure provision of accurate and balanced information about the subgroups.

Similarly, under Table 3 in the PI, the statement that prolongation of PFS 'was demonstrated in patient individual subgroups' should be changed to 'most individual patient subgroups' as the existing statement implies all, and together with just a truncated forest plot, does not demonstrate those subgroups where the HR crossed 1, which introduces uncertainty about the treatment effect.

The PI includes a paragraph about the treatment effect in pre/perimenopausal women which brackets together the PFS for each group receiving palbociclib and fulvestrant and then the placebo and fulvestrant arms. It is difficult to follow and should just present the median PFS and HR for each of these groups

In the update report using an earlier cut-off date of 16 March 2015, discontinuations due to withdrawal of consent occurred in 1.2 % (4 patients) in the palbociclib and fulvestrant arm but now based on the 23 October 2015 cut-off are reported as 0.9% (3 patients) with a later cut-off date - the sponsor is requested to explain why there are now fewer presented (Clinical Questions).

Multivariate analysis

Multivariate analysis of PFS treatment effect indicated that those with ECOG 1 or 2 performance status has a statistically significantly lower chance of a reduced PFS or death (HR 1.402; 95% CI: 1.053, 1.866, p=0.02) compared with those with ECOG 0. Similarly those without visceral metastases had a better outcome than those with visceral metastases.

Comment: These results confirm the already understood poor prognosis associated with these factors.

7.2.2.13 Results for other efficacy outcomes

In the updates with 23 October 2015 and 16 March 2015 cut-off dates, results were also presented for OR, 'CBR', DoR; with 112 (57% of the required 198 OS events) deaths at the most recent cut-off (23 October 2015), the OS data are too immature for analysis.

Objective response

In the ITT population OR (CR/PR) rates were higher in the treatment than the control arm, but in the analysis from the data cutoff date of 23 October 2015:

- the ITT investigator-assessed OR rate was 21.0% (95% CI: 16.9-25.7) in the palbociclib plus fulvestrant arm and 8.6% (95% CI: 4.9-13.8) in the placebo plus fulvestrant arm;
- the odds ratio was 2.78 (95% CI: 1.56-5.60) in favour of palbociclib plus fulvestrant treatment, with a stratified 1-sided p-value of 0.0001.

The sponsor provided additional analyses for endpoints that were not listed in the study design with this latest data cut-off, including the OR for patients with measurable disease.

Table 16: Study A5481023 Summary of objective response, clinical benefit response and duration of objective response – Investigator assessed as of 23 October 2015, ITT population

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

Data source: Table 1023.560.4, Table 1023.560.5, Table 1023.560.7, and Table 1023.560.9.
CBR=clinical benefit response; CI=confidence inter ooval; CR=complete response; DOR=duration of objective response; NA=not applicable; NE=not estimable; OR=objective response; PR=partial response; SD=stable disease.
a. 1-Sided exact test stratified by the presence of visceral metastases and sensitivity to prior hormonal therapy per randomization.
b. 95% CI calculated using the exact (Clopper-Pearson) method.
c. CBR=CR + PR + SD ≥24 weeks.
d. Based on the Brookmeyer and Crowley method.

In the ITT population, 4 patients (2.9%) achieved a CR in the control arm compared with none

(0%) in the treatment arm, while 21% in the treatment arm achieved a PR compared with 6.3% in the control arm. SD was reported in 52.5% (42.5%≥24 weeks) of the palbociclib and fulvestrant arm compared with 41.3% (31%≥24 weeks).

The objective progression rate (progression without any response) was 17% in the palbociclib and fulvestrant arm compared with 33% in the comparator arm.

Comment: For the first time, the OR is now statistically significantly improved in the palbociclib and fulvestrant arm. However, the OR for those with measurable disease was not a secondary endpoint and involves a subgroup analysis that was not prespecified and therefore should not be included in PI and the sponsor is requested to remove this in providing an updated PI.

Clinical benefit response

The rate of achieving a PR or SD≥ 24 weeks, but not CR as no CRs were recorded, was higher in the palbociclib and fulvestrant arm compared with the placebo and fulvestrant arm: 66.6% (95% CI: 61.3-71.5) versus 39.7% (95% CI: 32.3-47.3) based on investigator assessment. The odds ratio was 3.05 (95% CI: 2.07-4.61) also in favour of palbociclib plus fulvestrant with a 1-sided p-value of <0.0001.

Comment: 'CBR' is defined as being a CR, PR or SD for ≥24 weeks. As no CRs were achieved in the palbociclib and fulvestrant, the PI should clearly state this in conjunction with any statement made about the CBR rate and its statistical significance. This clarification in the PI thus avoids overstating the apparent benefits of treatment with palbociclib and fulvestrant from this trial (especially as there were 3 CRs in the fulvestrant arm with only half the number of patients enrolled).

Duration of response (investigator-assessed)

None of the results from the 3 time points provided was statistically significant, with overlapping 95% confidence intervals, but as the data have matured, the difference between the 2 arms has continued to decrease:

23 October 2015 data cut-off date

- median DOR was 10.4 months (95% CI: 8.3-NE) in the palbociclib plus fulvestrant arm and 9.0 months (95% CI: 5.6-NE) in the placebo plus fulvestrant arm.

16 March 2015 data cut-off date

- median of 9.3 months (95% CI: 4.0, not estimable) in the palbociclib plus fulvestrant arm versus 7.6 months (95% CI: 5.5, 9.3) in the placebo plus fulvestrant arm.

5 December 2014 study cut-off:

- median of 9.3 months (95% CI: 4.0, not estimable) in the palbociclib plus fulvestrant arm versus 5.7 months (95% CI: 3.7-5.7) in the placebo plus fulvestrant arm

Comments:

1. there is a progressive narrowing of the difference between the two arms over time indicating the value of mature clinical data.
2. the investigator-assessed duration of response was not statistically significant (overlapping 95% confidence intervals) in either Study 1008 or Study 1023. This would suggest that adding in palbociclib to existing endocrine therapies potentially improves response rates, but not the durability of that response.

Patient-reported outcomes

All data for these variables are from the main CSR with a data cut-off date of 5 December 2014. Completion rates were calculated on the percentage of patients who completed at least 1

question from baseline to cycle 14.

Furthermore, the following was specified in the SAP as to the handling of missing values in PROs:

'For QLQ-C30 and QLQ-BR23, if at least half of the constituent items for the multi-item functional or symptom scale have been answered, then the score for that scale may be pro-rated based on the non-missing items.'

Comment: Completing just one question (or even 15-20/30) is a very low requirement to be eligible to be included in the completion rate, and where it is not complete extrapolations from other parts of the questionnaire have been deemed significant for those who have completed 15 or more responses. It is not possible to determine how many study participants have completed sufficient questions to allow a meaningful evaluation of the resulting data, nor for how many sponsor has 'pro-rated' the data. The value of such 'pro-rated' data is uncertain as the very nature of these values is that they are subjective. Further clarification is only being required for participation rates and potential impact of pro-rating if the sponsor wishes to pursue retention of the information in the PI, as this evaluator's analysis of the data does not support the PI claims currently made – see below, Clinical Question.

EORTC QLQ-C30

Higher scores indicate a positive effect on quality global and functioning in the scales for this assessment, while higher symptom scores indicate worsening symptoms. The SAP specifies that a 10-point or higher change in scores from baseline is considered clinically significant.

Completion rates were calculated on the percentage of patients who completed at least 1 question from baseline to cycle 14.

- 96.9% to 100% in the palbociclib plus fulvestrant arm and 95.8% to 100% in the placebo plus fulvestrant arm

Global QoL

The estimated difference in overall change from baseline score for global QOL was 3.1 (95% CI: 0.3, 6.0). The sponsor used the 95% CI to determine there was a statistically significant difference in favour of the investigational treatment.

Functional scales

The CSR states: 'The difference between the two treatment arms in change from baseline scores for emotional functioning was found to be statistically significant (2.7 [95% CI: 1.1, 4.3] versus -1.9 [95% CI: -4.2, 0.5]; p=0.0016) favoring palbociclib plus fulvestrant. The estimated difference in overall change from baseline score for emotional functioning was 4.6 (95% CI: 1.7, 7.4).

Symptom scales

None of the values for change from baseline for the 9 symptoms assessed (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation diarrhea, and financial difficulties) reached the required change from baseline to be considered of clinical signficance.

Comment: The 95% confidence intervals for all the functional scales overlap 1, and the change in global health status is only 3.1 points (Figure 11 of the CSR). No parameters reach the SAP's stipulated change of ≥ 10 point change from baseline required to be considered of clinical significance. Accordingly, all the claims in the last paragraph of the Clinical Trials Section of the PI should be removed.

If the sponsor wishes to retain this assessment, a justification against the criteria in the SAP (≥10 point shift from baseline) as well as the following information needs to be included in the s31 response: the sponsor is requested to provide the following information: the number of patients who completed all questions of the EORTC-QLQ-C30/the number of patients

completing≤29 questions. See Clinical Questions

Time to deterioration in pain

A time to event analysis was prespecified for pain. An analysis of TTD in pain defined as time between baseline and first occurrence of increase of ≥ 10 points in pain was carried out based on survival analysis methods using a Cox Proportional hazards model and log rank test.

- Median TTD in pain was 8 months (95% CI 5.6, not estimable) in the palbociclib plus fulvestrant arm compared with 2.8 months (95% CI, 2.3, 5.4) in the placebo plus fulvestrant arm.
- HR of 0.642 [95% CI 0.487, 0.846]; p <0.001) indicating palbociclib plus fulvestrant significantly delayed TTD in pain symptom compared with placebo plus fulvestrant.

Comment: This prespecified analysis represents a clinically meaningful delay in worsening of symptoms with palbociclib and fulvestrant treatment. Inclusion of a brief statement in the PI would be considered acceptable.

Functional Scale – QLQ-BR23

The EORTC QLQ-BR23 functional scales consist of the 4 scales body image, sexual functioning, sexual enjoyment, and future perspective. The sponsor reports no statistically significant changes occurred as a result of treatment and has no claims in the PI for this assessment.

Symptoms scales - QLQ-BR23

The EORTC QLQ-BR23 symptom scales consist of the 4 symptoms systemic therapy side effects, breast symptoms, arm symptoms and upset by hair loss. No symptom scales reached the prespecified change from baseline.

Comment: It is noted that alopecia was a cause of some distress and this is listed as an AE in the PI for palbociclib and fulvestrant so clinicians will be aware. This should be included in the CMI as endocrine therapies often result in some thinning of hair, but significant hair loss is uncommon.

The Side Effects section of the CMI is poorly written: the wording for possible side effects is very long and does not provide a simple list and clear instructions. Nor does it contain any reference to neutropenia and a risk of infection.

EQ-5D Index and Visual Analog scores

No minimally important difference was pre-specified in the SAP to guide as to a significant change in this instrument.

Comment: In the absence of a prespecified figure for minimal important difference, a treatment effect cannot be established.

EQ-5D Health State profile

The first part of the EQ-5D consists of 5 descriptors of current health state, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The percentage of patients with extreme problem was low in both treatment arms at baseline and did not change notably from baseline.

EQ-5D Index Scores

The overall EQ-5D index score on treatment was found to be statistically significantly greater in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm (0.74 [95% CI: 0.72, 0.76] versus 0.70 [95% CI: 0.67, 0.73]; p=0.0308). Similarly, the between-treatment comparison based on change from baseline in overall EQ- 5D index score favored the palbociclib plus fulvestrant arm over the placebo plus fulvestrant arm (0.006 [95% CI: -0.01, 0.03] versus -0.031 [95% CI: -0.06, 0.00]; p=0.0308).

Comment: The 95% confidence intervals overlap for each of sets of results, rendering them not statistically significantly different.

EQ-5D Visual Analog scores

The visual analog scale within the EQ-5D assesses general health status. No significant difference was reported between the treatment arms, although the sponsor reported both groups experienced a statistically significant decrease from baseline.

Other results

ER, PR, HER2 from local laboratory results

- these were available in 97.7% of the palbociclib and fulvestrant arm and 96% of the placebo and fulvestrant arm;
- 3 patients had ER-negative, and 2 of these had PR-positive disease; the other was unknown;
- 70% of the palbociclib and fulvestrant arm and 67.2% of the placebo and fulvestrant arm had PR-positive disease;
- HER2 was ultimately confirmed to be negative for all patients except one

ER, PR, HER2 by central analysis

ER and PR were assessed by IHC while HER2 expression was first assessed with IHC assay. A FISH test was applied if the IHC results showed 2+ staining (equivocal).

- Tissue slides/blocks from 490 of 521 enrolled patients were sent to the central laboratory for analysis. The samples from 87 patients either had no breast tumour cells in the tissue or were not evaluable based on hematoxylin and eosin stain assessment.
- 224 (64.6%) patients in the palbociclib plus fulvestrant arm and 115 (66.1%) patients in the placebo plus fulvestrant arm were categorized as having ER-positive disease.
- Overall, 41 patients were shown to have ER-negative disease, 26 (7.5%) patients in the palbociclib plus fulvestrant arm and 15 (8.6%) patients in the placebo plus fulvestrant arm;
- In total, 28 patients were shown to have centrally confirmed ER- and PR-negative disease: 20 patients in the palbociclib plus fulvestrant arm and 8 patients in the placebo plus fulvestrant arm.
- By IHC, a total of 166 (47.8%) patients in the palbociclib plus fulvestrant arm and 90 (51.7%) patients in the placebo plus fulvestrant arm were confirmed to have HER2-negative disease;
- A total of 72 (20.7%) patients in the palbociclib plus fulvestrant arm had equivocal IHC results (IHC 2+ staining):
  - 10/72 patients were confirmed to have HER2-positive disease by FISH test, respectively; FISH failed in 4 patients and rest were found to have HER2-negativedisease
- A total of 34 (19.5%) patients in the placebo plus fulvestrant arm also had equivocal HER2 results:
  - 5 of these 34 patients were confirmed as having and HER2-positive disease by FISH, the FISH test failed in 1 patient and rest were HER2 non-amplified.

Table 17: Study A5481023 Local laboratory review of ER, PR and HER2 status

Palbociclib (PD-0332991) Protocol A5481023 - (Date of Data Cut-off: 5Dec2014)
Summary of Baseline Qualitative Result for Tumor Tissue Biomarkers from Local Laboratory - Intent to Treat

	Palbociclib (PD-0332991)+ Fulvestrant (N=347)	Placebo + Fulvestrant (N=174)
ER: n(%)		
Positive	339 (97.7)	167 (96.0)
Negative	1 (0.3)	2 (1.1)
Missing	7 (2.0)	5 (2.9)
PR: n(%)		
Positive	243 (70.0)	117 (67.2)
Negative	91 (26.2)	49 (28.2)
Missing	13 (3.7)	8 (4.6)
HER2: n(%)		
Positive	2 (0.6)	2 (1.1)
Negative	341 (98.3)	171 (98.3)
Equivocal	3 (0.9)	1 (0.6)
Missing	1 (0.3)	0

For ER and PR results of IHC method: 0 is classified as 'Negative'; 1+, 2+, 3+ and Positive are classified as 'Positive'.
For HER2 results of IHC method: 0,1+ are classified as 'Negative'; 2+ as 'Equivocal' and 3+ as 'Positive'.
For 4 subjects Positive result of HER2 was reported due to erroneous reporting of Negative laboratory result as Positive as per CRF. HER2 Negative status were confirmed by investigator.
For 4 subjects Equivocal result of HER2 was confirmed Negative by confirmatory tests.
Missing data indicates that the corresponding analyte has no record or has a record with missing data. It also includes one subject (SSID 10791001) with a discrepant PR IHC result (i.e., both a Negative and a Positive IHC score).

Progression-free survival and central laboratory results

ER-negative

- The investigator-assessed median PFS in the ER-positive subset of the palbociclib plus fulvestrant arm was 9.2 months, which is substantially longer than the median PFS (3.7 months) of the ER-positive subset of the placebo plus fulvestrant arm. Due to only 8 PFS events in the ER negative group, the median PFS was not reached at the time of analysis. The median PFS for the ER negative group was 3.8 months in the placebo plus fulvestrant arm.

PR-negative

- For patients in the palbociclib plus fulvestrant arm assessed for PR expression at the central laboratory, the investigator-assessed median PFS was 9.2 months and 5.9 months in the PR-positive subset and PR-negative subset, respectively.
- In the placebo plus fulvestrant arm, the median PFS was 5.4 months for the PR-positive subset and 3.5 months for the PR-negative subset.

HER2-negative

- In the palbociclib plus fulvestrant arm, the median PFS of the HER2-negative subset was longer than the median PFS of the HER2-positive subset (9.2 months versus 7.5 months). But there were only 5 PFS events in the 19 centrally confirmed HER2-positive patients.
- The median PFS of the HER2-negative group was 3.7 months in the placebo plus fulvestrant arm. The median PFS of the HER2-positive subset was not reached due to the low number of only 2 PFS events.

Summary

The inclusion criteria required patients to have advanced or metastatic breast cancer that was ER-positive and/or PR-positive, and HER2-ve. 403/521 patients' tumours were evaluable for central testing and of these 28 were ER-/PR- and 15 were confirmed to be HER2 amplified with a further 5 uncertain due to failure of FISH testing. These revised outcomes were relatively balanced between the arms but the sponsor's review of the outcomes (which appear to be based on immature data) do not suggest a balanced outcome.

Thus there have been very significant protocol violations for at least 43 patients out of the 403 (10.7%) who had evaluable samples, subsequently being found to be ineligible to participate. A further 5 remain uncertain due to difficulties with the FISH test for HER2. Missing data prevent an analysis and confirmation of the status of the remaining 118 patients, and these too are a protocol deviation as provision of adequate samples was an inclusion criterion.

No information was found by the evaluator as to how many of the biopsy samples used in the central testing were from a biopsy sample taken following their most recent episode of progression to determine ER/PR/HER2 status and the sponsor is requested to provide this information as it has been shown that a discordant rate between primary and secondary breast cancers has been reported to be as high as 25-30%: Amir et al (2012) reported rates of 16% such discordance for ER and PR status in a prospective study.

Comments:

1. ER, PR and HER2 centrally determination has been shown to be discordant between primary and secondary breast cancer in a high proportion of patients, which may be in part due to prior treatments as well as clonal heterogeneity.
2. A review of the protocol deviations in the CSR does not include these events as a major protocol deviation (none could be found under 'Inclusion/Exclusion'), yet it would appear more significant than many of the events listed there in terms of potential to affect efficacy. Triple negative and HER2-positivebreast cancers are aggressive subtypes and the former does not respond to endocrine therapy at all, and the latter may if ER-positive but that information is not provided; in any case, failure of prior last endocrine therapy may select for and/or indicate those where HER2 is the predominant driver of cell division and disease progression.
3. This information is a clinically relevant 'real world' issue, where patients have not been treated with the standard of care (for example, anti-HER2 therapy) due to tumour testing issues.
4. Failure to provide an adequate sample for central testing is also a protocol violation, and does not appear to be recorded as such.
5. Given the importance of these, both in terms of potential effect and the numbers involved (10.7% of the evaluable population), the evaluator believes these should be regarded as, and included in the protocol violations. The results are too important to be considered 'exploratory', especially as central testing was prespecified.
6. Had central testing been required prior to randomisation then these issues would not have arisen.
7. A sensitivity analysis, removing all those who were ineligible for enrolment, to determine whether there was any effect on the ITT PFS analysis has not been performed and is requested. Furthermore, although limited by small numbers, an analysis of the PFS in this subgroup should be performed, as well as a further sensitivity analysis excluding those whose data were missing as well as those who were ineligible should also be performed (Clinical Question). These should be presented as a forest plot against the observed PFS outcome for the ITT population.
8. No information has been provided on the patients whose samples were PR-positive but not ER-positive. The sponsor is requested to provide the numbers in each arm and the outcomes for this small subset as the indication is currently seeking registration in a population described as 'hormone receptor positive' which could mean ER-negative/PR-positive.

Table 18: Study A5481023 Central Laboratory review of ER, PR and HER2

	Palbociclib (PD-0332991)+ Fulvestrant (N=347)	Placebo + Fulvestrant (N=174)
ER IHC: n(%)		
Positive	224 (64.6)	115 (66.1)
Negative	26 (7.5)	15 (8.6)
Missing	97 (28.0)	44 (25.3)
PR IHC: n(%)		
Positive	154 (44.4)	90 (51.7)
Negative	92 (26.5)	39 (22.4)
Missing	101 (29.1)	45 (25.9)
HER2 IHC: n(%)		
Positive	9 (2.6)	5 (2.9)
Negative	166 (47.8)	90 (51.7)
Equivocal	72 (20.7)	34 (19.5)
Missing	100 (28.8)	45 (25.9)

For ER and PR results of IHC method: if H-Score is >=1 then result is 'Positive', if H-Score is <1 then result is 'Negative'.
For HER2 results of IHC method: 0,1+ are classified as 'Negative'; 2+ as 'Equivocal' and 3+ as 'Positive'.
Among the 72 HER2 IHC equivocal cases in the Palbociclib + Fulvestrant arm, results of HER2 FISH testing was negative in 58 cases, positive in 10 cases, and failed in 4 cases.
Among the 34 HER2 IHC equivocal cases in the Placebo + Fulvestrant arm, results of HER2 FISH testing was negative in 28 cases, positive in 5 cases, and failed in 1 case.
One subject with missing qualitative HER2 result is HER2 negative according to FISH method.
Missing data may indicate that the tumor samples were not adequate for testing or test procedures failed.

7.2.2.14 Evaluator commentary

Study A5481023 was a randomised, placebo-controlled, double blind study examining the effects of adding palbociclib to fulvestrant compared with fulvestrant alone in women with locally recurrent or metastatic ER-positive and/or PR-positive, HER2- breast cancer who were postmenopausal and whose disease had most recently progressed on an aromatase inhibitor, and also included premenopausal women whose disease had progressed following tamoxifen (with or without ovarian suppression), with ovarian suppression with goserelin required in conjunction with the fulvestrant.

The primary endpoint of investigator-assessed PFS was robustly demonstrated for the ITT population, and the benefit appeared consistent regardless of menopausal status prior to the commencement. While no complete responses were achieved with the combination of palbociclib and fulvestrant, 4 were seen in the fulvestrant alone arm; there was an improvement in the PR and SD rates, with these two figures contributing to the high figure for clinical benefit rate. The OR (made up of PR and CR) was statistically significantly improved in the palbociclib and fulvestrant arm for the first time at the most recent data cut-off (that is, no overlapping 95% confidence intervals).

No improvement in duration of response was observed between the treatment arms (a finding also reported in the first line studies). Overall survival data are too immature for a meaningful analysis, and the study is ongoing and remains blinded to report this at a later time point. The sponsor should provide this information when available.

A blinded independent central review was conducted in 40.5% of the ITT population, selected at random and did not demonstrate within that subpopulation that there was any apparent investigator bias with respect to the PFS outcomes. Extrapolation of this assumption to the entire ITT population is not considered valid, nor any analyses that rely upon partially replaced investigator data for the ITT population with data with BICR assessments; while the chance of bias is considered low for the remaining population, any remaining uncertainty is a consequence of undertaking only a limited independent review process.

The sponsor has been requested to provide additional information and sensitivity analyses after a central review demonstrated discordance between the central and local laboratories in determining ER, PR and/or HER2 status, with 10.7% of those with evaluable samples not meeting the study inclusion criteria as per central review. The sponsor has also been requested to provide a breakdown of the numbers and outcomes for those with ER-/PR-positive disease as this population is currently encompassed by the proposed indication, but no efficacy outcomes are provided specifically for this group. Until this information is provided, any potential recommendation may require that the indication is restricted to those with ER-positive disease only.

Similarly, it is not clear what percentage of patients had local or locoregional recurrence (without metastatic disease), and whether they derived the same benefit as those with metastatic disease. The sponsor has been requested to provide the breakdown of numbers in each arm and efficacy outcomes as this population is identified specifically in the indication. Any recommendation regarding approval in this group cannot be made without this information (note is made that the population should be identified as 'locally advanced' not 'advanced' in the indication which can encompass distant disease as well, and therefore is used less commonly in Australia).

The evaluation of the patient-reported outcomes was hampered by methodological issues:

- the presentation of participation and completion rates (if 1 or more questions were answered, then this was deemed to have been completed);
- pro-rating to fill in data in missing responses for those who had answered >50% of the questions in a questionnaire;
- either the absence of nominating a minimal important difference or disregard for that value as nominated in the SAP.

The only patient-reported outcome endpoint the evaluator considered established as having both statistical and clinical significance was the time to deterioration in pain scores, which was prolonged in those receiving palbociclib and fulvestrant compared with those receiving fulvestrant alone.

The PI is currently not satisfactory, and requires amendments and updating and re-evaluation once those have been done. This includes updating in line with the latest data cut-off date presented (23 October 2015 cut-off date for the text, figures and tables), taking note of the comments made in regard to the text in the PI comments by this evaluator.

7.2.3 A5481008 'PALOMA-2' hereafter referred to as Study 1008.

The top-line summary report dated 21 April 2016 using a data cut-off date of 26 February 2016 was provided from this randomised, multicentre, double-blind Phase III study of palbociclib plus letrozole versus placebo plus letrozole for the treatment of postmenopausal women with ER-positive, HER2- breast cancer who have not received any prior systemic anticancer treatment for advanced disease.

The sponsor provided 12 pdf documents for evaluation of Study A5481008:

1. 1 with Serious adverse event narratives (with some hyperlinks to CIOMS narratives watermarked with 'DRAFT'; others with no hyperlinks which appear to be the cases from 08 May 2015) dated 16 Dec 2015 – this appears to supersede the 08 May 2015 document – this information is blinded as to treatment group so not evaluable to inform regarding safety of palbociclib.
2. 1 with serious adverse event narratives (no hyperlinks) dated 08 May 2015 – this information is stated to be blinded as to treatment group and superseded by pdf dated 16 Dec 2015. The absence of hyperlinks prevented any checks of the CIOMS provided to confirm this.
3. 1 with CIOMS watermarked 'DRAFT' labeled 'Death Narratives' with each blinded as to treatment group dated 16 Dec 2015.
4. 1 with CIOMS watermarked 'DRAFT' labeled Death Narratives; with each blinded as to treatment group and superseded by pdf dated 29 July 2015.
5. 1 with CIOMS watermarked 'DRAFT' labeled 'Other Serious Adverse Event' blinded as to treatment group dated 16 Dec 2015.

6. 1 with CIOMS watermarked 'DRAFT' labeled 'Other Serious Adverse Event' dated 29 July 2015 blinded as to treatment group and superseded by document dated 16 Dec 2015.
7. Final Protocol, Amendment 5, 02 December 2014
8. Final Protocol, Amendment 6, 07 April 2015
9. Final Protocol, Amendment 7, 15 October 2015
10. Statistical Analysis Plan, 2 December, 2014 (not finalized and not incorporating Protocol Amendments 6 and & 7)
11. 130-page document labeled 'Topline Summary Tables' dated 19 April 2016
12. 38-page document labeled Study A5481008 – 'Topline summary of safety and efficacy' dated 21 April 2016

Notably, the following information is not included:

- results from the blinded independent central review assessments for all efficacy endpoints
- Results for 7/11 planned secondary objectives, that is, there were no results presented for OS (data immature), quality of life, QTc, PK/PD and there was a limited presentation of biomarker studies undertaken.

Comment: The documents highlighted in red are those considered to provide evaluable efficacy and safety data. Three of the first 6 documents include duplicated information, and the information in all 6 documents is blinded with respect to study treatment allocation and therefore not evaluable. The SAP has been evaluated but is stated not to be a finalized version and does not incorporate Amendments 6 and 7, which occurred after the date of this document. The Protocol Amendments 5 and 6 have been reviewed but are superseded by the later version with Amendment 7 (see below). Given this is in effect, the pivotal study in support of the proposed first line indication this is not considered sufficient to satisfactorily demonstrate safety and efficacy for registration purposes. It is reiterated that Australia does not have a provisional registration process.

7.2.3.1 Study design, objectives, locations and dates

The study design is as follows:

This is an ongoing international, multi centre, randomised, double-blind, placebo-controlled parallel-group Phase III trial comparing the efficacy and safety of PD-0332991 in combination with letrozole versus placebo plus letrozole in postmenopausal women with ER-positive/HER2-advanced breast cancer, not amenable to curative treatments. Eligible patients will have histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease and will be candidates to receive letrozole as first-line treatment for their advanced disease. Crossover is not permitted.

This study had the following objectives:

Primary Objective:

- To demonstrate that the combination of PD-0332991 with letrozole is superior to placebo plus letrozole in prolonging progression-free survival (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 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 PD-0332991 at therapeutic doses in combination with letrozole on QT interval in this patient population;
- To determine trough PD-0332991 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 ribononucleic acids (RNAs) relevant to the cell cycle (for example, CCND1 amplification, CDKN2A deletion), drug targets (such as CDK 4/6), and tumor sensitivity and/or resistance (Ki67, pRb) in tumour tissues.

The study will use an External Data Monitoring Committee (E-DMC).

The following amendments are presented as they are considered key changes to the study design:

Amendment 2, 03 Jan 3014

Preliminary results from two clinical pharmacology studies A5481018 and A5481021 suggested that palbociclib exposure may be decreased when administered in a minimally fasted state or concomitantly with proton-pump inhibitors. Therefore the protocol was amended to revise the study drug administration instructions from administration in a minimally fasted state to administration with food and also to prohibit the concomitant use of proton-pump inhibitors.

Amendment 3, 21 March 2014

Taking into account the preliminary results from studies A5481018 and A5481021, it was assumed that drug exposures before and after implementation of Amendment 2 might be different in patients who took palbociclib in a minimally fasted state (fast from 1 hour before to 2 hours after dosing) and/or concomitantly with proton-pump inhibitors compared to those patients who did not. This difference could potentially reduce the statistical power to detect the true treatment effect of palbociclib in the intent to treat (ITT) population under the current study design. As a result, the protocol is being amended prior to the interim analysis to increase the sample size from 450 patients to 650 patients to preserve the desired statistical power.

This amendment included the requirement for ophthalomological examinations based on an interim identification of a potential risk of cataracts.

Comment: Cataract formation should be included as a potential identified risk in the safety specification of the RMP.

Amendment 5, 02 December 2014

In the current study design, an interim analysis will be performed after approximately 266 PFS events have occurred (about 65% of total PFS events needed for final analysis) using O'Brien-Fleming efficacy boundary (Lan-DeMets procedure). Under these conditions, the study could be stopped for efficacy if $z \geq 2.5469$ which would equate to a hazard ratio (HR) ≤ 0.6979, or about 4 months improvement in median PFS if the median PFS of the control arm is exactly 9 months as the study design assumed. In this instance, the interim efficacy boundary, while reaching statistical significance, may not represent a clinically meaningful improvement. The interim analysis is being revised in this protocol amendment 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. This amendment also included the requirement for measuring baseline and subsequent based on an interim identification of a potential risk of hyperglycaemia.

Comment: Hyperglycaemia should be included as a potential identified risk in the safety specification of the RMP.

Amendment 7, 15 October 2015

In order to better understand the potential influence of palbociclib on response to subsequent anti-cancer treatments, the study is being amended to collect the date of disease progression while on subsequent anti-cancer therapy in addition to the follow-up anti-cancer therapy details already collected (regimen number, name of therapy, and start/stop dates).

7.2.3.2 Inclusion and exclusion criteria

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. Histologically or cytologically confirmed diagnosis of oestrogen-receptor positive (ER-positive) breast cancer based on local laboratory results.
3. Previously untreated with any systemic anti-cancer therapy for their locoregionally recurrent or metastatic ER-positive 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/mm^3 (1.5 x 10^9 /L);

Platelets≥ 100,000/mm^3 (100 x 10^9 /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
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 edema, 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 (radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomisation.
4. Prior neoadjuvant or adjuvant treatment with a non-steroidal aromatase inhibitor (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 randomisation with:
   - Food or drugs that are known to be CYP3A4 inhibitors (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 (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 randomisation. Patients who received prior radiotherapy to $\geq$25% of bone marrow are not eligible independent of when it was received.
8. Diagnosis of any other malignancy within 3 years prior to randomisation, 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 (hypocalcemia, hypokalemia, hypomagnesemia).
11. Any of the following within 6 months of randomisation: 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 ischaemic attack, or symptomatic pulmonary embolism.

12. Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection.
13. Known hypersensitivity to letrozole, or any of its excipients, or to any palbociclib/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 I-IV) within 2 weeks before randomisation and/or during participation in the active treatment phase of the trial.
18. Recent or active suicidal ideation or behaviour.

Comment: The inclusion criteria are broader than for Study 1003, including patients with past cerebral metastases or spinal cord compression, and ECOG 2 performance status (although there were relatively few patients with ECOG 2 enrolled).

Active or recent suicidal ideation or behaviour are unusual exclusion criteria and were not exclusion criteria for Study 1003 but were in for Study 1023. This might suggest a signal or issue had emerged. The sponsor is requested to explain the rationale behind this exclusion criterion and provide details of any details where palbociclib might have been implicated in causing patients to commit suicide or become suicidal that is, while taking or after recently stopping palbociclib (Clinical Questions).

7.2.3.3 Study treatments

Patients randomised to Arm A (experimental arm) will receive:

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

Patients randomised to Arm B (control arm) will receive:

- Placebo orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment;

in combination with

- Letrozole, 2.5 mg, orally once daily (continuously).

Patients are to continue to receive their assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. Patients may continue treatment as assigned at randomisation beyond the time of RECIST-defined disease progression at the discretion of the investigator if that is considered to

be in the best interest of the patient and as long as no new anticancer treatment is initiated. In this case, the patient would continue with routine safety assessments as per the Schedule of Activities for the active treatment period.

7.2.3.4 Efficacy variables and outcomes

Disease assessments will be performed every 12 weeks (7 days) from the date of randomisation. Patients with bone lesions identified at baseline will also have repeat bone scans performed every 24 weeks (±7 days) from the date of randomisation, regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan, or MRI.

Specific instructions for bone-only disease are as follows:

- Treatment outcome will be recorded in the CRF as complete response (CR), stable disease (SD) or progression (PD).

Interpretation will be PD if:

- The malignant nature of one or more new lesions identified with bone scan is confirmed with X-ray, or CT, or MRI scan,
- Flare observed in bone scan is followed by confirmation of progression with other imaging modalities,
- Clinical worsening of the disease is assessed by bone scan and disease progression (that is, new lesion(s)) is confirmed with other imaging modalities.
- Unequivocal progression of existing bone lesions.

Interpretation will be SD if:

- The malignant nature of all the new lesions identified with bone scan is not confirmed.

In the following cases the patient will be censored at the date of prior tumor assessment with no PD: 1) on-study fracture; 2) on-study management of pain (palliative radiation therapy, palliative surgery), 3) clinical worsening not objectively confirmed; 4) on-study change of therapy. In all the censored cases (no objectively documented PD) tumour assessment will be performed until PD. Also, it will be at the discretion of the investigator to discontinue the study treatment. It is suggested to institute palliative radiotherapy (for example, lesions at risk for spontaneous micro-fractures or painful lesions) before study initiation as well as palliative surgery if possible and clinically appropriate.

Subjective progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumour assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Comment: This study protocol addresses the challenges in characterizing symptomatic bone lesions likely to indicate disease progression in those with bone-only disease, not accompanied by an objective change in the bonescan. These are critical and seek to avoid the uncertainties arising from the significant censoring of patients who discontinued without objective evidence of PD in Study 1003; this affected the statistical significance of the primary endpoint on blinded independent review assessment in that study. Such patients are an important and substantial subset of those with metastatic ER-positive breast, and form 22.7% of this total study population.

This will require the BICR data to be available to assess the impact of these protocol changes on

censoring rates and statistical significance. It has not been included in the top-line summary.

Tumour assessments will be performed until radiographically and/or clinically (that is, for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anticancer therapy or discontinuation of patient from overall study participation (for example, death, patient's request, lost to follow-up), whichever occurs first.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (that is, for photographed or palpable lesions) documented PD as per RECIST v.1.1 will continue to have tumour assessment performed during the follow-up visits every 12 weeks (±7 days) and bone scans (as applicable) every 24 weeks (±7 days) until RECIST-defined disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (for example, death, patient's request, lost to follow-up), whichever occurs first.

Comment: It is likely that any patient considered to have progressed after this first line therapy will be treated relatively soon after clinical progression is determined and study treatment discontinued and almost certainly within the 24-week interval proposed for the additional follow-up bonescan.

Patients discontinuing the active treatment phase will enter a follow-up period during which survival and new anti-cancer therapy information will be collected every 6 months from the last dose of investigational product. The follow-up period will conclude at the time of the final OS analysis.

Efficacy analyses will be performed using the local radiologist's/investigator's tumour assessments as the primary data source. However, a blinded independent third-party core imaging laboratory will complete a retrospective review of radiographic images and clinical information collected on-study to verify the protocol-defined endpoints of disease response and progression determinations as assessed by the investigator.

Endpoints

Primary Endpoint

- Progression-Free Survival (PFS).

Secondary Endpoint(s)

- Overall Survival (OS): date of randomisation to date of death due to any cause;
- 1-year, 2-year, and 3-year Survival Probabilities;
- Objective Response (OR: Complete Response or Partial Response by RECIST v1.1);
- Duration of Response (DR): complete response (CR), partial response (PR), or stable disease (SD) $\geq$24 weeks according to the RECIST version 1.1
- Disease Control (DC: CR + PR + Stable disease ≥ 24 weeks/number of patients in that arm);
- ECG analysis including corrected QT interval (QTc), PK/PD analysis of QTc;
- Tumour tissue biomarkers, including genes (for example, copy numbers of CCND1, CDKN2A), proteins (for example, Ki67, pRb), and RNA expression (for example, cdk4, cdk6);
- Trough plasma concentration of PD-0332991;
- EuroQol (EQ-5D) Score
- Functional Assessment of Cancer Therapy - Breast (FACT-B);

- Type, incidence, severity (as graded by National Cancer Institute Common
- Terminology Criteria for Adverse Events [NCI CTCAE] version 4.0), seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities.

All primary and secondary endpoints based on radiological (and photographical where applicable) assessments of tumour burden (ie PFS, OR, DR, DC) will be derived using the local radiologist's/investigator's assessment. Tumour assessments will also be performed in retrospective by a blinded independent third-party core imaging laboratory and the data will be used for secondary supportive analyses.

The primary efficacy analyses will be based on the intent-to-treat (ITT) population, defined as all patients randomised to the study. Some efficacy analyses will also be performed on the as-treated (AT) population, defined as patients who receive at least 1 dose of study treatment (that is, palbociclib/placebo or letrozole), with treatment assignments designated according to actual study treatment received. Time-to-event endpoints, including PFS, DR, and OS will be summarised using Kaplan- Meier methods and displayed graphically. The median event time and 2 sided 95% confidence interval for the median will be provided for each endpoint. Stratified log rank tests will be used to compare PFS and OS between the treatment arms.

The 1-year, 2-year, and 3-year survival probabilities will be estimated using the Kaplan-Meier method and a 2 sided 95% confidence interval for the log [-log(1-year, 2-year or 3-year survival probability)] will be calculated using a normal approximation using the Greenwood's formula and then back transformed to give a confidence interval for the 1-year, 2-year, and 3-year survival probability itself.

Following the End of Treatment visit, survival status will be collected in all patients (telephone contact is acceptable) every 6 months (±7 days) from the last dose of study treatment. Information on subsequent anti-cancer therapy will also be collected

The objective response rate (ORR) will be summarised by treatment arm along with the corresponding exact 2 sided 95% confidence interval calculated using a method based on the F distribution. Response rate comparisons between the 2 treatment arms as randomised will be assessed using Cochran-Mantel-Haenszel (CMH) test with the same stratification factors as for the PFS analysis.

Patient reported outcomes of health-related quality of life and health status will be assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) and EuroQol-5D (EQ-5D) instruments.

Tumour tissue samples were required to confirm ER status, but no other specific biomarkers were prospectively defined.

7.2.3.5 Randomisation and blinding methods

Randomisation by interactive randomisation technology (IRT) following receipt and approval by the sponsor of the study documentation including patients meeting the above criteria and written informed consent, will occur using the stratification factors described below.

The IRT assigned a unique patient identification number and also assigned study medication. If a patient does not receive the correct study treatment for their allocated treatment arm, the reason was to be clearly documented in CRF.

Breaking the blind

Blinding codes should only be broken in emergency situations for reason of patient safety. Blinding codes may also be broken after a patient discontinues treatment due to disease progression, as determined by the treating investigator using RECIST v.1.1 criteria, but only if deemed essential to allow the investigator to select the patient's next treatment regimen and after discussion and agreement with the sponsor. Code should not be broken in the absence of

emergency situations or progressive disease as per RECIST v.1.1 (for example, in case of clinical deterioration, increase in tumour markers or any other evidence suggestive of disease progression but in the absence of RECIST-defined disease progression). When the blinding code is broken, the date and reason for unblinding must be fully documented in source documents and entered on the case report form. However, every effort should be made by the site staff to ensure that the treatment arm in which the unblinded patient is assigned is not communicated to any sponsor personnel or designee involved in the conduct of the trial.

7.2.3.6 Analysis populations

Intent-to-Treat Population (ITT)

The ITT population was to include all patients who are randomised, with study drug assignment designated according to initial randomisation. The ITT population will be the primary population for evaluating all efficacy endpoints and patient characteristics.

As-Treated Population (AT)

The AT population was to include all patients who receive at least 1 dose of study treatment (ie,

PD-0332991/placebo or letrozole/placebo), 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 endpoints may be assessed in this population as well.

Efficacy Analysis

All efficacy analyses will be based on intent-to-treat (ITT) population. Some efficacy analyses will also be performed on the AT population.

7.2.3.7 Sample size

At least 650 patients will be randomised 2:1 between the experimental arm (Arm A: at least 433 patients treated with PD-0332991 plus letrozole) and the control arm (Arm B: at least 217 patients treated with placebo plus letrozole).

Patients will be stratified by:

- site of disease (visceral versus non-visceral)
- disease-free interval since completion of prior (neo)adjuvant therapy:
  - de novo metastatic;
  - ≤ 12 months;
  - >12 months;
- the nature of prior (neo)adjuvant anticancer treatment received
  - prior hormonal therapy
  - no prior hormonal therapy

The sample size for this study is determined based on the assumptions that the median PFS for patients with advanced/metastatic breast cancer receiving placebo plus letrozole in the first line treatment setting is 9 months and a risk reduction by 31% (hazard ratio of 0.69) or an improvement by 44% to a median PFS of 13 months in the palbociclib plus letrozole treatment arm is clinically meaningful. A total of 347 events are required in the 2 arms of the study based on a 2:1 randomisation to have 90% power to detect a difference assuming a true hazard ratio of 0.69 in favor of the palbociclib plus letrozole arm using a one-sided log-rank test at a significance level of 0.025. Assuming a 15% drop-out rate on either treatment arm, a non uniform accrual accomplished over a 15-month period and follow-up that will continue for about 10 months after the last patient is enrolled, a total sample size of approximately 650

patients (approximately 433 patients in the palbociclib plus letrozole arm and approximately 217 patients in the placebo plus letrozole arm) is 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. The OS outcome of a Phase III clinical trial in a similar patient population demonstrated a median OS of 34 months for the arm receiving letrozole. Using this value as an assumption with a hypothesized 26% risk reduction (a hazard ratio of 0.74) or 35% improvement in median OS (from 34 months to 46 months) in patients randomised to receive PD-0332991 plus letrozole and a follow-up period of approximately 68 months, evaluation of 390 events using a one-sided log-rank test is required for a significance level of 0.025 and power of 80% to detect a difference. OS will be hierarchically tested for significance at its interim analysis, provided the primary endpoint, PFS, is statistically significant at the interim PFS analysis, or at the final PFS analysis.

Comment: The ability to detect an effect on OS will be affected by the following:

numerous lines of therapy, including some with proven effect on OS are available for use upon progression;

although switching to palbociclib was not permitted within the study, it is approved for second line usage in combination with fulvestrant in the US;

7.2.3.8 Statistical methods

The Statistical Analysis Plan version 2 dated December 2014 was provided but states on page 6 'The SAP is being amended to reflect the changes in Protocol Amendments 2 (January 3, 2014), 3 (March 21, 2014), 4 (September 18, 2014), and 5 (December 2 2014).'

The Protocol Amendments documents provided in this submission included Protocol Amendments 6 and 7, and any resulting changes to the SAP have not yet been made. All information about the study conduct and statistical analysis is taken from Protocol amendment 7.

Comments:

1. Both the date of the SAP document and this first statement imply that required amendments to the SAP are not yet complete for Amendments 2-5, and Amendments 6 and 7 are not discussed at all in this document. Amendments 6 and 7 pertain to collection of data beyond progression and are thus unlikely to affect the sample size for the primary endpoint analysis. However, Amendments 2- 5 fundamentally affected the study design and conduct, including amongst other changes, an alteration to the number of patients to be recruited and changes to the interim analysis efficacy boundary. The impact of such changes not yet finalized require a more up to date, finalised version of the SAP to be provided with a clear indication as to what has been changed compared with the currently available SAP (as was done for Study A5481003 updated SAP).

The SAP states the study is designed to have one interim analysis and the final analysis based on the primary endpoint of PFS. A formal efficacy stopping boundary (Haybittle-Peto) for rejecting the null hypothesis will be used for the interim analysis. The purposes for the interim analysis are to allow early stopping of the study for futility or efficacy, to assess safety of the combination regimen, and to potentially adjust the sample size. The interim analysis will be performed after approximately 226 patients have documented progressive disease or die (approximately 65% of the total events expected). If the value of the test statistic exceeds the Haybittle-Peto efficacy boundary ($z \geq 4.2059$, $p \leq 0.000013$), the trial may be stopped for efficacy. Under exponential distribution assumption, this boundary equates to a hazard ratio of ~0.55 or smaller in favor of the palbociclib plus letrozole arm versus the letrozole alone arm. Alternatively, as appropriate, the sample size of the study may be adjusted using the method outlined by Cui et al. If the results of the interim analysis indicate serious safety concerns, the sponsor will communicate with the Health Authorities regarding stopping the clinical trial.

An interim analysis for efficacy is also planned for the secondary endpoint of OS. The analysis will be performed at the time of the interim or final PFS analyses if the primary endpoint PFS analysis is positive. The nominal significance levels for the interim and final analyses for OS will be determined by using the Lan-DeMets procedure with an O'Brien-Fleming stopping rule. The overall significance level for the efficacy analysis of OS will be preserved at 0.025 (one-sided test). OS will be hierarchically tested for significance at the time of PFS analyses, provided the primary endpoint, PFS, is statistically positive at the interim or final PFS analyses. If OS does not yield a significant result at these analyses, OS will be tested at the final OS analysis. If PFS is not significant at the interim and/or final PFS analyses, OS will not be statistically evaluated.

7.2.3.9 Participant flow

Between 28 February 2013 and 29 July 2014, 666 women were randomised 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).

444 patients were randomised to the palbociclib plus letrozole arm, and 222 patients were randomised to the placebo plus letrozole arm.

The study is ongoing and the data cut-off date is February 26, 2016 and report date is 21 April 2016.

On 12 September 2015, the External Data Monitoring Committee recommended that the study be continued as planned after reviewing results from the prespecified interim analyses of efficacy and safety. The number of PFS events for the interim analysis was 236, which represented about 68% of the expected events for the study. It is stated the sponsor accepted the E-DMC recommendation but remained blinded to the results of the interim analysis.

7.2.3.10 Major protocol violations/deviations

No data or summary information was presented specifically addressing these issues.

Comment:

1. The clinical evaluator has identified that for at least 6% of patients (established from the difference in numbers between subgroup who relapsed >12 months after completion of adjuvant endocrine therapy as determined at randomisation and by CRF information), there was discordance between the baseline information provided at randomisation and that subsequently recorded on the CRF. As these were stratification factors, this implies that patients were not stratified correctly which then makes establishment of balance in each arm difficult and potentially compromises the accuracy of any subgroup analyses where discordance is noted. It also introduces uncertainty regarding which is the more accurate dataset.
2. It is noted that the presentation on the updated PFS outcomes of this study at the annual meeting of the 2016 American Society of Clinical Oncology, that Dr Richard Finn presented analyses using the CRF-derived population.

No information is presented about investigator audit sites.

7.2.3.11 Baseline data

Table 19: Study A5481008 Summary of demographic and baseline characteristic by treatment (ITT population)

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)

Source: Table 14.1.2.1, Table 14.1.2.5, Table 14.1.2.5.1, Table 14.1.2.6, Table 14.1.2.7, Table 14.1.2.8.
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.

In the above table, the distribution across the arms is well-balanced for the factors presented, except for the following prognostic factors:

- ECOG 0 (45.9% control arm versus 57.9% for the palbociclib and letrozole arm): +12% favouring the treatment arm;

- >3 disease sites (46.9% control arm versus 42.5% for the palbociclib and letrozole arm): -4.4% favouring the treatment arm;
- ≥ 65 years of age: 36.5% control arm versus 40.8% for the palbociclib and letrozole arm); +4.3% in favour of the treatment arm (identified in Study 1003 as predicting a poorer prognosis).

A review of the tables identified some inconsistencies across the tables for example, with respect to the rates presenting with Stage IV disease at diagnosis compared with de novo metastatic disease. Further discrepancies are noted between the stratification factors based on randomisation and as reported in the CRF:

Reported de novo metastatic disease rates

From Table 14.1.2.5.1 31.5% for the total population ('Stage IV at initial diagnosis') – the apparent discrepancy from other rates is not corrected by adding in locoregional advanced disease

From Table 14.1.2.6 33% for total population from randomisation data

37.3% according to the CRF (a discrepancy of 19 patients in the treatment arm and 7 in the control arm cf randomisation data)

The sponsor is requested to state which reported rate was used for primary efficacy analysis of the data, and how such discrepancies are handled in the statistical analysis. (Clinical Questions)

The treatment arms were balanced with respect to prior surgeries, radiation, systemic therapies, and prior aromatase usage in adjuvant setting (48.1% of total population).

7.2.3.12 Results for the primary efficacy outcome – investigator assessment

The final analysis of the primary progression-free survival (PFS) endpoint was performed after the first 331 patients had documented progressive disease (PD) or death based on investigator assessment. 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).

- 43.7% in the treatment arm and 61.7% of the control arm had events
- estimated HR was 0.576 (95% CI: 0.463-0.718; 1-sided p<0.000001) in favour of palbociclib plus letrozole
- 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

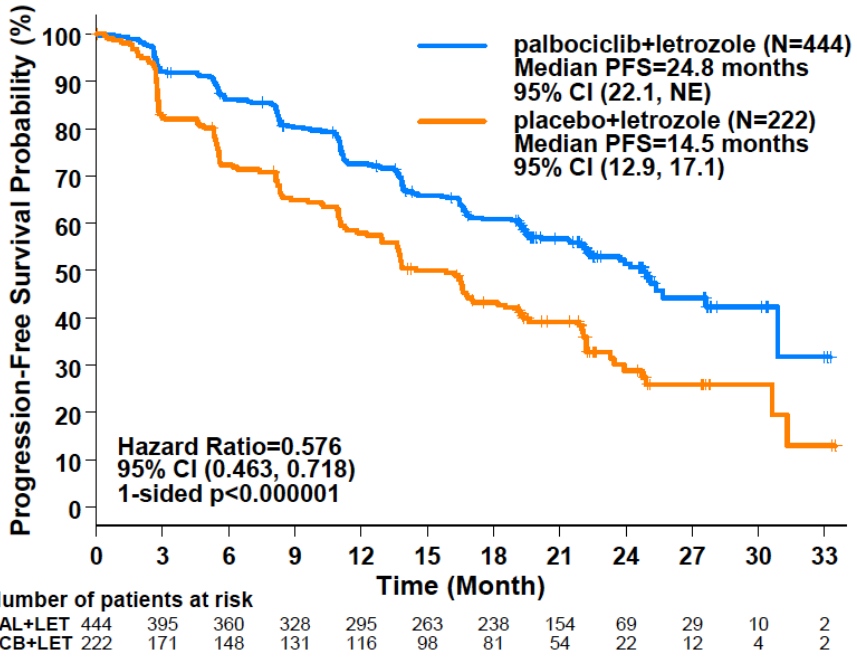
Comment: Based on the investigator assessments, there is a statistically significant improvement in PFS for the overall population. PFS based on the BICR assessment is not provided.

Table 20: Study A5481008 Progression-free survival, objective response, duration of response, and clinical benefit/response/disease control rates (Investigator Assessment, ITT population). Source Table 3, Topline summary

Primary Efficacy Results				
	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
Secondary Efficacy Results				
	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

Source: Tables 14.2.1.1.1, 14.2.3.1.1, 14.2.3.2.1, 14.2.5.1.1, 14.2.7.1.1.1, 14.2.7.1.2.
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; PFS=progression-free survival; PR=partial response; SD=stable disease.
a. Included 1 patient with bone-only disease at baseline; all other patients had measurable disease at baseline.

Figure 12: Study A5481008 Kaplan-Meier curves for progression-free survival (Investigator Assessment, ITT population) taken from Figure 2 Topline summary



Source: Figure 14.2.7.1, Table 14.2.1.1.1.
Abbreviations: CI=confidence interval; LET=letrozole; N=number of patients in population; NE=not estimable; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

The reasons for censorship based on the investigator assessment were summarised.

The censoring rates indicate similar absolute differences in discontinuations without disease progression across both arms. It is unclear how many patients 'in follow up for progression' were still on study drug (Clinical Questions) as this could include some where progression had not been established radiologically yet.

Clinical worsening in the absence of objective radiologically confirmed progression was handled differently in this study compared with Study 1003 and was required to be declared as PD only once there was radiological confirmation; clinical progression and discontinuation due to suspected progress was to be declared due to global deterioration and the numbers are even in both arms.

There were 11 (2.5%) deaths without progression in the treatment arm compared with 3 (1.4%) in the control arm. Details of these are required to understand causality (Clinical Questions), and determine if there was any link to treatment – these are not currently available.

It is noted that subgroup analyses of these data yield a non-significant PFS for the de novo metastatic population for PFS due to overlapping confidence intervals using population identified using the randomisation criteria. (HR 0.729 95% CI: 0.486, 1.093; p=0.063) compared with a HR 0.674 (95% CI: 0.457, 0.993), p=0.022) when using the CRF data.

Comment: Uncertainty exists as to whether there is a benefit for those with de novo metastatic disease. Whether this represents an increased responsiveness to the control arm which generally did better than in other subgroup analyses cannot be checked against the group who had received no prior systemic treatment for their disease (irrespective of stage of presentation) as these data could not be located in the Tables or Topline summary. Provision of these data is requested (Clinical Questions).

The results for the BICR assessment are considered important to validate the findings.

7.2.3.13 Results for other efficacy outcomes

The sponsor has provided 3 'key secondary outcomes' based on investigator assessment: OR, DoR, Disease control

Objective Response – Investigator assessment

Confirmed ORR for patients with measurable disease at baseline in the palbociclib plus letrozole arm was 55.3% (95% CI: 49.9-60.7) and in the placebo plus letrozole arm was 44.4% (95% CI: 36.9-52.2).

The odds ratio was 1.55 (95% CI: 1.05-2.28), significantly in favour of palbociclib plus letrozole with a 1-sided p-value of 0.0132.

The overall confirmed ORR rate for all patients in the palbociclib plus letrozole arm was 42.1% (95% CI: 37.5-46.9) and in the placebo plus letrozole arm was 34.7% (95% CI: 28.4-41.3) based on investigator assessment. The odds ratio was 1.40 (95% CI: 0.98-2.01) in favour of palbociclib plus letrozole with a 1-sided p-value of 0.0310.

In terms of the best overall tumour response, adding palbociclib to letrozole resulted in:

similar CR rate: 2% versus 2.3%

improved PR rate 40.1% versus 32.4%

lower objective progression (that is, progressive disease without a response): 7.7% versus 16.7%

Comment: Adding in palbociclib increased response rates and more than halved the clinical failure rate of first line letrozole treatment.

Duration of Response

The duration of response (DOR) in patients with measurable disease at baseline in the palbociclib plus letrozole arm was 22.5 months (95% CI: 19.8-28.0) and in the placebo plus letrozole arm was 16.8 months (95% CI: 15.4-28.5).

Comment: The confidence intervals are overlapping indicating this did not achieve statistical significance. It is unclear whether a more pronounced benefit would be seen in those previously treated where a lower response to letrozole would be anticipated.

Disease Control

The disease control rate (DCR) in the palbociclib plus letrozole arm was 84.9% (95% CI: 81.2-88.1) and in the placebo plus letrozole arm was 70.3% (95% CI: 63.8-76.2) based on investigator assessment. The odds ratio was 2.39 (95% CI: 1.58-3.59) also significantly in favour of palbociclib plus letrozole with a 1-sided p-value of <0.0001.

Comment: DCR includes stable disease which is a clinically relevant response but is difficult to interpret where radiological imaging underpins the means of determining progression. This analysis would benefit from validation by the independent review assessment of disease progression.

Biomarker assessment – Investigator assessment

No biomarker assessments were prespecified in the Protocol, and the only reported outcome is that of Retinoblastoma status.

Retinoblastoma (Rb) Protein Expression and Progression-Free Survival (Investigator Assessment)

568 of 666 enrolled patients had samples suitable for biomarker analysis (Biomarker Analysis Set)

- 379 patients in the palbociclib plus letrozole arm

- 189 patients in the placebo plus letrozole arm

563 patients had evaluable Rb testing results (validated assay)

- 512 (90.9%) tumours were Rb positive:
  - 345 (92.2%) in combination arm and 167 (88.4%) patients in the placebo
  - 51 (9.1%) patients' tumours were Rb negative.
  - 29 (7.8%) patients were in the combination arm and 22 (11.6%) patients were in the control arm

The sponsor presented the following investigator assessed median PFS rates according to Rb status.

Table 21: Study A5481008 Progression-free survival by Rb Status across treatment (Investigator assessment, Biomarker Analysis Set)

	Median PFS[a] (Months)			
	Palbociclib Plus Letrozole	Placebo Plus Letrozole	Hazard Ratio[b]	Log-Rank[c] p-value
Positive				
N	345	167		
Estimate	24.2	13.7	0.531	<0.0001
95% CI	(21.4-25.7)	(11.0-16.5)	(0.416-0.680)	
Negative				
N	29	22		
Estimate	NR	18.5	0.675	0.1619
95% CI	(11.4-NR)	(2.9-NR)	(0.308-1.481)	

Source: Table 14.6.4.1.2
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.

These results are immature with a median PFS in the Rb-negative population in the treatment arm not reached. The HR crosses 1 but it is difficult with the small numbers involved to make a meaningful statement about whether Rb negativity is predictive of a lesser response. These data do not preclude patients who might have their tumour status determined as negative, being offered treatment or enrolled in future palbociclib trials.

Additional information not provided in the dossier but presented at the American Society of Clinical Oncology meeting in Chicago.

The median PFS by Investigator assessment, based on there being 194 (44%) events in the treatment arm and 137 (62%) in the control arm, was 24.8 months (95% CI: 22.1, NR) versus 14.5 months (95% CI: 12.9, 17.1), respectively; HR 0.58 (0.46, 0.72); p<0.000001

The median PFS by BICR, based on 152 (34%) events in the treatment arm and 96 (43%) in the control arm was 30.5 months (95% CI: 27.4, NR) versus 19.3 months (95% CI: 16.4, 30.6) with a HR 0.65 (0.51, 0.84); p=0.0005.

Comment: These data appear to confirm the benefit but discrepancies between the figures used in the ITT population were noted for example, the de novo disease population was reported at ASCO as 37.2% of the entire population

7.2.3.14 Evaluator commentary

Study A5481008 is an ongoing randomised, controlled, double blind Phase III study designed to demonstrate that adding palbociclib to letrozole improved a range of outcomes including PFS as

the primary endpoint, and secondary outcome measures of OS, ORR, DoR, disease control rate, quality of life as well as provide further information about the pharmacokinetics and pharmacodynamics of palbociclib and also biomarkers and responses. The efficacy analyses were to be done with investigator assessments with a secondary assessment by a blinded independent review committee. A higher level of detail was included in this protocol regarding bone-only disease measurements, and the handling of progression without objective evidence of relapse and together with the double blind, randomised nature of the study sought to overcome the issues that affected Study 1003.

The limited data and results presented here provide support for a statistically and clinically significant improvement in PFS for those receiving palbociclib and letrozole compared with letrozole alone. This included an improvement in the response rates to treatment, with a halving of upfront treatment failure (best tumour response of objective progression), although the observed improvement in duration of response was not statistically significant.

However, while these investigator-assessed results appear to support the benefit seen in Study 1003, a large number of the study outcomes and assessments required to satisfactorily establish efficacy have not been presented – most notably, 5/10 of the efficacy endpoints, all the analyses of all outcomes by BICR assessment. It is not possible to evaluate the impact of the changes introduced in this study protocol with respect to the handling of progression without measurable disease without more information, particularly from the BICR.

Within the study, there was some discordance between the baseline information provided at randomisation which affected the stratification and has had an impact on the efficacy analyses, particularly on the subgroup analyses, depending which dataset is used for the ITT population. The full impact of these cannot be understood and contextualised without presentation of the study protocol deviations. It is not sufficient to provide the analyses for these groups according to the differing information source (that is, randomisation versus CRF). A more rigorous approach should include:

- Presentation of the number of patients for whom there was any discordance between the randomisation information and CRF;
- Whether these patients were from a single or limited number of investigation centres - it is noted that in Study 1003, the FDA clinical site audit identified a single site as having a significant number of protocol deviations but that analyses with these patients censored were not reported to significantly affect the outcomes;
- Presentation of sensitivity analyses for the efficacy outcomes censoring the data from these patients incorrectly classified.

While these are included in the Clinical Questions section as a reference for the clinical evaluator when Study 1008 CSR is submitted, this clinical evaluator considers that the responses to these would not, in isolation from a full evaluation of the rest of the full CSR for Study 1008, be sufficient to demonstrate efficacy satisfactorily. However, this information and analyses are recommended to be included in the preparation of the CSR for submission to the TGA. They are listed in the Clinical Questions section so that they can be readily captured and responded to by the sponsor and checked by the evaluator.

Given this is essentially the pivotal study in support of the proposed first line indication, and the wide usage if registered in this line of treatment, there should be a full dataset, analyses and secondary analyses by the BICR submitted for evaluation. The clinical evaluator notes that this was the recommendation of the TGA at the presubmission meeting in October 2015.

It is appropriate that no information has been included regarding Study 1008 in the Product Information as the top line summary has not provided sufficient information to satisfactorily establish efficacy for the proposed first line usage. Given the first line indication is not supported on the evidence supplied to date, all information pertaining to Study 1003 and the

proposed usage with letrozole should be removed from the PI. However, the clinical evaluator recommends that this be resubmitted as a new application for first line treatment with the full CSR for Study 1008.

7.3 Analyses performed across trials: pooled and meta analyses

None performed.

7.4 Evaluator's conclusions on clinical efficacy

The sponsor indicates that the currently promising efficacy data for use of palbociclib added to letrozole, and the improvement in PFS in combination with fulvestrant justifies that the indication should be broadened to allow approval of palbociclib in combination with 'endocrine therapy'. Currently registered endocrine therapies in Australia include tamoxifen, the non-steroidal aromatase inhibitors letrozole and anastrozole, and the steroidal aromatase inhibitor, exemestane as well as toremifene and megestrol acetate; these last two are not commonly used in clinical practice in Australia.

However, the clinical evaluator does not currently support registration for the combination with letrozole; this may change with each of the following addressed:

- future submission of the Study 1008 CSR for evaluation (incorporating the issues raised in this evaluation report);
- satisfactory responses to the clinical questions arising from the studies submitted in support of this usage;
- submission with the 1008 CSR of a PI providing up to date information that satisfactorily supports the safe and effective use of this combination.

Should each and all of the above be satisfied, and safety and efficacy demonstrated satisfactorily for the proposed usage in combination with letrozole, then consideration could be given at that time to extending the usage to anastrozole. Exemestane is not currently approved as a first line therapy for the treatment of metastatic breast cancer in Australia, and with the ready availability of letrozole and anastrozole (both approved as first line), extrapolation to first line usage seems unnecessary as these would be used in the first instance. It is noted that there is a study underway investigating the use of exemestane with palbociclib, which should address safety and efficacy for this usage and the sponsor can consider whether the GEICAM study investigating exemestane and palbociclib adequately supports an application for an extension of indications.

There are no data submitted in support of the safety and efficacy in combination with tamoxifen. Notable adverse events in the studies presented here were thrombosis and thromboembolic events. Given both tamoxifen and megestrol acetate are known to increase the risk for such events, data from randomised controlled, preferably blinded studies are required to support the safety of each in combination with palbociclib in the metastatic setting (another independent risk factor for thrombosis). Furthermore, tamoxifen is associated with inferior outcomes in the treatment of metastatic breast cancer compared with the nonsteroidal aromatase inhibitors as monotherapy; this, taken together with the known risk of venous thrombosis and thromboembolism with tamoxifen, and now of palbociclib treatment, means neither the safety nor the efficacy in combination with palbociclib is known and a benefit-risk assessment cannot be made. This combination is currently being studied in the metastatic setting by independent researchers but only open label Phase II studies were identified. It is being studied in a different disease setting as part of the randomised, controlled Phase III study 'PENELOPE B', where palbociclib or placebo is an add-on to standard adjuvant therapy,

including tamoxifen, for women with ER-positive breast cancer at high risk of relapse following completion of neoadjuvant therapy. However, this study may not provide sufficient safety data (noting that thrombotic risk is higher in metastatic disease) and is subject to there being sufficient numbers enrolled taking tamoxifen to allow a subgroup analysis of safety and efficacy, as well as whether this is a prespecified subgroup and the study powered for such an analysis. Furthermore, any efficacy data generated will not support usage in a potentially more heavily pretreated metastatic population.

8 Clinical safety

There is no integrated safety summary incorporating the data from the latest cut-off dates for all studies, and the populations in the SCS in the TGA dossier and the 90-day safety update overlap are different such that the latter document updates some, but not all studies in the SCS.

Comment and clinical question:

The sponsor is requested to provide a table which integrates exposure from all clinical studies (referencing the source studies) and presents:

1. the total number of patients treated to date:
    i. at the proposed dose level and regimen (palbociclib 125 mg QD 3/1)

       in combination with fulvestrant

       in combination with letrozole at the proposed dose

       in combination with letrozole at any dose level

    ii. as monotherapy

       at the proposed dose and schedule

       at any other dose
2. the median duration of treatment for all those patients and an interquartile range
    i. in combination with fulvestrant
    ii. in combination with letrozole at the proposed dose
    iii. in combination with letrozole at any dose level

The data provided included the main CSR for 2 studies (1023 and 1003) with limited updates provided in 2 subsequent safety summaries both of which has overlapping datasets that is, neither had the same dataset and the cut-off dates were different:

The Module 2 Summary of Clinical Safety data (SCS), dated as approved on 26 Oct 2015 including data up to a cut-off of 2 January 2015

This document does not appear to be the SCS referred to by the 90-day safety update given none of the hyperlinks from the 90-day safety update link to the corresponding sections and datasets in that document. Continuity between the datasets, and any certainty that the references are indeed updates for the datasets provided in the SCS provided, are thus lost. The sponsor is requested to state whether a different SCS was provided to the US.

Studies included in this were drawn from Phase I, II and III studies in range of cancers, although most commonly, breast cancer. Additional sources included PK studies in healthy volunteers, postmarketing reports from the US (equivalent of PSUR) and an access program.

The following is taken from the Module 2 Summary of Clinical Efficacy:

Overall, a total of 1640 patients with malignant disease, including advanced breast cancer, were evaluated for safety in 8 Pfizer-sponsored Phase I-III clinical studies of palbociclib included in this SCS. Of these 1640 patients, 725 (44.2%) received at least 1 dose of palbociclib either given alone (N=103 [Studies 1001, 1002, and 1010 Phase I Part 1 {Ph1P1}]) or as a component of combination therapy (N=622 [Studies 1003, 1023, 1004, 1010 Phase I Part 2 {Ph1P2} and Phase II, and 1034]); 77 (4.7%) received a comparator drug (letrozole alone in Study 1003); 172 (10.5%) received placebo (in combination with fulvestrant [Faslodex®] with or without goserelin in Study 1023); and 666 (40.6%) received blinded treatment, palbociclib or placebo (in combination with letrozole in ongoing double blind Phase III Study 1008)….This SCS primarily focuses on safety results reported in Study 1003, Study 1023, and the completed Phase I portion of Study 1010.

Comment: Study 1002 was conducted in patients with mantle cell lymphoma using a different dosing strategy and Study 1004 was conducted in patients with multiple myeloma in a different dosing strategy and combination. These are not considered to contribute to the understanding of safety for the proposed usage. Very limited, but more recent data are available from the Top-line summary for Study 1008 and this will be used for the evaluation.

In addition, a total of 407 healthy subjects were evaluated for safety in 16 Pfizer-sponsored Phase I clinical studies of palbociclib. Further, safety data reported for a total of 505 patients participating in 17 ongoing Investigator-Initiated Research (IIR) studies in which palbociclib was given either alone in patients with malignant solid tumours, including breast cancer, or as a component of combination therapy in patients with breast cancer were summarised in the SCS.

90-day US safety update

This A5481023 supplemental New Drug Application (sNDA) 90-Day Safety Update (SU) provides a comprehensive review of updated cumulative safety data of palbociclib reported in completed Phase III Study A5481023 as of the 31 July 2015 data cutoff date'. No formal report date could be located but the date on the side of the report is 30 December 2015.

The 90-day safety update incorporated 7 Pfizer-sponsored studies representing 1503 patients (that is, different number of patients from the SCS) provided updates for cancer studies using a later cut-off (31 July 2015), and also for Study 1027, a randomised Phase III trial investigating the effect of adding palbociclib to letrozole therapy in Asian postmenopausal women with metastatic breast cancer; Study 1039, a drug-drug interaction study in healthy subjects receiving modafinil and palbociclib monotherapy.

Table 22: List of studies included in the 90-day safety update provided to the US for sNDA for Study 1023.

Table 1. Pfizer-Sponsored Completed and Ongoing Clinical Studies of Palbociclib in Patients With Malignant Disease, Including Advanced Breast Cancer, Summarized in the A5481023 sNDA SCS and This 90-Day SU

Population/ Study No.	Study Title	Included in the SCS[a] (6 Studies) Total No. of Treated Patients (N=1503) (Total No. Treated With Palbociclib [N=588])[b]	Study Status[c]	Included in This SU as of 31 July 2015 (6 Studies) Total No. of Treated Patients (N=1661) (Total No. Treated With Palbociclib [N=726])[d]	Study Status[c]
Patients With Advanced Breast Cancer Receiving Either Palbociclib or Placebo as a Component of Combination Therapy or Letrozole Alone					
A5481023	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	517 (345)[e]	Completed	517 (345)[e]	Completed
A5481003	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	Phase 1: 12 (12) Phase 2: 160 (83)[f]	Completed	Phase 1: 12 (12) Phase 2: 160 (83)	Completed
A5481034	An Expanded Access Study of Palbociclib in Combination With Letrozole as Treatment of Post-Menopausal Women With Hormone Receptor Positive, HER2 Negative Advanced Breast Cancer for Whom Letrozole Therapy is Deemed Appropriate	93 (93)	Ongoing	238 (238)	Ongoing
A5481008	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	666 (~444)[g]	Ongoing	666 (~444)[g]	Ongoing
A5481027	A Multicenter, Randomized, Double-Blind Phase 3 Study of Palbociclib (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Previously Untreated Asian Postmenopausal Women With ER (+), HER2 (-) Advanced Breast Cancer	Not included	NA	20 (~10)[h]	Ongoing
Japanese Patients With Malignant Solid Tumors, Including Advanced Breast Cancer, Receiving Palbociclib Alone or in Combination With Letrozole					
A5481010[i]	A Phase 1/2 Study of the Efficacy, Safety, and Pharmacokinetics of Oral PD-0332991, a Cyclin-Dependent Kinase 4 and 6 (CDK 4/6) Inhibitor, as Single Agent in Japanese Patients With Advanced Solid Tumors or in Combination With Letrozole for the First-Line Treatment of Postmenopausal Japanese Patients With ER (+) HER2 (–) Advanced Breast Cancer	Phase 1: 18 (18)[j] Phase 2: 32 (32)	Phase 1 completed; Phase 2 ongoing	Phase 1 Part 2: 6 (6) Phase 2: 42 (42)	Phase 1 completed; Phase 2 ongoing
Patients With Malignant Disease Receiving Palbociclib Alone					
A5481001[k]	A Phase 1 Clinical, Pharmacokinetic, and Pharmacodynamic Evaluation of Two Schedules of PD-0332991, A Cyclin-Dependent Kinase Inhibitor, in Patients With Advanced Cancer	5 (5)	Completed	Not included[l]	NA

The clinical evaluator notes that the data cut-off dates for the Studies for the 90-day safety update, the Summary of Clinical Safety and the actual CSR are as follows:

- Study 1003
  - 90-day safety update: cut-off date of 31 July 2015;
  - Module 2 SCS: cut-off date 2 January 2015;
  - CSR cut-off of 29 November 2013;
- Study 1023
  - 90-day safety update: cut-off date of 31 July 2015;
  - CSR cut-off date: 05 December 2014 (same as main SCS);
  - Module 2 SCS cut-off date: 05 December 2014 (same as main CSR);
  - PI data: cut-off date: 5 December 2014;
- Study 1008
  - Top-line summary: data cut-off date 26 February 2016;
  - 90-day safety update: cut-off date of 31 July 2015 that is updated by the more recent, limited data (from data cut-off date 26 February 2016) provided with the Study 1008 'top-line summary');
  -
  - PI data – no data or text included for efficacy or safety of this proposed usage;
- In addition, 2 ongoing Pfizer-sponsored clinical studies of palbociclib, Phase III Study 1027 in Asian patients with advanced breast cancer and Phase I Study 1013 in subjects with hepatic impairment who were otherwise healthy, are included in this SU for the first time;

- A postmarketing access program in the US and Canada, Study 1034, with an updated cut-off compared with the SCS;

The clinical evaluator notes the following about the 90-day safety update:

- data for Study 1008 has been updated by the top line summary's later cut-off date;
- adverse events but not the full CSR for a study of palbociclib in volunteers without cancer with hepatic impairment (Study 1013) is included that is, providing limited supportive information relevant to the proposed usage;
- Although postmarketing adverse event data are incorporated in this report (6 months from 03 February 2015-31 July 2015), a more complete 1-year report has been provided and this will be evaluated and presented separately.

25 studies of Investigator-initiated studies of palbociclib in solid tumours including breast cancer, used alone or in combination are presented.

- CIOMS and detailed narratives are said to be provided: there are no hyperlinks from the text to these directly, and for many, these could not be located; no detailed narratives were located, only draft CIOMS and line listings;
- Deaths and other SAEs reported in these studies are summarised by the following patient populations:

Patients with breast cancer receiving palbociclib monotherapy

Patients with breast cancer receiving palbociclib plus nonchemotherapy (endocrine therapy)

Patients with non-breast malignant solid tumours receiving palbociclib monotherapy

Patients with breast cancer receiving palbociclib plus chemotherapy

Comments:

1. The PI contains no safety data from Study 1008[2], and therefore cannot be evaluated with respect to this usage (See Clinical Questions).
2. The most relevant population providing safety data for the proposed usage are those 1015 women (61.9%) who had advanced or metastatic breast cancer and received at least 1 dose of palbociclib 125 mg QD on Schedule 3/1 in combination with endocrine therapy (either letrozole, or fulvestrant +/- goserelin). See 'Exposure' below.
3. All data from Study 1027 is still blinded therefore the safety data are summarised blinded for treatment. Thus, this does not offer evaluable data for the proposed usage and will not be summarised or considered further.
4. Of the investigator-initiated studies, the first 3 patient populations above might yield supportive data for the proposed indications but the toxicities arising from chemotherapy will confound any assessments of safety for palbociclib.

8.1 Studies providing evaluable safety data

The studies from the palbociclib development program providing evaluable safety data in support of the proposed usages are Studies 1023, 1003, 1008 (very limited), 1010, 1001 with additional information in a 90-day safety update from Study 1027 (not evaluable) and Study 1034 (very limited), but no CSR for either.

[2] Not included in early draft of PI

8.1.1 Palbociclib and fulvestrant combination

- The CSR from Study 1023 with a safety update provided in the 90-day safety update; the latter updates the information from the CSR and therefore has been used by the evaluator.

Comment: As previously noted, the PI does not include information from this 90-day safety update and an updated PI needs to be provided by the sponsor .

8.1.2 Palbociclib and letrozole combination

- This includes data from a Phase I/II randomised, open label, controlled study, and 1 Phase I/II study in Japanese patients:
  - 'top-line summary' data for Study 1008;
  - Full CSR for Study 1003 (29 November 2013) with an update in the Module 2 SCS (2 January 2015), and then limited further update in the 90-day safety update (31 July 2015) of 'Selected cumulative safety data summarised in this section include information on deaths and other SAEs along with patient disposition, geographic region, as well as baseline demographics and ECOG PS reported as of 31 July 2015 in Studies 1003, 1034, 1008, 1027' (90-day safety update)
  - 1010 Ph1P2 and Phase II, 1013, and IIR studies.
  - Study 1010 Phase I Part 2 (Ph1P2) and Phase II in Japanese patients
  - safety update and 'other serious adverse events narratives' draft CIOMS for Study 1027 which are blinded as to treatment allocation and therefore not evaluable;
  - Study 1034 (expanded access program), no CSR or discussion other than in safety update within 90-day safety update but limited presentation of CIOMS;
  - No Integrated safety summary for this proposed usage has been provided incorporating data from Studies 1003 and 1008;
  - Summary of Clinical Safety with a report date of 26 October 2015, cut-off date of 2 January 2015 for Study 1003 and 5 December 2014 for Study 1023, which integrates the safety from a range of studies including those using palbociclib monotherapy. This has largely been updated for Study 1023 and partly updated for Study 1003 by the 90-day safety update, and contains no safety information about Study 1008 and the top-line summary for Study 1008.

No integrated safety summary has been provided for the letrozole and palbociclib safety data (Clinical Question).

8.1.3 Other studies providing safety data

25 Phase I, II and III investigator-initiated research (IIR) studies in a range of solid tumours, in combination with a range of other treatments or as monotherapy; 17 of these are included in the Summary of Clinical Safety and 25 in the 90-day safety update.

Overall, safety data on deaths and other SAEs were summarised in the 90-day safety update for a total of 1028 patients participating in these 25 IIR studies, in which palbociclib was given either alone in patients with malignant solid tumours, including breast cancer, or as a component of combination therapy in patients with breast cancer.

Comment: The evaluator proposes to evaluate the randomised controlled data for each proposed indication separately, given the differing profiles of the co-administered treatments. Non-randomised data from the combination and from monotherapy will be evaluated for additional signals. Where palbociclib is used in combination

with another treatment other than an aromatase inhibitor or fulvestrant (for example, chemotherapy) this will not be considered to provide relevant safety information regarding the proposed usage in this application. Similarly, where palbociclib is used as monotherapy in other solid tumours, any safety issues will be considered and interpreted in light of known adverse events associated with the underlying malignancy.

8.1.4 Adverse event reporting

Study protocols were available for Studies 1003, 1023 and 1008 and the reporting of the adverse events and abnormal test findings are based on these definitions:

An adverse event is:

'An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage.'

'Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

Test result is associated with accompanying symptoms, and/or

Test result requires additional diagnostic testing or medical/surgical intervention, and/or

Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

Test result is considered to be an AE by the investigator or sponsor.'

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.'

Comments:

In the palbociclib development program, AEs were reported in accordance with FDA and ICH guidances. Uncertainty in AE data could still be present (as for any trial, despite following standard guidances), because, for example:

1. Reporting adverse event only if the patient is symptomatic or action is required could lead to underreporting of AEs, particularly for abnormal laboratory testing or diagnostic tests which may be significant but are frequently asymptomatic.
2. Relying on the investigator to nominate AEs by making attributions about a new medicine (that is, identifying the event or abnormal measurement as relevant, significant and/or related and therefore, recognizing that action is required) could lead to underreporting of both clinical and laboratory AEs.
3. There can be inter-investigator variability in reporting of outcomes, as well as potentially bias where a study is open label (Study 1003) and within blinded studies where distinct toxicity profiles could lead to assumptions about treatment allocation, effectively unblinding treatment(palbociclib causes significant neutropenia).

8.1.5 Pivotal studies that assessed safety as the sole primary outcome

No pivotal studies were provided that assessed safety as the sole primary outcome.

8.1.6 Pivotal and/or main efficacy studies

The Phase III Study 1008 is considered the pivotal study for the proposed palbociclib and letrozole combination, and the Phase I/II Study 1003 is considered supportive due to smaller numbers and significant methodological issues (see Efficacy section)

Study 1023 is the pivotal study for the proposed combination of palbociclib and fulvestrant. No other studies examined this combination for the proposed usage.

8.1.7 Other studies

Phase I/II Study 1003 in patients with advanced breast cancer receiving palbociclib in combination with letrozole or letrozole alone.

Phase I/II Study 1010 in Japanese patients with advanced malignant solid tumours, including breast cancer, receiving palbociclib alone (phase 1 part 1) or in combination with letrozole (Phase I part 2 and Phase II).

8.1.7.1 Studies with evaluable safety data: dose finding and pharmacology

Phase I Study 1001 A Phase I Clinical, Pharmacokinetic, and Pharmacodynamic Evaluation of 2 Schedules of Oral PD 0332991, a Cyclin-Dependent Kinase Inhibitor, in Patients With Advanced Cancer

Most early dose finding studies are of palbociclib monotherapy (for example, Study 1001, Study 1010 Phase I Part 1) and offer limited safety information for the proposed usage in combination. Together with other monotherapy PK or PD studies, these will be evaluated for additional safety signals.

8.1.7.2 Studies evaluable for safety only

A small postmarketing study, Study 1034 provides limited safety information from the 90-day safety update and the limited narratives/CIOMS provided. No CSR is provided.

A safety update from Study 1027, a randomised Phase III study in Asian subjects, is included together with some CIOMS (marked as 'draft') which are blinded to treatment allocation; no CSR is provided. These data are as such, not evaluable.

8.2 Studies that assessed safety as the sole primary outcome

No studies were provided that assessed the safety as the sole primary outcome for the proposed usages.

8.3 Patient exposure (taken from 90-day safety update for Study 1023, Top-line summary for Study 1008)

Of 1661 patients with solid tumours identified in the 90-day safety update, 1160 women (69.8%) had advanced or metastatic breast cancer and received at least 1 dose of palbociclib 125 mg QD on Schedule 3/1 in combination with endocrine therapy (either letrozole, or fulvestrant +/- goserelin)

- 835 patients (70.8%) received palbociclib plus letrozole of whom
  - 95 participated in completed open-label, randomised Study 1003;
    - 12 of the 95 patients in Study 1003 initially received palbociclib alone on Schedule 2/1 in Cycle 1 of the Phase I part of the study then switched to the Schedule 3/1 in combination with letrozole taken continuously starting with Cycle 2;

  - 48 participated/are participating in Study 1010 in Japanese patients
    - 6 patients in the completed Ph1P2 portion
    - 32 patients in the ongoing Phase II portion of the study);
  - 444 (based on a 2:1 patient randomisation ratio for palbociclib versus placebo [666 × 2/3 = 444]) are participating in ongoing randomised, double-blind Phase III Study 1008;
  - 20 patients in Study 1027, randomised 1:1, and still blinded as to whether they were receiving palbociclib or placebo in combination with continuous letrozole;
  - 238 are participating in ongoing open-label Expanded Access Protocol 1034;
- 345 of the 1015 patients (34.0%) with advanced breast cancer received palbociclib plus fulvestrant with or without goserelin in completed randomised, double-blind Phase III Study 1023.

8.3.1 Study 1023 (as of 31 July 2015)

- 345/347 patients randomised to the palbociclib plus fulvestrant arm received at least one treatment;
  - 209/347 patients (60.2%) in the palbociclib plus fulvestrant arm had permanently discontinued
- 172/174 patients randomised to the placebo plus fulvestrant arm received at least one treatment;
  - 138/174 patients (79.3%) in the placebo plus fulvestrant arm were permanently discontinued;

Hence, 136/347 patients (39.2%) in the palbociclib plus fulvestrant arm and

34/174 patients (19.5%) in the placebo plus fulvestrant arm were ongoing as of 31 July 2015.

8.3.1.1 Duration of exposure

The median duration of palbociclib treatment was more than 2-fold longer than that of placebo (330 [1 – 596] days and 137 [14 – 611] days, respectively). The median number of days on palbociclib (total number of days on which palbociclib was actually administered) was also more than 2-fold greater than that on placebo treatment (221 [1 – 436] days and 102 [14 – 460] days, respectively). The median relative dose intensity estimated for palbociclib was lower than that for placebo (89.8% [22% - 107%] and 99.5% [69% - 108%], respectively).

The duration of fulvestrant treatment and days on this treatment were greater in the palbociclib plus fulvestrant arm than in the placebo plus fulvestrant arm. In addition, the proportion of patients who had their fulvestrant dosing interrupted was also greater in the palbociclib plus fulvestrant arm than in the placebo plus fulvestrant arm. Of note, the study protocol did not allow for the fulvestrant dose to be reduced, but a single fulvestrant dose could be skipped or dosing delayed because of fulvestrant-related toxicity.

The median durations of fulvestrant treatment in the palbociclib plus fulvestrant arm (341 days) and the placebo plus fulvestrant arm (145 days) were slightly longer than those of palbociclib (330 days) and placebo (137 days) treatments in these arms.

8.3.2 From the main CSR (data cut-off 5 Dec 2014)

In the palbociclib plus fulvestrant arm, 71 pre-menopausal patients are included in the AT population. Only 70 pre-menopausal patients were treated with goserelin; 1 patient was randomised incorrectly to the pre-menopausal stratum in IMPALA while post-menopausal

status was confirmed in the CRF.

In the palbociclib plus fulvestrant arm, 70 premenopausal patients received goserelin for a median duration of 183.0 days (range: 28 to 1254 days), and in the placebo plus fulvestrant arm, 36 premenopausal patients received goserelin for a median duration of 166.0 days (range: 28 to 1441 days).

Comment: Ovarian suppression may have commenced prior to and be continued beyond the duration of the study treatment, reflecting the prior and subsequent choices of therapy.

Comment: The increase in duration of treatment for both medicines reflects the longer PFS, while the longer median duration of fulvestrant especially compared with palbociclib in that combination arm most likely reflects fewer dose interruptions required for that medicine due to toxicities. The lower dose intensity reflected the need for treatment interruptions and dose reductions with palbociclib in combination with fulvestrant compared with placebo as would be expected due to placebo having no active ingredient. It does indicate that there is a reasonable level of dose-related toxicities with palbociclib but the duration of treatment reassures that this was manageable with strategies such as dose reduction, interruption and supportive measures.

8.3.3 Study 1008 – top-line data summary as of data cut-off 26 February 2016

As of this cut-off date:

199/444 (44.8%) patients were still receiving palbociclib and letrozole arm:

245/444 (55.2%) had discontinued permanently mostly due to objective progression or relapse (38.5%) but 12.6% were due to AE, global deterioration, or refusal

61/222 patients (27.5%) were still receiving the placebo and letrozole arm:

161/222 (72.5%) had discontinued permanently mostly due to objective progression or relapse (56.8%) with 12.7% were due to AE, global deterioration, or refusal

No data on median duration of exposure, dose intensity, and dose reductions were provided for either arm for this pivotal study.

8.3.4 Study 1003 – Phase I/II study as of data cut-off 31 July 2015

8.3.4.1 Phase I PK/safety

12 postmenopausal women with ER-positive, HER2-negative advanced breast cancer were assigned to palbociclib plus letrozole treatment of which all received at least 1 treatment.

- 10 patients were permanently discontinued from treatment, while 2 patients were ongoing as of that data cutoff date as of 31 July 2015;
- as of 2 January 2015 cut-off (SCS) – no update in the 90-day safety update
  - median duration of palbociclib treatment in was approximately 12.3 months (373.5 days [range: 63 days - 2081 days]);
  - median relative dose intensity for palbociclib was 90.2% (range: 77.7% - 100.3%);
  - 3 patients (25.0%) had their palbociclib dose reduced, 8 patients (66.7%) had their palbociclib dose interrupted, and 11 patients (91.7%) had their treatment cycle delayed.

8.3.4.2 Phase II

165 women were randomised in this study:

- 83/84 postmenopausal women with ER-positive, HER2-negative advanced breast cancer were randomised to palbociclib plus letrozole treatment received at least 1 treatment;
  - 76 patients (90.5%) receiving palbociclib plus letrozole were permanently discontinued from treatment, while 7 patients (8.3%) were ongoing as of July 31 2015;
- 77/ 81 postmenopausal women with ER-positive, HER2-negative advanced breast cancer were randomised to letrozole alone received at least 1 treatment;
  - 75 patients (92.6%) were permanently discontinued from treatment, while 2 patients (2.5%) were ongoing as of July 31 2015.

As of 2 January 2015 (SCS) – no update in the 90-day safety update

- median duration of palbociclib treatment was approximately 13.8 months (421.0 days [range: 7 days 1615 days]);
- median relative dose intensity for palbociclib was 94.7% (range: 48.5% - 284.4%);
- median duration of letrozole treatment duration in the palbociclib and letrozole arm was approximately 14.1 months (428 days [range: 7 days – 1615 days]).

In the letrozole arm:

- median treatment duration in the letrozole alone arm was approximately 7.6 months (231 days [range: 28 days – 1241 days);
- median relative dose intensity for letrozole was 100% for the letrozole alone arm (range: 81.5% – 100%).

8.3.5 Study 1010

Phase I part 2 portion

- 6 postmenopausal Japanese women with ER-positive, HER2-negative advanced breast cancer were assigned to palbociclib plus letrozole treatment of whom all received at least 1 treatment
- median age was 62 years (range: 59 years – 76 years). 4 (66.7%) were younger than 65 years of age, 2 patients (33.3%) were 65 years of age or older at baseline.
- 50.0% had an ECOG PS of 0, 50% ECOG PS of 1.
  - 2 patients were permanently discontinued from treatment, while 4 patients were ongoing as of 31 July 2015.

As of January 2 2015 (SCS) – no update in 90-day safety update

- median duration of treatment was approximately 19 months (584.5 days [range: 28 days - 649 days]);
- median relative dose intensity was 71.2% (range: 59.3% – 98.6%).

Phase II

- 42/43 postmenopausal Japanese women with ER-positive, HER2-negative advanced breast cancer were assigned to palbociclib plus letrozole treatment of whom 42 received at least 1 treatment in the Phase II portion of Study 1010 as of 31 July 2015
- median age was 62.5 years (range: 43 years – 84 years). 26 patients (61.9%) were younger than 65 years of age and 16 patients (38.1%) were 65 years of age or older at baseline.
- All but 3 patients (92.9%) had an ECOG PS of 0 at baseline

– 3/43 (7%) permanently discontinued from treatment, while 39 (90.7%) were ongoing as of July 31 2015.

Comment: The 90-day safety update included 10 more patients than the SCS, a more recent summary of deaths and SAEs. No updated median duration of treatment was presented. It is not possible to make comparisons between the safety dataset summaries as new patients have joined, affecting the duration of treatment and also the denominator for adverse events. This study should be submitted with either more mature data or with a single, completely updated safety set to permit evaluation. The evaluator has evaluated the currently presented data for new safety signals but cannot comment further on the safety in this population.

8.4 Adverse events

8.4.1 All adverse events (irrespective of relationship to study treatment)

8.4.1.1 Integrated safety analyses

No integrated safety analyses are provided by the sponsor for studies 1003 and 1008, given the latter is a top line summary rather than a CSR. This is considered essential to provide accurate information for inclusion in the PI, particularly if the sponsor includes any further study updates when providing the CSR for Study 1008. See Clinical Questions.

8.4.1.2 Main/pivotal studies that assessed safety as the sole primary outcome

None provided.

8.4.1.3 Pivotal and/or main efficacy studies

Combination of palbociclib and fulvestrant – Study 1023

Treatment-emergent adverse events (TEAEs) were common in both arms: 98.8% (62.3% Grade 3, 13% Grade 4, 1.2% Grade 5) in the palbociclib and fulvestrant arm compared with 90.7% (19.8% Grade 3, 2.3% Grade 4 and 1.7% Grade 5), in the placebo and fulvestrant arm. These are presented in order of decreasing frequency in the table below.

Comment: No updated table summarising the incidence of any AE by whether serious, Grade 3 or 4, grade 5, permanent discontinuations etc was provided for the cut-off July 31 2015. The table for the 5 December 2014 no longer adequately summarises what is known about the outcomes in this study.

The most commonly reported treatment emergent adverse events (TEAEs) in the palbociclib and fulvestrant arm were neutropenia (89%; 'neutrophil count decreased', 'neutropenia'), fatigue (41.2%), nausea (33.9%), and vomiting (18.8%), bone marrow suppression as evidenced by neutropenia, white blood cell decreased (29.3%), anaemia (29%), leukopenia (25.8%), thrombocytopenia (23.1%)(captured in terms: 'platelet count decreased' and 'thrombocytopenia'), headache (25.8%), diarrhoea (23.5%) and alopecia (18%), decreased appetite (15.9%). Gastrointestinal TEAEs of stomatitis (13% - see evaluator comment below) and oropharyngeal pain (12.5%), as well as rash (11 versus 5.2%) were reported more commonly than in the comparator arm.

Grade 3 or 4 events were very common in the palbociclib and fulvestrant arm (75.3%) and were largely made up of Grade 3 or 4 events of neutropenia (69.6%) with thrombocytopenia (0.6%) and WBC count decreased (0.6%). Dyspnoea accounted for the 0.6% and the remaining events accounting for the 3.5% of Grade 3 or 4 TEAEs are not presented (Clinical Questions). The 4 deaths were listed as being due to: disseminated intravascular coagulation (1), disease progression (1), hepatic failure (1), and general physical health deterioration (1).

Table 23: Study A5481023 Summary of all causality, treatment-emergent adverse events experienced by at least 10% of patients in either arm – all treated patients as at 31 July 2015 (Source 90-days safety update)

	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.

Of 240 patients experienced a Grade 3 or 4 episode described as neutropenia or neutrophil count decreased, 225 patients had a temporary discontinuation from treatment, 110 had a dose reduction and only 1 is reported as having to discontinue permanently (90-day safety update).

The most commonly reported TEAEs in the placebo and fulvestrant arm were fatigue (29.1%), nausea (27.9%), headache (19.8%), diarrhoea (19.2%), arthralgia (18%), constipation (15.7%), and pain in the extremity (15.1%). Alopecia rates were 6.4%.

Grade 3 or 4 events occurred in 22.1% with 3 deaths reported (1.7%). These adverse events were spread across 12 adverse events classifications with no clear pattern emerging (see Table below). Grade 4 TEAEs experienced by patients in the placebo plus fulvestrant arm were reported for 1 patient (0.6%) each and included white blood count decreased/febrile neutropenia, pathological fracture, cholecystitis, and hypoxia. The deaths from acute respiratory distress syndrome, cerebral haemorrhage and progressive disease, were attributed to the disease under study.

Rates of arthralgia, back pain, hot flushes, dyspnoea, pain, dizziness and injection site pain were similar between the arms.

Comment:

1. No discussion of the data by SOC collating MedDRA preferred terms was provided for TEAEs.
2. The use of TEAEs, rather than laboratory abnormalities underreports these treatment-related events and these should be included, especially for the haematological

abnormalities.

Table 24: Study A5481023 Summary of the all-causality, treatment-emergent adverse events experienced by at least 10% of patients, presented by maximum severity grade and frequency (Source Table 7, 90-day safety update)

	Number (%) of Patients (N=517)											
	Palbociclib + Fulvestrant (N=345)						Placebo + Fulvestrant (N=172)					
MedDRA PT*	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades
Any TEAE	10 (2.9)	67 (19.4)	215 (62.3)	45 (13.0)	4 (1.2)[b]	341 (98.8)	54 (31.4)	61 (35.5)	34 (19.8)	4 (2.3)	3 (1.7)[c]	156 (90.7)
Neutropenia	3 (0.9)	47 (13.6)	152 (44.1)	26 (7.5)	0 (0)	228 (66.1)	1 (0.6)	3 (1.7)	0 (0)	0 (0)	0 (0)	4 (2.3)
Fatigue	85 (24.6)	49 (14.2)	8 (2.3)	0 (0)	0 (0)	142 (41.2)	32 (18.6)	16 (9.3)	2 (1.2)	0 (0)	0 (0)	50 (29.1)
Nausea	85 (24.6)	32 (9.3)	0 (0)	0 (0)	0 (0)	117 (33.9)	43 (25.0)	4 (2.3)	1 (0.6)	0 (0)	0 (0)	48 (27.9)
WBC count decreased	11 (3.2)	40 (11.6)	48 (13.9)	2 (0.6)	0 (0)	101 (29.3)	3 (1.7)	3 (1.7)	0 (0)	1 (0.6)	0 (0)	7 (4.1)
Anaemia	43 (12.5)	46 (13.3)	11 (3.2)	0 (0)	0 (0)	100 (29.0)	11 (6.4)	8 (4.7)	3 (1.7)	0 (0)	0 (0)	22 (12.8)
Headache	71 (20.6)	16 (4.6)	2 (0.6)	0 (0)	0 (0)	89 (25.8)	27 (15.7)	7 (4.1)	0 (0)	0 (0)	0 (0)	34 (19.8)
Leukopenia	4 (1.2)	28 (8.1)	57 (16.5)	0 (0)	0 (0)	89 (25.8)	1 (0.6)	0 (0)	1 (0.6)	0 (0)	0 (0)	2 (1.2)
Diarrhoea	64 (18.6)	17 (4.9)	0 (0)	0 (0)	0 (0)	81 (23.5)	25 (14.5)	6 (3.5)	2 (1.2)	0 (0)	0 (0)	33 (19.2)
Neutrophil count decreased	4 (1.2)	13 (3.8)	50 (14.5)	12 (3.5)	0 (0)	79 (22.9)	1 (0.6)	1 (0.6)	1 (0.6)	0 (0)	0 (0)	3 (1.7)
Constipation	57 (16.5)	12 (3.5)	0 (0)	0 (0)	0 (0)	69 (20.0)	24 (14.0)	3 (1.7)	0 (0)	0 (0)	0 (0)	27 (15.7)
Cough	53 (15.4)	13 (3.8)	0 (0)	0 (0)	0 (0)	66 (19.1)	14 (8.1)	9 (5.2)	0 (0)	0 (0)	0 (0)	23 (13.4)
Vomiting	45 (13.0)	18 (5.2)	2 (0.6)	0 (0)	0 (0)	65 (18.8)	22 (12.8)	3 (1.7)	1 (0.6)	0 (0)	0 (0)	26 (15.1)
Alopecia	57 (16.5)	5 (1.4)	0 (0)	0 (0)	0 (0)	62 (18.0)	11 (6.4)	0 (0)	0 (0)	0 (0)	0 (0)	11 (6.4)
Arthralgia	40 (11.6)	13 (3.8)	2 (0.6)	0 (0)	0 (0)	55 (15.9)	25 (14.5)	6 (3.5)	0 (0)	0 (0)	0 (0)	31 (18.0)
Back pain	32 (9.3)	19 (5.5)	4 (1.2)	0 (0)	0 (0)	55 (15.9)	18 (10.5)	9 (5.2)	3 (1.7)	0 (0)	0 (0)	30 (17.4)
Decreased appetite	38 (11.0)	14 (4.1)	3 (0.9)	0 (0)	0 (0)	55 (15.9)	10 (5.8)	3 (1.7)	1 (0.6)	0 (0)	0 (0)	14 (8.1)
Hot flush	43 (12.5)	11 (3.2)	0 (0)	0 (0)	0 (0)	54 (15.7)	23 (13.4)	5 (2.9)	1 (0.6)	0 (0)	0 (0)	29 (16.9)
Dyspnoea	24 (7.0)	20 (5.8)	1 (0.3)	1 (0.3)	0 (0)	46 (13.3)	9 (5.2)	4 (2.3)	2 (1.2)	0 (0)	0 (0)	15 (8.7)
Pain in extremity	30 (8.7)	16 (4.6)	0 (0)	0 (0)	0 (0)	46 (13.3)	14 (8.1)	9 (5.2)	3 (1.7)	0 (0)	0 (0)	26 (15.1)
Nasopharyngitis	29 (8.4)	16 (4.6)	0 (0)	0 (0)	0 (0)	45 (13.0)	9 (5.2)	5 (2.9)	0 (0)	0 (0)	0 (0)	14 (8.1)
Stomatitis	30 (8.7)	13 (3.8)	2 (0.6)	0 (0)	0 (0)	45 (13.0)	5 (2.9)	0 (0)	0 (0)	0 (0)	0 (0)	5 (2.9)
Thrombocytopenia	32 (9.3)	8 (2.3)	4 (1.2)	1 (0.3)	0 (0)	45 (13.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dizziness	39 (11.3)	4 (1.2)	1 (0.3)	0 (0)	0 (0)	44 (12.8)	15 (8.7)	2 (1.2)	0 (0)	0 (0)	0 (0)	17 (9.9)
Pyrexia	38 (11.0)	5 (1.4)	1 (0.3)	0 (0)	0 (0)	44 (12.8)	6 (3.5)	3 (1.7)	0 (0)	0 (0)	0 (0)	9 (5.2)
Oropharyngeal pain	39 (11.3)	4 (1.2)	0 (0)	0 (0)	0 (0)	43 (12.5)	10 (5.8)	2 (1.2)	0 (0)	0 (0)	0 (0)	12 (7.0)
Insomnia	30 (8.7)	7 (2.0)	1 (0.3)	0 (0)	0 (0)	38 (11.0)	10 (5.8)	4 (2.3)	0 (0)	0 (0)	0 (0)	14 (8.1)
Rash	34 (9.9)	3 (0.9)	1 (0.3)	0 (0)	0 (0)	38 (11.0)	9 (5.2)	0 (0)	0 (0)	0 (0)	0 (0)	9 (5.2)
Platelet count decreased	23 (6.7)	9 (2.6)	2 (0.6)	1 (0.3)	0 (0)	35 (10.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Injection site pain	19 (5.5)	3 (0.9)	1 (0.3)	0 (0)	0 (0)	23 (6.7)	18 (10.5)	0 (0)	0 (0)	0 (0)	0 (0)	18 (10.5)

Comments:

1. The most prominent adverse events for the palbociclib and fulvestrant arm are those related to bone marrow suppression when palbociclib is added to fulvestrant. The rates and severity of bone marrow suppression are so significant that all patients must be monitored closely and dose interruption and reduction considered. This is clearly stated in the PI. This is a side effect profile familiar to all oncologists and is considered manageable, especially with dose reduction. The duration of treatment attests to the effectiveness of these management strategies.
2. The strikingly different AE profile is likely effectively to lead to unmasking of treatment allocation. It would have been better to have had a 100% BICR of the efficacy data for this reason to ensure investigator bias is completely ruled out.
3. An update infection rate/febrile neutropenic rate has not been presented in this safety update for Study 1023 and this is needed, to ensure the figure quoted in the PI is accurate (Clinical Questions and PI comments). There needs to be a sentence describing the increased risk of neutropenia and longer duration of neutropenia with longer treatment as this may require closer monitoring for patients on longer term treatment.
4. Table 5 of the draft PI presents out of date data for Adverse Drug Reactions which is in the SOC format which needs to be updated. The collapsing of similar terms is useful but needs updating with the latest tables which are listed in the supporting tables for the 90-day safety update. No updated SOC data formatted or presented in that same way that is, as in Table 5, has been provided for evaluation in the 90-day safety update. This is required in the s31 response and to be inserted in the PI (see PI comments and Clinical Questions).

8.4.1.4 Combination of palbociclib and letrozole Study 1008 'Top-line summary'

All-causality adverse events were reported for 98.9% of patients in the palbociclib plus letrozole arm and for 95.5% of patients in the placebo plus letrozole arm.

Table 25: A5481008 Summary of of all-causality treatment-emergent adverse events (As-treated population) – source Table 6, Top-line summary

	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.

Comment:

1. While the total TEAE rates were similar, there was a striking imbalance in the severity of the events between the arms. Notably, Grade 3 or 4 events occurred in 52.3% more patients, compared with the placebo and letrozole arm. Not surprisingly, these resulted in higher rates of discontinuations from the study, of either palbociclib or letrozole, as well as higher rates of treatment interruption or dose reduction in the palbociclib and letrozole arm.
2. The table above for the Summary of all-causality treatment-related adverse events, states that 6.1% and 5.0% of patients permanently discontinued letrozole due to an AE in the experimental and comparator arms, respectively. This figure exceeds that for those permanently discontinuing the study due to an AE for those arms (2.5% and 1.8%, respectively). The sponsor is requested to provide details regarding how these patients were treated and followed up from this point of discontinuation.
    a. Was palbociclib or placebo continued as monotherapy in any patients? If so, how many in each arm?
    b. If both letrozole and the placebo or palbociclib were discontinued, what is the difference between the group permanently discontinuing the study and those labeled as permanently discontinuing letrozole?

The most common treatment-emergent, all grades, all-causality AEs (reported in ≥10% of patients either arm) were presented. These data were presented by individual MedDRA terms and thus the summary below is done by the evaluator, bringing together terms that capture similar or identical events. The most commonly reported treatment emergent adverse events (TEAEs) in the palbociclib and letrozole arm experienced by >20% of patients were neutropenia (85.8%; 'neutrophil count decreased', 'neutropenia'), fatigue (37.4%), nausea (35.1%), and vomiting (15.5%), arthralgia (33.3%), alopecia (32.9%), diarrhoea (26.1%), cough (25%), leucopenia (23.9%), anaemia (23.2%), back pain (21.6%), headache (21.4%) and hot flushes (20.9%).

Bone marrow suppression occurred much more commonly in the palbociclib than comparator arm: neutropenia/neutrophil count decreased (85.8% versus 6.4%), white blood cell decreased (16.2% versus 1.8%), anaemia (23.2% versus 9%), leukopenia (23.9% versus 0.5%).

Other TEAEs that occurred ≥ 5% more commonly in the palbociclib and letrozole arm than the comparator arm were: fatigue, nausea, alopecia, diarrhoea, cough, asthenia, stomatitis, decreased appetite, dry skin, abdominal pain, peripheral oedema, dysgeusia.

The most common TEAEs in the placebo and letrozole arm were arthralgia (33.8%), hot flushes (30.6%), fatigue (27.5%), nausea (26.1%), headache (26.1%) and back pain (21.6%). The only adverse events that was experienced more commonly by ≥5% patients in the comparator arm were hot flushes.

Comment:

1. The addition of palbociclib to letrozole resulted in a dramatic increase in severe adverse events. The most striking increase was in the rates of bone marrow suppression, as with Study 1023. However, there were also increases in adverse events that have significant potential to affect quality of life. No data were presented in the top line summary to address the impact of these adverse events on patient reported outcomes. This is important given this is a palliative treatment and there has not been a demonstrated improvement in overall survival to date.
2. Amongst most common reported TEAEs between the palbociclib arms in both Studies 1008 and 1023, there were 2 notable differences:
    a. The absolute rates of alopecia were more than double those receiving palbociclib in Study 1008 (32.9%) compared with Study 1023 (16.3%). The increase in alopecia in the palbociclib and letrozole arm over the comparator arm in Study 1008 (17.1%) was higher than the increase in the palbociclib and fulvestrant compared with comparator arm in Study 1023 (10.4%). More than one third of women experienced alopecia, while taking palbociclib and letrozole which is a distressing side effect for most patients.
    b. Events rates for TEAEs of thrombocytopenia were not reported as occurring below 10% in Study 1008. This is an artefact of the high cut-off threshold of ≥ 10% in either arm and use of separate MedDRA terms for TEAE reporting; the combination of treatment-related thrombocytopenia/platelet count decreased was 14.9% in the experimental arm and 1.4% in the comparator that is, a 10-fold increase in risk, with the lower cut-off of 5% reporting the treatment-related AEs. Furthermore with the lower threshold in the treatment-related events table, the adverse event of epistaxis also emerges which could be linked to the low platelets (this issue should be addressed when providing the CSR for Study 1008). Grade 3 or 4 thrombocytopenia occurred in 1.3% of the experimental arm with no cases in the comparator arm. When submitting the CSR for Study 1008, the sponsor is requested to include a table of TEAEs with a cut-off of ≥ 2% in either arm to assist identification of events that may require inclusion in the PI to inform clinicians and patients. The assessment of attribution of AEs considered treatment-related cannot be made without knowing the percentage listed as treatment-emergent. (Clinical Questions).

Events of severity Grade 3 or higher were very common and substantially higher in the palbociclib and letrozole arm than the placebo and letrozole arm (77.9% versus 26.1%). The rates of Grade 3 events, Grade 4 events and Grade 5 events were (respectively) 62.2%, 13.5% and 2.3% in the palbociclib and letrozole arm and 22.1%, 2.3% and 1.8% in the placebo and letrozole arm.

In the palbociclib and letrozole arm the majority of events of severity Grade 3 or higher were due to neutropenia or neutrophil count decreased (70.3% versus 1.4%) as well as other parameters indicating bone marrow suppression; other severe TEAEs that occurred more frequently in the palbociclib and letrozole arm than comparator were aspartate aminotransferase increased (2.3% versus 0.9%), alanine aminotransferase increased (2.3% versus 0), febrile neutropenia (1.8% versus 0%), back pain (1.4% versus 0), thrombocytopaenia (1.4% versus 0), general physical deterioration (1.1 versus 0.5%), pneumonia (1.1 versus 0.9), and urinary tract infections (1.1 versus 0%).

There were 10 deaths in the experimental arm and 4 in the comparator arm, with death from a pulmonary embolism in each arm the only TEAE recorded in this section – this is discussed

further in the section on on-study deaths below.

8.4.1.5 Other studies

Combination of palbociclib and letrozole Study 1003, Study 1010

Study 1027 is blinded and the data are not evaluable for the 20 patients randomised (1:1) enrolled to date.

Study 1003 was conducted as a Phase I, non-randomised safety and PK dose finding study of 12 patients and Phase II was a randomised, controlled open label comparison of palbociclib plus letrozole compared with letrozole alone; it was conducted in 2 parts, subsequently amalgamated for a single assessment of safety.

Comment**:** The randomised data will be the focus of the assessment and evaluation of safety with descriptive information from the 12 patients in the Phase I part evaluated for additional signals. Given the limited information about safety available and in the inability to evaluate severe events and deaths, there is reliance upon the safety information from this smaller study.

Safety Analysis sets

Phase I

Safety Analysis Set: All patients that receive at least one dose of any agent of the combination.

Phase II

All Treated as Treated Set (AT): All treated patients classified by the treatment actually received.

Phase II

165 women were randomised in this study:

- 83/84 postmenopausal women with ER-positive, HER2-negative advanced breast cancer were randomised to palbociclib plus letrozole treatment received at least 1 treatment;
  - 76 patients (90.5%) receiving palbociclib plus letrozole were permanently discontinued from treatment, while 7 patients (8.3%) were ongoing as of 31 July 2015;
- 77/ 81 postmenopausal women with ER-positive, HER2-negative advanced breast cancer were randomised to letrozole alone received at least 1 treatment;
  - patients (92.6%) were permanently discontinued from treatment, while 2 patients (2.5%) were ongoing as of July 31 2015

No updated treatment exposure was provided in the 90-day safety update; from the SCS the median duration of treatment in the Phase II part of the study for palbociclib was approximately 13.8 months (421.0 days [range: 7 days - 1615 days]) and for letrozole was approximately 14.1 months (428.0 days [range: 7 days - 1615 days]). In the letrozole alone arm, the median duration of treatment was approximately 7.6 months (231.0 days [range: 28 days - 1241 days]). In the Study 1003 CSR (cut-off date 29 November 2013), the median dose intensity was 90.2% (range: 77.7-100.3) for the palbociclib and letrozole compared with 100% for letrozole (range: 98.4-100) – no update is provided.

In the Study 1003 CSR (cut-off date 29 November 2013), 100% in the palbociclib and letrozole arm experienced an AE (compared with 84.4% in the letrozole alone arm), 14.5% discontinued due to AEs, 38.6% required a reduction in the palbociclib dose and 62.7% required a dose interruption.

The SCS updates the occurrence of TEAEs to 85.7% in the letrozole alone arm and there were more events also in the experimental arm, but the additional events are not specified between the reports.

Comment: The CSR dose intensity levels reflect that adding in palbociclib results in significant toxicities requiring dose interruptions or reductions compared with letrozole alone. No updated information was provided in the SCS – updated Table as per Table 68 of Study 1003 CSR requested).

Table 26: Study A5481003 Overview of treatment-emergent adverse events Phase II As treated set. Source CSR, cut-off date November 29 2013 -no updated table provided in SCS see Clinical Question)

	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)[a]
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.
[a] 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.

The most frequently reported TEAEs (≥ 20% of patients) in that treatment arm were neutropenia (74.7%), leukopenia (43.4%), fatigue (41.0%), anaemia (34.9%), nausea (30.1%), arthralgia (24.1%), hot flushes (22.9%), alopecia (21.7%), as well as decreased appetite and diarrhoea (20.5% each). The most frequently reported TEAE in the letrozole alone arm was fatigue (23.4%).

As of 2 January 2015, in Phase II (Ph2P1+Ph2P2), the following AEs were reported at a ≥ 10% greater frequency in the palbociclib plus letrozole arm compared with the letrozole alone arm:

Neutropenia/granulocytopenia/neutrophil count decreased (77.1% versus 5.2%);

Leukopenia (43.4% versus 2.6%);

Fatigue (41.0% versus 23.4%);

Thrombocytopenia/platelet count decreased (19.5% versus 1.3%);

Anaemia (34.9% versus 6.5%);

Nausea (30.1% versus 14.3%);

Alopecia (21.7% versus 2.6%);

Decreased appetite (20.5% versus 6.5%)

Dyspnoea (18.1% versus 7.8%)

Vomiting (14.5% versus 3.9%);

URT infection (13.3% versus 2.6%);

as of 2 January 2015 (SCS), the following were noted on review of the source tables:

Diarrhoea (20.5% versus 11.7%);

Neuropathy peripheral/ peripheral sensory neuropathy (14.4% versus 5.2%), including 1 patient with Grade 3 event in the palbociclib and letrozole arm.

Stomatitis (12% versus 2.6%)

No AEs were reported at a ≥ 10% greater frequency in the letrozole alone arm compared with the palbociclib plus letrozole arm.

Comment:

1. Using the cluster terms for MedDRA preferred terms to capture related events increased both the numbers and the proportion with severe AEs such as neutropenia thus the differential between the arms would be likely to increase further for many of the events if presented by SOC by MedDRA preferred terms.
2. Grade 1, 2 and 3 peripheral neuropathy is a prominent adverse event in this study and in Study 1023, and should be a Precaution and also included in the adverse drug reactions table in the PI (currently no mention of this anywhere). Frequency and severity have both increased over time which suggests a cumulative effect based on longer exposure (PI Comments).

80.7% of patients in the palbociclib and letrozole arm experienced at least one adverse event of ≥3 grading compared with 23.4% in the letrozole alone arm (no Grade 4 events). Grade 4 events occurred in 15 patients (18.1%) in the experimental arm: neutropenia (5/15), pulmonary embolism (5/15), fatigue (2/15), leukopenia, anaemia and bone pain (all one patient each). Grade 3 TEAEs were experienced by 61.4% in the experimental arm compared with 23.4% of the comparator arm.

Comment: Even with the high cut-off for reporting AEs of >10% in the palbociclib and letrozole arms and without using cluster terms - both of which would capture a larger number of high grade adverse events - there is a striking difference between the 2 arms indicating the addition of palbociclib is associated with a significant increase in toxicity, some of which are life-threatening. The draft PI currently does not adequately inform clinicians of these risks.

The CSR states that palbociclib and letrozole treatment was associated with an increased risk of developing stomatitis, constipation, asthenia, influenza, upper respiratory tract infection, nasopharyngitis, decreased appetite, bone pain, musculoskeletal pain, headache, epistaxis, dyspnoea, and cough; for back pain, the relative risk was <1. (CSR cut-off 29 November, 2013 – no update provided)

Comment: The clinical evaluator considers palbociclib and letrozole treatment is also associated with an increased risk of pulmonary embolism and peripheral neuropathy.

8.4.1.6 Phase I

The Phase I part of the study (12 patients) revealed no additional toxicities over and above those described in the Phase II section. An AE of cataract development was reported in the SCS. The dose-limiting toxicities were neutropenia (2 cases) and a rise in creatinine (1 case) subsequently attributed at least in part to concomitant zoledronic acid. Notably, 2 patients developed pulmonary emboli (1 Grade 4), but no patients discontinued treatment permanently

and no treatment-related or SAE-related deaths were reported. The overall rate of all-causality treatment-emergent Grade 3/4 Neutropenia was 91.7% (66.7% Grade 3, 16.7% Grade 4) and dose reductions of palbociclib due to any TEAE was 25.0%, with neutropenia the most common reason for dose reduction (16.7%).

8.4.1.7 Study 1010

Phase I Part 1

Dose limiting toxicities were consistent with those observed in other trials (neutropenia and thrombocytopenia).

Phase I Part 2

All 6 patients experienced a TEAE: 4 patients had Grade 3 events (neutropenia, white blood cell decreased, pyrexia, urinary tract infection) and 2 patients had Grade 4 events (neutropenia (2) and gastrointestinal perforation (1)).

A small postmarketing study, Study 1034 provides limited safety information from the 90-day safety update and the narratives provided. No CSR is provided.

8.4.2 Treatment-related adverse events (adverse drug reactions)

8.4.2.1 Integrated safety analyses

None provided.

8.4.2.2 Main/pivotal studies that assessed safety as the sole primary outcome

None provided

8.4.2.3 Pivotal and/or main efficacy studies

Combination of palbociclib and fulvestrant – Study 1023

Overall, 94.2% of patients in the palbociclib plus fulvestrant arm and 67.4% of patients in the placebo plus fulvestrant arm experienced at least 1 treatment-related AE as of the 31 July 2015 data cutoff date.

As shown in the table below, the most frequently reported treatment-related AEs (that is, ≥20% of patients) in the palbociclib plus fulvestrant arm were neutropenia (65.2%) and neutrophil count decreased (22.6%), fatigue (31.0%), white blood cell count decreased (29.3%) and leukopenia (25.8%), anaemia (26.4%), and nausea (25.2%). Nausea (22.1%) and fatigue (21.5%) were the most frequently reported treatment-related AEs for the placebo plus fulvestrant arm.

The following common treatment-related AEs were reported substantially more frequently as calculated by the clinical evaluator's calculation (that is, >9% difference in treatment-related AE frequency) for the palbociclib plus fulvestrant arm than for the placebo plus fulvestrant arm:

- neutropenia (65.2% versus 1.7%, respectively)
- neutrophil count decreased (22.6% versus 1.2%)
- white blood cell count decreased (29.3% versus 4.1%)
- leukopenia (25.8% versus 1.2%)
- anaemia (26.4% versus 8.1%)
- thrombocytopenia (12.8% versus 0.0%)
- platelet count decreased (10.1% versus 0.0%)
- alopecia (16.2% versus 5.8%)

- fatigue (31% versus 21.5%)
- stomatitis (11.6% versus 1.7%)

A rash occurred in 4.9% more (7.8% versus 2.9%) patients in the palbociclib and fulvestrant arm. The remainder of the treatment-related toxicities occurring at a frequency of at least 5 percent were similar (90-day safety update).

Comment: By altering the cut-off for the difference in rates from 10% to 9%, 2 more clinically relevant AEs were identified as occurring' more commonly in the experimental arm: stomatitis and fatigue.

No presentation of the less commonly occurring treatment-related adverse events could be located in the 90-day safety update, and a review of the main CSR provided a table with a cut-off of TEAEs occurring in at least 5% based on the older data cut-off of 5 December 2014) but no additional tables with discussion for less common events were presented.

The clinical evaluator has reviewed treatment-related events by SOC supplied (as of cut-off 31 July 2015) which revealed:

- hepatobiliary disorder events of 5.3% in each arm; however, the palbociclib and fulvestrant arm included one case of drug-induced liver injury and one case of hepatocellular injury and one of liver failure. No such cases were reported for the comparator arm, which included more general terms of hepatic pain, cholecystitis etc. It is noted that the drug-induced liver injury (Grade 3) was not considered an SAE, but the patient permanently discontinued.[3] The liver failure was listed as an SAE.
- The source tables with the data by SOC contain multiple terms that could be used to describe the same event eg 'neutropenia' and 'neutrophil count decreased'. The rate of 'dyspnoea', if that term plus 'dyspnoea exertional' are combined leads to a rate of 15% not 13.3% in the palbociclib and fulvestrant arm, and 8.7% in the comparator arm as reported. No grades of severity for these events of dyspnoea could be located but for the dyspnoea at the 5 December 2014, the event rates 10.7% in palbociclib and fulvestrant arm (0.3% Grade 4); 6.4% in the comparator (0.6% Grade 3).

Comment: Without a table providing side-by-side comparison of the adverse events of lower frequency, presented with similar terms collapsed to provide a single figure (as in the SOC presentation with like MedDRA terms collated, it is very difficult to determine whether there have been additional clinically significant adverse events occurring more commonly in the experimental arm. Given the importance of understanding these for both clinicians and patients, the sponsor is requested to present all the adverse events, (including all grades frequency, as well as Grade 3 and Grade 4) that occurred more often in the palbociclib and fulvestrant arm than the placebo and fulvestrant arm (Clinical Questions) These adverse events' preferred terms should be collated to capture the same event being classified by a different term.

Combination of palbociclib and letrozole – Study 1008 top-line summary (no CSR available)

2973 adverse events were reported as related to treatment in the palbociclib and letrozole arm. The sponsor reported the following in the summary provided: 'Treatment-related adverse events were reported for 96.4% of patients in the palbociclib plus letrozole arm and for 80.6% of patients in the placebo plus letrozole arm. Treatment-related serious adverse events were

[3] Clarification: There was a case report of hepatic failure assessed by the Sponsor to be unrelated to blinded therapy and fulvestrant and to any clinical trial procedure. For this case the investigator considered drug induced hepatitis could not be excluded and therefore two separate AEs were collected for this event. For further discussion see Response to Safety Question 18.

reported for 24 (5.4%) patients in the palbociclib plus letrozole arm and for 2 (0.9%) patients in the placebo plus letrozole arm. Permanent discontinuation from the study associated with treatment-related adverse events was reported for 1 (0.2%) patient in the palbociclib plus letrozole arm and for 1 (0.5%) patient in the placebo plus letrozole arm.'

Table 27: Study A5481008 Summary of Treatment-related, Treatment-emergent adverse events (As treated population)

	Palbociclib Plus Letrozole N = 444 n (%)	Placebo Plus Letrozole N = 222 n (%)
Any treatment-related AE	428 (96.4)	179 (80.6)
Any serious AE	24 (5.4)	2 (0.9)
Any Grade 3 or 4 AE	319 (71.8)	14 (6.3)
Any Grade 5 AE	0	1 (0.5)
Discontinued study due to AE	1 (0.2)	1 (0.5)
Discontinued palbociclib or placebo due to AE	25 (5.6)	3 (1.4)
Discontinued letrozole due to AE	11 (2.5)	3 (1.4)
Temporarily discontinued palbociclib or placebo due to AE	311 (70.0)	12 (5.4)
Temporarily discontinued letrozole due to AE	44 (9.9)	9 (4.1)
Dose reduction of palbociclib or placebo due to AE	158 (35.6)	2 (0.9)

Source: Table 14.3.1.2.1.
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.

The limited data available from the table summarising treatment-related TEAEs of any grade reported at ≥ 5% frequency in either arm introduced new adverse events in the palbociclib arm which were more frequent than in the comparator over and above those presented in the TEAE table with its cut-off reporting threshold of events occurring in ≥ 10% of patients in either arm. The Grade 3/4/5 was presented with a differing threshold again, of ≥ 1% in either arm. New events identified as a result:

- epistaxis (6.3% versus 2.7%);
- thrombocytopenia (9.0% versus 0.9%) /platelet count decreased (5.9% versus 0.5%);
- pruritus (5.0% versus 2.3%)

Comment:

1. The clinical evaluator was unable to evaluate attribution of causality made by the sponsor because:
    a. the ≥ 10% frequency (in either arm) threshold for cut-offs for baseline TEAEs was higher than the treatment-related (≥ 5%) resulting in:
        i. new events being reported;
        ii. no baseline figures for comparison between the two assessments for example, for epistaxis, pruritus;
    b. the only links and data provided in support are the source tables for these figures which do not provide a side-by-side comparison of AE rates between arms;
    c. no link to any narratives to assess the cases by the evaluator;
    d. all narratives are blinded and not evaluable;
2. No comments on these data and no recommendations for the PI can be made to reflect the proposed usage.

3. Table 10, top-line summary provide frequencies for treatment-related adverse events by frequency of at least 5% in either arm. Given rare events will be missed by presentation this way, the sponsor is requested to provide a table where the cut-off is 1% in either arm when submitting the CSR for Study 1008. THE same threshold should be used for the TEAEs – it would be acceptable to add in a table to capture this rate of events. It is recommended that these issues be addressed when submitting the Study 1008 to facilitate any evaluation.
4. These, and all subsequent data with relation to causality, could not be evaluated by the TGA.

The sponsor also provided a discussion and table for 'Adverse Drug reactions' in the palbociclib and letrozole arm, without a comparison with the placebo and letrozole arm.

The sponsor states (Study 1008 top-line summary):

'Adverse drug reactions (ADRs) were identified based on whether adverse events were reasonably associated with palbociclib treatment. The sponsor evaluated this potential association by examining the all-causality reporting frequencies on the palbociclib plus letrozole arm in comparison with the placebo plus letrozole arm. Further, the sponsor considered the mechanism of action of palbociclib, the available nonclinical toxicity data, and the overall assessment of adverse events by the investigators when judging whether reported adverse events were reasonably associated with palbociclib treatment. In cases of uncertainty or for confirmation, the adverse event experience from Studies 1003 and 1023, and from palbociclib monotherapy studies was also considered. The ADRs reported in Study 1008 are summarised in Table 14. In earlier determinations of ADR frequencies, Febrile neutropenia was listed as 'Uncommon' and Dysgeusia as 'Common'. Febrile neutropenia is now listed as 'Common' and Dysgeusia as 'Very Common'; no other changes in ADR frequencies were noted.'

Comment:

1. The sponsor has not provided the data, analyses or narratives on which these attributions were made;
2. It is not possible to establish and evaluate how these figures were reached (see above discussion on differing presentations of thresholds for different AE data);
3. No information about the comparator arm is included in the table for comparison.
4. These adverse events have not been presented adequately described elsewhere, and the attribution of what constitutes an ADR appears to be different from the 'treatment-related TEAE' classification for example, the rates of epistaxis here are presented as 9.3% whereas in Table 10 for the Treatment-related TEAEs, the frequency was 6.3%. This could be due to reporting terms but it is very unclear as to why there are different rates for the same term. The sponsor is requested if presenting such analyses in the CSR, to make it very clear as to how these two classifications differ.
5. Reference in the paragraph above is made to differences between this and 'earlier determinations of ADR frequencies', but there is no link or reference to where these 'earlier determinations can be found' for the evaluator to check that earlier data, noting this is a new chemical entity submission to the TGA and no prior submissions have been made for palbociclib.

8.4.2.4 Other efficacy studies

Combination of palbociclib and letrozole

Study 1003 Phase II

Overall, 78 patients (94.0%) in the palbociclib plus letrozole arm and 33 patients (42.9%) in the letrozole alone arm were reported to have experienced at least 1 treatment-related AE in this portion of the study. The most frequently reported treatment-related AEs (≥10% of patients) in

the palbociclib plus letrozole arm were neutropenia (73.5%), leukopenia (41.0%), anaemia (28.9%), fatigue (25.3%), Alopecia (21.7%), Hot flush (20.5%), thrombocytopenia (19.3%), arthralgia (16.9%), nausea (15.7%), and decreased appetite (10.8%). The most frequently reported treatment-related AEs in the letrozole alone arm were fatigue (14.3%), hot flushes (11.7%), and arthralgia (10.4%).

A summary table of treatment-related, treatment-emergent adverse events by MedDRA PT for at least 5 patients in the palbociclib and letrozole arm was presented.

Comments:

> *No additional information has been presented in the summary discussion to represent the outcomes when clinically related events are merged. A more clinically meaningful table would be generated by presenting the data by clustered MedDRA PT by SOC – it is noted that the ADR table proposed in the PI for fulvestrant and palbociclib usage uses this approach (although cannot be evaluated due to the data not being presented in the same way for the treatment-related events in that trial) – this, and any proposed table for inclusion in the PI based on this study or Study 1008 when it is submitted, should present the data by clustered MedDRA PT by SOC to allow evaluationComparison of treatment-emergent rather than treatment-related events avoids the possibility of biases in attribution of causality. Study 1010*

In the Ph1P2 portion of Study 1010, all patients experienced at least 1 treatment-related AE.

The most frequently reported (that is, ≥ 2 patients [33.3%]) treatment-related AEs were neutrophil count decreased and white blood cell count decreased (100% each) as well as platelet count decreased (50.0%) and fatigue (33.3%).

No update is provided in the 90-day safety update.

8.4.3 Deaths and other serious adverse events

8.4.3.1 Integrated safety analyses

None provided.

8.4.3.2 Main/pivotal studies that assessed safety as the sole primary outcome

N/A

8.4.3.3 Pivotal and/or main efficacy studies

Combination of palbociclib and fulvestrant – Study 1023

Deaths

A total of 4 patients (1.2%) who received palbociclib plus fulvestrant and 3 patients (1.9%) who received placebo plus fulvestrant died on study (during the period from the start of treatment up to and including 28 days after the last dose of study drug) as of 31 July 2015 in Study 1023. None of these on-study deaths were considered by the investigator to be related to study treatment.

Comment: After reviewing the information provided for these patients, the evaluator agrees that causes other than the study drugs are most likely.

Other serious adverse events (SAEs)

15.4% in the palbociclib plus fulvestrant arm and 18.0% in the placebo plus fulvestrant arm experienced at least one SAE.

The most commonly experienced treatment-emergent SAEs in the palbociclib and fulvestrant arm were: pyrexia (5 patients [1.4%]), neutropenia (4 [1.2%]) and pulmonary embolism (3 [0.9%]); deep vein thrombosis, disease progression, dyspnoea, febrile neutropenia, general

physical health deterioration, pharyngitis, pleural effusion, and suicide attempt (2 [0.6%] each).

No events of DVT or PE were reported in the placebo and fulvestrant arm.

Additional significant SAEs were depression (1 (0.3%)) and psychotic disorder (1 (0.3%)) which brings the total psychiatric events in this arm to 4 patients (1.2%) compared with none in the comparator arm.

Comments:

1. The use of MedDRA preferred terms means related events are presented separately, thus appearing less common.
2. It is noted that suicidal ideation or behaviour was exclusion criteria. The sponsor has already been requested to provide a rationale for this in terms of potential concerns about the impact of palbociclib, but with these findings, is now requested to expand and provide an explanation for this imbalance in this randomised controlled, double blind trial. These should be added to important potential risks in the RMP (Clinical Questions and Comments on RMP).

Among patients experiencing SAEs of any severity grade in the palbociclib plus fulvestrant arm (N=53), Grade 3 SAEs were reported for more than half of the patients (29/53 [54.7%]), and Grade 4 SAEs were reported for 8/53 patients (15.1%).

In the placebo plus fulvestrant arm, SAEs experienced by more than 1 patient each included ascites and pleural effusion (3 patients [1.7%] each) as well as pathological fracture and pneumonia (2 [1.2%] each).

A nonfatal SAE of 'Drug-induced liver injury +/- drug induced hepatitis' experienced by Subject No. [information redacted] in the palbociclib plus fulvestrant arm is included in the SAE list. The fatal SAE of Hepatic failure experienced by Subject No. [information redacted] because it was not marked as an SAE on the AE page of the CRF in error and, consequently, was not entered in the clinical database as the SAE.

The CIOMS for the patient with 'drug-induced liver injury[4]' was reviewed: this patient with baseline liver metastases had marginally elevated transaminases, and normal bilirubin.

alanine aminotransferase 77 IU/l (normal range: 5-60)

aspartate aminotransferase 58 IU/l (normal range: 5-55)

alkaline phosphatase 94 IU/l (normal range: 30-130)

bilirubin 8 µmol/l (normal range: 0-21)

INR 1.0 and prothrombin time (normal range: 10.5-13.5) 11.8 seconds.

[4] Clarification: There was a case report of hepatic failure assessed by the sponsor to be unrelated to blinded therapy and fulvestrant and to any clinical trial procedure. For this case the investigator considered drug induced hepatitis could not be excluded and therefore two separate AEs were collected for this event. For further discussion see Response to Safety Question 18.

Table 28: Clinical chemistry data

	Baseline 3/7/14	Day 15, cycle 1 22/7/14	Cycle 2, day 1 12/8/14	Cycle 2, day 15 27/8/14	Palbo-ciclib stopped 3/9/14; fulvest-rant last dose 6/8/14	End of treat-ment visit 17/9/14	Addi-tional tests results provided 14/10/14
ALT (normal range: 5-60)	77	79	186	172		249	92
AST (normal range: 5-55)	58	68	206	392		883	115
Bilirubin	8	4	9	9		29	22
CT target lesion change		N/A	stable		Not reason for discontinuation		

After commencing palbociclib and fulvestrant, the document includes the following statements:

'The investigator considered that there was a reasonable possibility that the event was related to fulvestrant and blinded therapy but not related to a concomitant drug or a clinical trial procedure. In the investigator's opinion 'Cancer antigen 15-3 continued to rise but drug induced hepatitis cannot be totally excluded'.'

It was reported that study drugs were discontinued due to symptoms and signs of drug-induced hepatitis and not due to liver failure. Drug-Induced hepatitis is not considered an SAE. The study drugs were never re-started. Last dose of Blinded therapy was on 03Sep2014; last dose of fulvestrant was on 06Aug2014. While progression of disease (not meeting RECIST 1.1 criteria-clinical progression) was a concern, drug-induced hepatitis could not be ruled out. The liver irregularity and ascites were not present on prior or baseline imaging; they were not at all considered likely to be due to prior hepatitis (infectious or otherwise) nor pre-existing cirrhosis.'

The sponsor's assessment is as follows: 'The Company considers the event hepatic failure unrelated to blinded therapy (Palbociclib or placebo) and fulvestrant and to any clinical trial procedure. The progressive marked deterioration of hepatic function after study drugs' discontinuation would argue against drug-induced toxicity. The documented increased hepatic metastases likely played a major role towards the event. It should be noted that the subject presented slight elevation of

alanine aminotransferase and aspartate aminotransferase at baseline.'

Comment:

1. the CIOMS has been provided for the patient who died with liver failure and disease progression ([information redacted]). The information from the investigator has not been provided separately and it is noted from the CIOMS, that the 2 events have been listed rather than just disease progression. It is difficult to determine any causality where the progressive deterioration in liver function has continued unabated in the presence of disease progression and liver metastases.
2. In contrast, the CIOMS indicates that for the patient with 'drug-induced liver injury' ([information redacted])[5] there was a substantial improvement in the liver function tests after discontinuing the study drugs, even though there is a background of progressive disease from which she died subsequently just over 2 months after the last dose of palbociclib. The evaluator agrees with the investigator and disagrees entirely with the conclusion of the sponsor who cite a 'progressive marked deterioration of hepatic function after discontinuation after study drugs' discontinuation' as a reason for this not being study related, when quite clearly, there was an improvement in liver function that would not be anticipated if this were solely progressive disease. The sponsor is requested to comment upon the quite dramatic improvement in liver function tests, the imaging results that suggest a new appearance to the liver contour, as these appear to have been overlooked in the causality assessment. The evaluator notes that there was mild liver dysfunction at the outset, potentially explained by the presence of liver metastases. The evaluator does not feel that this case in isolation is sufficient to require a Precaution in the PI but considers this raises sufficient concern that drug-induced liver injury should be listed as an important potential risk in the RMP (Comments on RMP, Clinical Questions).

A table of treatment-related SAEs was provided which excluded the cases of pulmonary embolism and also one case of the deep vein thromboses observed from being considered treatment-related. Similarly, the cases of suicide attempts were excluded. Within that list are significant AEs including neutropenia and neutropenic infection, viral and bacterial infections including pharyngitis, erysipelas, otitis media and bacteraemia, and cataract formation.

In addition, the evaluator considers the following treatment-emergent SAEs, which were not considered treatment-related by the sponsor, likely to be treatment-related:

A review of the narratives supplied (CIOMS) for these cases and on which attributions of causality appear to be based, raise concerns about the validity of the exclusion of several of the SAEs.

'Case Comment: the company considers there is not a reasonable possibility that the event pulmonary embolism is related to palbociclib, fulvestrant, or to any clinical trial procedure. Thromboembolic disorders are common complications of solid cancers.' This same logic was applied to discount both cases of pulmonary emboli, and also one of the deep vein thrombosis cases.

Comment: While solid tumours are associated with an increased risk of thrombosis and thromboembolism, it is not uncommon for that risk to be increased further by medications and this is certainly not a valid basis for discounting possible causality. Discounting each single case, so that only 1/4 episodes of thrombosis/thromboembolism is considered attributable to the treatment, ignores

[5] Clarification: There was a case report of hepatic failure assessed by the Sponsor to be unrelated to blinded therapy and fulvestrant and to any clinical trial procedure. For this case the investigator considered drug induced hepatitis could not be excluded and therefore two separate AEs were collected for this event. For further discussion see Response to Safety Question 18.

the growing body of evidence from 4 cases being observed in the experimental arm and none in the comparator. For this reason, the treatment-emergent AEs are considered more valid than those considered treatment-related. It is beyond the scope of this evaluation to re-assign causality for each adverse event, but the following examples are discussed.

'A typical pneumonia is likely an intercurrent illness' is reported for one patient developing an atypical pneumonia on palbociclib and fulvestrant.

This case of atypical pneumonia was discounted from being considered possibly treatment-related, despite 9 months of treatment with a drug known to cause myelosuppression and leukopenia. Even though the blood results were not frankly neutropenic at the time, there will still be a degree of immunosuppression and there is a strong potential for this to be treatment-related.

Similarly, there were 4 cases of depression (1), suicide attempts (2) and psychotic disorder (1) in those on palbociclib and fulvestrant, while no cases were observed in the placebo and fulvestrant arm.

Comment: Exclusion criteria did not permit enrolment of those with suicidal ideation and behaviours, so this would suggest a new onset. While there are multiple stressors associated with a diagnosis of metastatic cancer that would be the same for both arms noting that the comparator arm also experienced more disease progression. The evaluator accepts the likelihood of the event of psychosis being related to stopping an antipsychotic medication just prior to the trial commencing, but a potential causative role of palbociclib cannot be excluded for the other cases. This should be included in the RMP, given the imbalance between the arms, but there is not sufficient evidence to warrant inclusion in the PI as a Precaution.

The investigators' narratives were not provided to ensure that there had not been incorrect interpretations of the investigator's attribution – overall, the CIOMS reports were poorly written with many grammatical and typographical errors and some sentences that did not make sense and use of words that do not exist.

The PI needs to have a Precautions section on thrombosis and thromboembolism as with no cases in the comparator arm, it is considered likely that this is due to the addition of palbociclib to fulvestrant. The clinical evaluator notes the FDA label has a warning regarding this. It is noted that there is already a section on Infections under Precautions in the PI.

The case of hepatic failure was considered treatment-related by the investigator with the sponsor considering this was unlikely to be due to palbociclib given the potential for fulvestrant to cause abnormal liver function tests.

Comment: This does not exclude the potential for palbociclib to contribute to liver toxicity and this should be listed in the potential risks in the RMP (See RMP comments). The Clinical Evaluator also notes that there is an increased reporting of liver function test abnormalities in the palbociclib and letrozole arm in Study 1008 (not able to be further evaluated due to data not being provided). This further underscores the need to include this in the RMP and evaluation of the 1008 data may lead to a PI change and upgrading of that risk status in the RMP.

Combination of palbociclib and letrozole – Study 1008 top-line summary (no CSR available)

Deaths

Ten (10; 2.3%) patients in the palbociclib plus letrozole arm and 4 (1.8%) patients in the placebo plus letrozole arm died during the study treatment period (on-study, includes 28 days after the last dose of palbociclib or placebo). The death events are summarised below (Table 29). An additional 85 (19.1%) patients in the palbociclib plus letrozole arm and 34 (15.3%)

patients in the placebo plus letrozole arm died during the follow-up period, as of the data cutoff date of 26 February 2016.

The 90-day safety update provides more detail about just some of those SAEs that occurred up to the earlier cut-off date of 31 July 2015, including CIOMS. This is a subset of a subset of those described above but includes the following as treatment-related:

- death from a pulmonary embolism, infection
- SAE of infection ([information redacted])

Comment: All attribution is to 'blinded therapy' or letrozole but no information is provided about which treatment the patients actually received – letrozole or palbociclib and letrozole. In reviewing a case of suspected pneumonitis ([information redacted]) the blind was reported broken but the CIOMS does not declare which treatment the patient received. This is not considered an acceptable presentation of data for regulatory purposes if severe events are not disclosed to the regulator, especially when the blind has been broken. No comment on the case can be made and no recommendation regarding statements in the PI can be made.

Table 29: Study A5481008 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.

Comment:

1. It is not clear why the distribution of deaths is known for the two arms but the data that provided that information cannot or has not been provided for evaluation. All the CIOMS are blinded to treatment allocation. The sponsor is invited to comment.
2. There are more on-study deaths and without being able to evaluate these, this raises the concern of potential toxicities that are fatal. Without such information, no benefit-risk assessment can be made and no information included in the PI for clinicians and patients to have an informed discussion.
3. Treatment attribution is thus limited to whether it is considered related to the blinded treatment which is not a meaningful assessment for regulatory purposes.
4. There is inconsistent reporting within the top-line summary of causality with the causes of death being listed as other/unknown in the table above with no further discussion, but the table linked to the permanent discontinuations due to TEAE provides the following list of AEs leading to deaths in the palbociclib and letrozole arm:
   a. Cardiac (4)
   b. Pulmonary embolism (1)

c. Respiratory failure (1)

d. 'Death' (1)

e. disease progression (3)

5. The only links and data provided is the one source table for these figures in the report, and there is no link to any narratives to allow the clinical evaluator to evaluate the attribution of causality for these deaths. These, and all subsequent data with relation to causality, could not be evaluated by the evaluator due to the limited reporting.
6. All CIOMS provided with the top-line summary were blinded with respect to treatment allocation and cannot be evaluated. There was no cross-referencing to the 90-day safety update, which included more detail and some of the blinded CIOMS for the deaths and SAEs reported from the earlier cut-off date for that report (31 July 2015 versus 26 February 2016 for the top-line summary). It is not clear why these, together with those reported from the later cut-off could not have been included in the top-line summary data.
7. No comments on these data can be made and no recommendations for the PI can be made to reflect the proposed usage.
8. These issues require submission of the full CSR for evaluation.

Other serious adverse events

Serious adverse events were reported for 87 (19.6%) patients in the palbociclib plus letrozole arm and for 28 (12.6%) patients in the placebo plus letrozole arm.

The sponsor states the following in the top-line summary: 'Most serious AEs were reported

for <1% of patients in either treatment arm, except 1.6% (7 patients) had Febrile neutropenia in the palbociclib plus letrozole arm and 1.4% (3 patients) had Pulmonary embolism in the placebo plus letrozole arm. The treatment-emergent, all-causality serious AEs that were experienced by ≥ 2 patients in either treatment arm are summarised in the Study 1008 top-line summary.'

Comment: No link is made to any narratives and all the CIOMS provided were blinded with respect to treatment allocation thus the findings reported in the top-line summary but could not be evaluated by the clinical evaluator. No comments on these data can be made and no recommendations for the PI can be made to reflect the proposed usage.

8.4.3.4 Other efficacy studies

Combination of palbociclib and letrozole Study 1003

Deaths

1 patient died while on study in the palbociclib and letrozole arm and none died on study in the letrozole alone arm as of July 31 2015.

Other SAEs

21 patients (25.3%) in the palbociclib and letrozole arm experienced at least 1 SAE in this portion of the study as of July 31 2015. Only SAEs of Pulmonary embolism (4 patients [4.8%]) and Back pain (2 [2.4%]) were experienced by more than 1 patient each. Three new SAEs (Acute kidney injury, Arthralgia, and Osteonecrosis of jaw) experienced by 1 patient (1.2%) each were reported as of 31 July 2015, compared with SAE information provided in the SCS as of 02 January 2015.

Colitis ischaemic was the only SAE considered to be related to palbociclib experienced by a patient in the Phase II portion of this study as of 31 July 2015. This Grade 3 SAE was experienced by a 55-year-old woman ([information redacted]) after about 5 months of

treatment with palbociclib plus letrozole. The diagnosis was made by colonoscopy and biopsy, and the event resolved with treatment consisting of aspirin, low molecular weight heparin, and an antispasmodic agent. Palbociclib and letrozole were permanently discontinued as a result of the event, and the patient recovered.

Comment: This is discussed in the Adverse Events of Special Interest section, and should be included in a Precaution stating Thrombotic and Thromboembolic events, as an arterial event. The clinical evaluator considers that the pulmonary embolism events are likely to be treatment-related (see Adverse Events of Special Interest). The event of dyspnoea occurred in a [information redacted] year-old who had a pleural effusion, and a clinical presentation that would be consistent with congestive heart failure.

As of 31 July 2015, 6 patients (7.8%) had experienced SAEs in the letrozole alone arm of which none was reported in the palbociclib plus letrozole arm – none of these was considered treatment-related. These SAEs were experienced by 1 patient (1.3%) each and included Anaemia, Cardiac failure, Erysipelas, Hip fracture, Ileus, Oesophageal achalasia, Plasma cell myeloma, Subcutaneous emphysema, and Upper limb fracture.

Studies evaluable for safety only

Study 1010

Deaths

As of 31 July 2015, no deaths occurred on study (within 28 days of discontinuation) -1 death on study from a subarachnoid haemorrhage occurred almost 3 months after stopping study treatment.

Other SAEs

As of 31 July 2015, a total of 3 patients experienced at least 1 SAE in this portion of the study. An SAE of gastrointestinal perforation shown in Study 1010 is not included in the total count of 3 patients as this SAE was reported in the Ph1P2 portion of Study 1010. All SAEs reported in the Phase II portion of the study were experienced by 1 patient each and included febrile neutropenia (1 patient), vomiting, malaise, cerebral haemorrhage, dizziness, and subarachnoid haemorrhage. The subarachnoid haemorrhage was reported as fatal; although death associated with this SAE was not considered by the sponsor to be an on-study death (almost 3 months after the patient received her last treatment).

The reported cases of febrile neutropenia and subarachnoid haemorrhage were considered to be related to treatment by either the investigator or the sponsor, or both.

Comment:

1. No CIOMS or detailed narrative is provided for the patient with a subarachnoid haemorrhage.
2. Draft CIOMS were provided for the patients with neutropenia (1) and cerebral haemorrhage (1). No information about risk factors for a cerebral haemorrhage such as thrombocytopenia was provided so relation to treatment cannot be excluded. The event of febrile neutropenia appears to be treatment-related.

Investigator-initiated Research (IIR)

Palbociclib monotherapy studies in breast cancer patients

1 death from respiratory failure was reported and considered to be most likely due to the underlying disease.

Comment: After review of this case, the evaluator is in agreement that the death appears most likely to be disease-related.

Other SAEs

4 patients with breast cancer who received palbociclib alone in IIR studies experienced SAEs of neutropenia, febrile neutropenia, colitis ischaemic, hypercalcaemia and (1 patient each) as of 31 July 2015. 3 of these patients also experienced second SAEs of pyrexia, asthenia, and pneumonia. The episodes of febrile neutropenia, neutropenia and ischaemic colitis were considered treatment-related.

Palbociclib plus Nonchemotherapy (endocrine therapy) Studies in Patients with Breast Cancer

2 patients died: one after the end of the study period (33 days) from hepatic failure and electrolyte imbalance, the other with disease progression and malaise, 13 days after discontinuing exemestane and palbociclib.

Comment: No link to CIOMS or narratives was provided to identify or review these cases. The case of hepatic failure and electrolyte imbalance was identified in the long list of pdfs for SAEs provided, but the other is too non-specific to identify. A cause of death for the former may be disease progression, but the evaluator agrees with the German Breast Group investigators that a contributing effect from palbociclib to the hepatic failure cannot be excluded. This adds further weight to the existing recommendation that drug-induced liver injury be included in the safety specification of the RMP.

As of 31 July 2015, a total of 16 patients receiving study treatment in this population experienced at least 1 SAE of whom 8 received blinded treatment. The SAEs experienced by more than 1 patient each were disease progression, breast cancer metastatic, and dyspnoea (2 patients each).

SAEs experienced by 4 patients were considered related to treatment by either the investigator or the sponsor, or both: Anaemia and Platelet count decreased (same patient), Leukopenia (1 patient), Hepatic failure and Electrolyte imbalance (same patient), and Dyspnoea (1 patient).

Comment:

1. The safety update report states that detailed narratives are available in Appendix 2 for all 4 patients where the events were considered treatment-related. The evaluator could not locate them in Appendix 2 and the sponsor is requested to provide these for the two patients below (anaemia, thrombocytopenia and leukopenia are well-established adverse events with palbociclib so the reports will be unlikely to add new information). Simple line reportings of the events were located.
    a. The patient ([information redacted]) with dyspnoea and pneumonia was discontinued from palbociclib on day 232 (why?) and then developed dyspnea and a nosocomial infection on day 257. Pneumonitis or interstitial lung disease need to be considered.
    b. For the patient ([information redacted]) with hepatic failure and electrolyte imbalance, although she died after the 28-day end of study period, her symptoms began 23 days after stopping palbociclib. No conclusions can be drawn given the blinding and a detailed report will indicate whether this case meets Hy's law.

Palbociclib monotherapy studies in patients with non-breast malignancies

As of 31 July 2015, a total of 24 deaths in this patient population were reported:

- 18 were associated with fatal SAEs;
    - 16 were considered to be deaths on study (including cases with missing information on either day of death or day of last treatment, or both);
        - the reports states 2 patients had fatal SAEs considered treatment-related but the

clinical evaluator notes 3 cases are listed here – details of all 3 patients are required as these could not be located

  - 2 cases (Case No. [information redacted] and Case No. [information redacted]) involving patients who experienced fatal SAEs of disease progression, liposarcoma metastatic, and death were not considered to be deaths on study (last dose of study treatment prior to death >28 days earlier).

- 6 were associated with SAEs not reported as fatal
  - 2 ([information redacted]) were considered to be deaths on study (information on day of death not provided in [information redacted]).

Comments:

1. The 90-day report cites IIR SU Table 5.8.1.2 as including 2 patients with fatal SAEs considered treatment-related but the clinical evaluator notes 3 cases are listed here – no detailed narratives as stated in the report in Appendix 2 could be located for any of these 3 patients and the clinical summaries in the notes for the patient with sudden death do not provide the evaluator with the original report to evaluate sponsor. The sponsor is requested to provide detailed narratives for the patient with sudden death and the third patient not described at all described as dying of 'death'. The evaluator agrees with the sponsor and investigator that the event of lung infection is likely to be related to palbociclib treatment.
2. The PI does not carry adequate information about the risk of the infections observed with palbociclib. It should state 'Infections, sometimes fatal, have been observed in patients taking palbociclib…'(PI Comments)

Other SAEs

As of 31 July 2015, 78 patients experienced at least 1 SAE. The most frequently reported SAEs (that is, >2 patients) were disease progression (13 patients); vomiting (9); anaemia and urinary tract infection (8 each); abdominal pain (7); nausea (6); dehydration (5); dyspnoea, pneumonia, and pyrexia (4 each); as well as acute kidney injury, atrial fibrillation, diarrhoea, febrile neutropenia, headache, muscular weakness, platelet count decreased, and small intestinal obstruction (3 each).

Comment: Most of these are well described AEs observed in other randomised controlled trials. AEs presented here requiring further close investigation and consideration in randomised trials are acute kidney injury and muscular weakness (peripheral neuropathy 3-fold higher with palbociclib and fulvestrant compared with fulvestrant alone, Study 1023).

8.4.4 Discontinuations due to adverse events

8.4.4.1 Integrated safety analyses

None provided.

8.4.4.2 Main/pivotal studies that assessed safety as the sole primary outcome

N/A.

8.4.4.3 Pivotal and/or main efficacy studies

Combination of palbociclib and fulvestrant – Study 1023

The overall frequency of TEAEs, 68.4% of which were Grade 3/4 severity, associated with permanent discontinuation from treatment was 5.5% in the palbociclib plus fulvestrant arm and 3.5% in the placebo plus fulvestrant arm of Study 1023 as of 31 July 2015 and are summarised

in the table below. The sponsor attributed causality of bone pain, drug-induced liver injury and nausea to the fulvestrant component of the treatment.

Comment: As discussed above, palbociclib cannot be excluded from contributing to the drug-induced liver injury[6], and with the 6% higher incidence of treatment-emergent nausea in this arm compared with the placebo and fulvestrant arm, nausea cannot be solely attributed to fulvestrant.

Table 30: Study A5481023 Treatment-related discontinuations in patients receiving palbociclib and fulvestrant

Table 17. Summary of All-Causality, Treatment-Emergent Adverse Events (All Cycles) Associated With Permanent Discontinuation From Treatment Experienced by Patients Receiving Palbociclib Plus Fulvestrant in Study A5481023 as of 31 July 2015 by MedDRA PT — All Treated Patients

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.

Combination with letrozole and palbociclib – Study 1008 top-line summary (no CSR available)

43 (9.7%) patients permanently discontinued from treatment due to treatment-emergent, all-causality AEs in the palbociclib plus letrozole arm versus 13 (5.9%) patients in the placebo plus letrozole arm. Most of those AEs were reported as a single event. In the palbociclib plus letrozole arm, 5 (1.1%), 3 (0.7%), and 3 (0.7%) patients discontinued due to Neutropenia, Alanine aminotransferase increased, and Disease progression, respectively. In the placebo plus letrozole arm, 2 (0.9%) patients discontinued due to fatigue. The all-causality AEs associated with permanent discontinuation for ≥ 2 patients in either treatment arm are summarised in Table 31.

[6] Clarification: There was a case report of hepatic failure assessed by the Sponsor to be unrelated to blinded therapy and fulvestrant and to any clinical trial procedure. For this case the investigator considered drug induced hepatitis could not be excluded and therefore two separate AEs were collected for this event. For further discussion see Response to Safety Question 18.

Table 31: Study A5481008 Summary of all-causality treatment-emergent adverse events associated with 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.

The clinical evaluator reviewed the supporting table for events occurring in one patient that were not reported. The data in that table are MedDRA terms presented by SOC, providing a degree of collation of similar events that is not presented in the top-line summary table above. The following are noted:

- There were 10 deaths in the palbociclib and letrozole arm with the following causes:
  - 4 were related to cardiac events;
  - 1 was attributed to 'death';
  - 2 due to respiratory, thoracic, mediastinal disorders (pulmonary embolism, respiratory failure);
  - 3 were attributed to disease progression.

Overall discontinuations due to AEs when classified by SOC in order of decreasing frequency were:

- Investigations
  - Hepatic enzyme increased/aspartate transaminase increased/alanine transaminase increased: 6 patients (1.4%) including Grade 4 (2 patients) and Grade 3 (3 patients)
- Neutropenia/neutrophil count decreased: 7 patients (1.6%)
- Cardiac disorders: 5 patients (1.1%)
- Respiratory, thoracic, mediastinal disorders: 5 patients (1.1%) including Grade 3 pneumonitis (1 patient)
- Renal and urinary disorders: 3 patients (0.7%) including 2 patients with 'acute kidney injury'
- Skin and subcutaneous tissue disorders: rash or dermatitis in total of 3 patients (all Grade 1 or 2)
- Nervous system disorders: 1 patient with cerebral haemorrhage, 1 with cerebrovascular accident

Comment: No narratives to assess these significant events including the deaths and any

possible relation to treatment. This requires submission for full evaluation of the CSR for Study 1008. This table provided information on the listing of TEAEs leading to deaths, which have been added to the section above on deaths on study.

Temporary discontinuations

Combination of palbociclib and fulvestrant – Study 1023

There was a 5-fold increase in TEAEs associated with temporary discontinuation from treatment in the palbociclib plus fulvestrant arm (69.3%; 65.4% Grade 3 or 4)) compared with the placebo plus fulvestrant arm (12.8%; 6.4% Grade 3 and 0 Grade 4)) as of that data cutoff date. There was a 10-fold increased risk of developing a Grade 3 or 4 toxicity in the experimental arm compared with the comparator arm. The conditions leading to a temporary discontinuation are similar to those listed for all-causality TEAEs, and include laboratory test abnormalities, nausea, vomiting diarrhea, fatigue, pain, thrombosis and a range of infections (9 different types recorded). Treatment for ten patients (2.9%), either at that time or subsequently, was discontinued permanently due to AEs.

Comment: The significance of the toxicity of the addition of palbociclib to fulvestrant becomes apparent with the figures of dose interruption, adjustment and discontinuation. Furthermore the severity is clearly indicated by the observed 10-fold increased risk of a Grade 3 or 4 toxicity (in fact no Grade 4 toxicities were observed in the placebo and fulvestrant arm). While most of these are due to haematological abnormalities and may be without symptoms, many of the remaining adverse events are associated with significant morbidity and severity.

Combination with letrozole and palbociclib – Study 1008 top-line summary (no CSR available)

The only information provided was in the top-line summary where temporary discontinuations due to an AE were listed as 9.9% in the palbociclib and letrozole arm compared with 4.1% in the placebo and letrozole arm.

Comment: No supporting data or analyses were presented and no evaluation of, or comment on the very limited information provided can be made.

Dose reductions due to TEAEs

Combination of palbociclib and fulvestrant –Study 1023

128 patients (37.1%) in the palbociclib plus fulvestrant arm had their palbociclib dose reduced as of 31 July 2015:

- 118 patients (34.2%) had their dose reduced from 125 mg QD to 100 mg QD, and
- 41 patients (11.9%) 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).

In the placebo plus fulvestrant arm, only 3 patients (1.7%) had their placebo dose reduced as of 31 July 2015.

TEAEs of neutropenia, febrile neutropenia, leukopenia, thrombocytopenia, stomatitis and fatigue accounted for 124/128 of palbociclib dose reductions/modifications as of 31 July 2015. A total of patients (35.9%) in the palbociclib plus fulvestrant arm and 3 patients (1.7%) in the placebo plus fulvestrant arm experienced these TEAEs as of that data cutoff date. SAEs leading to dose reduction/modification in the palbociclib plus fulvestrant arm included neutropenia (2 patients [0.6%]) as well as febrile neutropenia, pericarditis, gastro-oesophageal reflux disease, intestinal obstruction, pyrexia, otitis media acute, pharyngitis, electrocardiogram QT prolonged, neutrophil count decreased, and rash maculo-papular (1 [0.3%] each).

As of the 31 July 2015 cut-off date, the median time to first dose reduction was 57 days (range 27-459) on the palbociclib and fulvestrant arm. For the 9% of patients requiring a further dose reduction to 75 mg, the median time on the 100 mg dose was 197 days (range 56-450).

Comment: This is clinically relevant information as the range indicates that continuous monitoring is required as dose reductions may be required after the first cycle or many months after commencement or dose reduction. This also supports the advice that a full blood count should be obtained prior to each cycle. This monitoring information is currently in the Precautions section but should also be included in the Dosage and Administration section, together with the information about the median times to dose reduction.

The change to a different schedule (2 weeks on/2 weeks off) was not described in the Protocol and the benefits of this dose in the 3.8% who switched to this regimen cannot be assured. It is not clear what palbociclib dose was taken in this regimen (please provide this information). It would be apparent to the investigator that the patient was receiving palbociclib due to the AE profile, and this may have introduced a bias in wanting to continue if there was a clinical benefit observed but problematic toxicities. That so many changed to this regimen suggests a degree of unmasking. The sponsor is requested to provide an explanation of whether these non prespecified alterations were included in the protocol deviations and also whether these patients' outcomes were included in the efficacy analyses, and whether any subgroup efficacy analyses were performed for those on this regimen (Clinical Questions).

Combination with letrozole and palbociclib – Study 1008 top-line summary (no CSR available)

The only information provided was in [Table 9] of the top-line summary where dose reductions due to an AE were listed as 35.6% in the palbociclib and letrozole arm compared with 0.9% in the placebo and letrozole arm.

Comment: There is a substantial difference between the toxicities of the two arms as indicated by the dose reductions required. It is not possible to determine what the precipitating events were which led to the dose reductions nor whether the rechallenge was tolerated and these dose reductions were effective. In particular, significant toxicities were apparent in this study requiring discontinuation (for example, acute kidney injury, elevated liver enzymes, pulmonary fibrosis) and it is not possible to determine the rates of these, whether they were treatment-related and whether dose reduction strategies were effective.

Without the appropriate supporting data, analyses and narratives, it is not possible to evaluate this information, or comment on the very limited information provided can be made. Significantly, no comment can be included in the PI as to how best to manage the adverse events listed in the TEAE section.

8.4.4.4 Other efficacy studies

Study 1003

Phase II

As of 2 January 2015 cutoff, 13 patients (15.7%) in the palbociclib plus letrozole arm and 2 patients (2.6%) in the letrozole alone arm experienced TEAEs associated with permanent discontinuation from treatment. The only TEAEs associated with permanent discontinuation of more than 1 patient in the palbociclib plus letrozole arm were neutropenia (6.0%]) and fatigue (2.4%), although other notable TEAEs resulting in discontinuation included pulmonary embolism (2 other patients discontinued temporarily due to pulmonary embolisms), ischaemic colitis, weight loss and asthenia (all 1 patient each). The only TEAEs associated with permanent discontinuation from treatment in the letrozole alone arm were arthralgia and nausea (1.3% each).

Dose reductions and temporary discontinuations

31 of the 83 patients (37.3%) in the palbociclib plus letrozole arm experienced TEAEs associated with palbociclib dose reduction in this portion of the study. Most frequently reported TEAEs (≥ 2 patients [2.4%]) leading to dose reduction in that treatment arm included neutropenia (28.9%), leukopenia (7.2%), thrombocytopenia/platelet count decreased (3.6%), and fatigue (2.4%). Overall, a total of 27 patients (32.5%) experienced haematological TEAEs associated with palbociclib dose reduction.

Comments:

1. Granulocytopenia and neutropenia are the same events, as are thrombocytopenia and platelet count decreases and have been collated by the evaluator.
2. Adverse events included petechiae and the sponsor has been requested to provide data on the platelet count for this patient at that time, as well as a correlation between the risks of bleeding, bruising etc particularly and low platelet counts for all patients who have received palbociclib in the trials presented in the dossier. (Clinical Question)

5 of the 31 patients (6.0%) in the palbociclib plus letrozole arm in the Phase II portion of the study who had experienced TEAEs associated with dose reduction experienced later treatment-related AEs associated with permanent discontinuation from treatment.

Temporary discontinuations due to TEAEs in the palbociclib and letrozole arm were very common (63.9%), with 49.4% of these due to Grade 3 events, 7.2% due to Grade 4 events. Most of these were haematological toxicities, particularly neutropenia (53% including all MedDRA related terms) but prominent also were stomatitis/mucosal inflammation (4.8%), vomiting (2.4%) and fatigue (2.4%). 5 of the 53 patients (6.0%) in the palbociclib plus letrozole arm in the Phase II portion of the study who had experienced TEAEs associated with temporary discontinuation from treatment experienced later treatment-related AEs associated with permanent discontinuation from treatment. In comparison only one patient (1.3%) required a temporary discontinuation in the letrozole alone arm.

Phase I

11/12 patients in the Phase I arm required a treatment interruption and dose reduction but none discontinued permanently.

Study 1010

In the Ph1P2 portion of Study 1010, 1 patient (16.7%) experienced Neutrophil count decreased associated with permanent discontinuation from treatment.

In addition, TEAEs associated with permanent discontinuation from treatment were experienced by 1 patient (16.7%) in the Ph1P1 portion of Study 1010.

Study 1001

11 patients experienced TEAEs associated with permanent discontinuation.

No updated data are provided in the 90-day safety update for either Study 1001 or 1010.

8.4.5 Adverse events of special interest

The events of special clinical interest summarised in this section include myelosuppression (neutropenia-related and thrombocytopenia-related events), prolongation of time from beginning of the QRS complex to the end of the T wave as shown on the ECG (QT interval), eye disorders with a focus on cataracts, respiratory disorders with a focus on interstitial lung disease and pneumonitis, and venous thromboembolic disorders.

Data, analyses and discussion were only presented for Study 1023. No specific information was available, nor was there any discussion of these key adverse events identified in the top-line

summary from Study 1008.

Comment: This is a significant omission of key safety data and analyses which require evaluation prior to the evaluator making any recommendations about registration for the proposed usage with letrozole and which are also required to inform the PI.

8.4.5.1 Integrated safety analyses

None provided.

8.4.5.2 Main/pivotal studies that assessed safety as the sole primary outcome

N/A

8.4.5.3 Pivotal and/or main efficacy studies

Neutropenia

The SCS states for Studies 1003 and 1023 that the cluster term of NEUTROPENIA comprise MedDRA preferred terms for AEs of neutropenia and neutrophil count decreased.

Comment: These underreport events of low neutrophils due to the abnormal laboratory findings not being required by the protocol to be defined as AEs, as well as granulocytopenia, which may be low neutrophils. This approach has led to underreporting of the frequency and severity of adverse events in both trials, Study 1023 and 1003. Analyses of events provided in the 90-day update for neutropenia for Study 1023 for example, time to first event of neutropenic and duration etc have been presented variously based on the cluster term or abnormal laboratory term. Any presentation of the data in the PI should present the total numbers of events of the abnormal laboratory terms, and use analyses based on these figures in any representations in the PI to minimise the impact of this reporting bias.

Combination of palbociclib and fulvestrant – Study 1023 (as of July 31 2015)

Consistent with the pharmacological activity of palbociclib (that is, cell cycle inhibition), one of the potential primary target organ systems for palbociclib identified from nonclinical studies is the haematolymphopoietic system. Myelosuppression is also observed in clinical studies of palbociclib.

Patients could have more than one episode and only the highest grade was reported.

From [Table 21] 90-day safety update, TEAEs coding to either PT Neutropenia or PT Neutrophil count decreased in the All Treated (AT) set:

- palbociclib plus fulvestrant arm
  - 287/345 patients (83.2%)
    - 228 or 240 patients with Grade 3/4 severity (66.1% as proportion of AT set); 47 patients with Grade 1/2 severity (13.6% AT set)
- placebo plus fulvestrant arm
  - 7/172 patients (4.1%)
    - 1 patient with Grade 3 severity, 0 Grade 4 (0.6% as proportion of AT set)

Comments:

1. Was a patient able to be recorded as having both neutrophil count decreased and neutropenia by MedDRA PT? If so, the sponsor is requested to provide the number of patients where this has occurred and revise the figures collating any potential double reporting for these patients for these 2 events.(Clinical Question)
2. The figures do not appear to tally between Tables 7 and 21 compared with Table 22 for the

number of patients reported to have Grade 3/4 events as defined by the cluster term NEUTROPENIA (Table 21 and subsequent text). 287 patients were reported to have NEUTROPENIA events of any severity (based on figures from Table 7); with the text following Table 21 stating 240 of these patients had Grade 3/4 severity (citing Table 7). However, Table 22 demonstrates that the number of patients with maximum grade of 3 was 191 patients and with a maximum of Grade 4 was 37 and this equals 228 patients. The sponsor is requested to state which are the correct figures and explain how these differences were arrived at. (Clinical Question).

By clinical laboratory findings - abnormal neutrophil counts (not defined as increase or decrease in table 37, 90-day safety update so conservatively taken as all neutropenia by evaluator)

- palbociclib plus fulvestrant arm
  - 326/339 patients (94.4%) - 2254 events (any severity)
    - 225 patients with Grade 3/4 severity, all as shift from Grade ≤2 at baseline to Grade ≥ 3 postbaseline that is, treatment-emergent (66.4% of AT set)
- placebo plus fulvestrant arm
  - 23/167 patients (13.8%) – 30 events (any severity)
    - 0 patients had Grade 3 decreases and 2 had Grade 4 decreases (1.2% of AT set - both were a shift from baseline so treatment-emergent)

Comment:

1. The TEAEs should be a subset of the clinical laboratory abnormalities, as this AE grading is based on a blood test. The sponsor is requested to explain how there are discrepancies between the clinical laboratory abnormalities and the MedDRA PT reported AEs including:
   a. More patients are reported to have Grade 3/4 neutropenia or neutrophil count decreased by MedDRA PT compared with those determined by clinical laboratory abnormalities (228 or 240 versus 225);
   b. 2 patients in the comparator arm had Grade 4 events on blood tests which were not recorded as TEAEs. In a blinded study, any Grade 4 events of neutropenia should be reported as AEs but the 2 events in the placebo and fulvestrant arm were not recorded as AEs. (Clinical Question).

The sponsor attributed causality to palbociclib and fulvestrant in 98.7% of cases reported for TEAEs but no attribution is made for clinical laboratory abnormalities although this is likely to be similar.

Febrile neutropenia

The sponsor states that 3 events of febrile neutropenia occurred in the palbociclib and fulvestrant arm (1 Grade 3 neutropenia and 2 Grade 4) and one event in the comparator arm but no events of neutropenic sepsis or neutropenic infection were reported until a report in November 2015 (after cut-off date) of a patient ([information redacted]) whom the investigator described as the 'Reported cause of death were neutropenic sepsis, multiple organ failure and disease progression' with the CIOMS recording the investigator attribution as 'unrelated to blinded therapy, fulvestrant, concomitant drugs or to a clinical trial procedure'. The sponsor states this SAE to be unrelated to treatment. Palbociclib had been discontinued 22 days earlier and the last dose of fulvestrant was 46 days prior to presentation. The CIOMS records that the neutrophils were 0.35 x 10^3/mm^3 on the day of presentation. Two days later it had increased to 1.61 x 10^3/mm^3, and blood cultures were declared positive for Escherichia coli indicating neutropenic sepsis. The patient died 3 days later. No post mortem was performed.

Comment: The evaluator disagrees with the sponsor regarding this case. The patient was neutropenic and had a documented bacterial infection to account for the presentation with septic shock (neutropenic sepsis), within the Protocol-defined safety period defined as within 28 days of taking palbociclib. There was an accompanying low platelet count and anaemia, which would be consistent with residual toxicities after the recent discontinuation of palbociclib with its known profound myelosuppressive effects (as well as very commonly causing anaemia). The median duration of neutropenia reported for those experiencing ≥ Grade 3 neutropenic events (21 days; range: 1-167) indicate that this may well have contributed to this presentation and a causative effect of treatment cannot be excluded as is stated by the sponsor. The investigator's narrative was not provided (just a draft CIOMS) and it is to be noted that the investigator would not have had this information about duration of neutropenia when making the attribution of causality and may be unaware of the potentially very long duration of neutropenia associated with palbociclib; this differs significantly from the neutropenia associated with chemotherapy which could reasonably have been expected to have resolved within a 22 day timeframe. This is considered important clinical information and the range (1-42) should be included in the information about median duration for Grade 3 neutropenia in the Neutropenia section in the Precautions in the PI. 90-day Safety Update attests further this with 40.5% of patients experiencing a TEAE of Infection while neutropenic. On balance, the evaluator considers this patient's cause of death should be considered treatment-related and the PI should include in the Precautions statement that infections, sometimes fatal, have been observed in patients on palbociclib. Sepsis, chronic disease, bone marrow infiltration cannot be ruled out as a contributing factor to the observed pancytopenia, but the most likely cause is palbociclib treatment.

Actions for sponsor: Include fatalities in descriptions of infection in the Precautions section. Add neutropenic sepsis, sometimes fatal and median durations of neutropenia to Precautions section of PI.

Febrile neutropenia experienced by 3 patients in the palbociclib plus fulvestrant arm of

Study 1023 (Cycle 1 Week 3, Cycle 5 Week 4, and Cycle 5 Week 5) was of Grade 3 severity and was considered treatment-related; while febrile neutropenia experienced by 1 patient in the placebo plus fulvestrant arm of this study was of Grade 4 severity but not considered related to treatment.

Neutropenia was almost universally detected in the palbociclib and fulvestrant arm: 326/339 patients (96.2%), including 189 patients (55.8%) with Grade 3 decreases and 36 patients (10.6%) with Grade 4 decreases in these counts compared with 23/167 patients (13.8%) in the placebo plus fulvestrant arm with any abnormal absolute neutrophil count (0 Grade 3, 2 (1.2%) Grade 4).

Comment: The hyperlinks to the Summary of Clinical Safety from the 90-day safety update are all incorrect and direct the evaluator to an unrelated section of that summary document. It appears the discussion of additional events and data in the 90-day safety summary is not referring to the same Summary of Clinical Safety data presented to the TGA.

The sponsor presented data analysing the baseline characteristics of those developing Grade 3/4 neutropenia, and reports no clear predictive factors. While a high percentage of patients developing Grade 3 neutropenia went on to develop Grade 4 neutropenia at a later treatment time point, there was no clear pattern and this was also observed in those with lower grade earlier neutropenic AEs. Dose reduction strategies were effective but events of high-grade neutropenia were still observed in some patients despite this.

Comment: The onset of significant and severe neutropenia is not predictable and requires ongoing monitoring throughout the treatment period.

Time to onset of neutropenia (based on Clinical laboratory findings)

The median time from first dose to the ≥Grade 3 neutrophil count was shorter in the palbociclib plus fulvestrant arm (30.5 [13 – 587] days) than in the placebo plus fulvestrant arm (214 [15 – 538] days).

In the palbociclib plus fulvestrant arm, the median time from first dose to onset of first neutropenia episode of any severity grade (15 days), Grade ≥2 (15 days), Grade ≥3 (16 days), or Grade 4 (19 days) was shorter than 1 treatment cycle.

Comment: The PI figures for this do not reflect the 31 July cut-off data and require updating (PI Comments), as the updated data with its much higher upper limit of the range (from 140 days to 317 days) indicate clearly that an episode of neutropenia can occur for the first time at any time during treatment. There are appropriate recommendations for monitoring on day 14 of the first 2 cycles and prior to the commencement of each cycle in the PI.

Median duration of neutropenia (based on Clinical laboratory abnormalities)

The median duration of any grade neutropenia by patient (that is, duration of all episodes combined) reported in the palbociclib plus fulvestrant arm was 179 (3 – 573) days across all cycles, while the median duration of Grade ≥3 neutropenia and Grade 4 neutropenia across all cycles was 21 (1 – 167) days and 10.5 (2 – 28) days, respectively.

Neutropenia and infections (based on Clinical laboratory abnormalities)

The sponsor reported that 40.5% of patients who had a laboratory finding of neutropenia (any severity grade) in the palbociclib plus fulvestrant arm experienced concomitant TEAEs within the MedDRA SOC Infections and infestations as follows:

- 8 patients (2.5%) with any severity grade neutropenia experienced a concomitant Grade 3/4 TEAE within this SOC;
- 3 patients (1.3%) with Grade 3/4 neutropenia had a concomitant Grade 3/4 TEAE within this SOC (Grade 3 Erysipelas, Grade 3 Upper respiratory tract infection, and Grade 4 Cellulitis (1 patient each).

Comment: The evaluator considers that the patient described above who died of neutropenic sepsis 24 days after discontinuing palbociclib should be included in this analysis and also in the PI. The Precautions section ought to state that neutropenia and neutropenic sepsis were observed in patients receiving palbociclib and fulvestrant in the Neutropenia Section. Severe infections including fatal infections have been observed in patients receiving palbociclib and fulvestrant should be included in the Infections section in the Precautions.

Infections

TEAEs within the MedDRA SOC Infections and infestations were more common in patients in the palbociclib plus fulvestrant arm (47.0%) than in the placebo plus fulvestrant arm (30.8%); however, the frequency of Grade 3/4 TEAEs was similar between the 2 treatment arms (3.2% and 2.9%, respectively).

The most frequently reported infections or infestations (that is, ≥2% of patients) for the palbociclib plus fulvestrant arm were:

- nasopharyngitis (13.0%);
- upper respiratory tract infection (9.3%);

- urinary tract infection (7.5%);
- bronchitis (3.2%);
- rhinitis (2.9%);
- influenza (2.6%);
- sinusitis (2.3% each);
- conjunctivitis (2.3% each).

There was a background rate of nasopharyngitis (8.1%), upper respiratory tract infection (7.0%), urinary tract infection (6.4%), and influenza (4.7%) in the placebo plus fulvestrant arm (pneumonia [2.3%] was also reported most commonly for that treatment arm.)

Exposure and neutropenia

Comment: This would be consistent with the observed effect of fewer episodes of neutropenia when the dose is reduced.

Combination of palbociclib with letrozole - 1008 top-line summary

No data were presented for evaluation

8.4.5.4 Other efficacy studies

Combination of palbociclib and letrozole –Study 1003, Study 1010

(Study 1027 does not provide evaluable data due to ongoing blinding of treatment allocation).

Study 1003

As of 2 January 2015 as reported in the SCS, TEAEs of neutropenia occurred in:

- 75.9% of those receiving palbociclib and letrozole in the Phase II part of the study
  - 42 patients (50.6%) Grade 3 severity – 3 patients discontinued permanently
  - 5 patients (6.0%) Grade 4 severity – 2 discontinued permanently
- 91.7% of patients in the Phase I part of the study
  - 8 patients (66.7%) Grade 3, 2 patients (25%) Grade 4 – none discontinued permanently

Based on laboratory abnormalities data, 3 patients had Grade 4 events in the Phase I part yet the MedDRA PT of neutropenia indicates only 2 patients.

Comment: Neutropenia is established by a blood test and clinical laboratory measurement, regardless of MedDRA PT. The sponsor's protocol did not require laboratory abnormalities of Grade 4 to be considered AEs, unless accompanied by symptoms or some specific change in the study drugs or concomitant therapy. Consequently, no accounts of any treatment discontinuations or other outcomes are presented for the 3rd patient with laboratory findings of Grade 4 neutropenia (Clinical Question).

Phase II

NEUTROPENIA was reported most frequently (63 patients [75.9%]), and considered treatment-related in 62/63 patients.

Grade 1 2 patients (2.4%);

Grade 2 14 patients (16.9%);

Grade 3 42 patients (50.6%) - 41 patients Neutropenia,1 Neutrophil count decreased;

Grade 4 5 patients (6.0%)

NEUTROPENIA was experienced by 4 patients (5.2%) in the letrozole alone arm and considered

related to treatment in 2 patients:

Grade 1: 1 patient; Grade 2: 2 patients; Grade 3: 1 patient.

Comment: Letrozole is not normally associated with neutropenia, particularly Grade 3 events.

By contrast, in the Phase II study, clinical laboratory measurements identified 77/82 (93.9%) patients with abnormal neutrophil counts including 47 patients with Grade 3 events (57.3%) and 5 patients (6.1%) with Grade 4 events, all of which occurred after commencing treatment that is, treatment-emergent (shift from ≤Grade 2 to ≥Grade 3 from baseline was the same 63.4%).

In the letrozole alone arm, 13/77 patients (16.9%) had abnormal laboratory findings of absolute neutrophil counts of whom 2 (2.6%) had Grade 3 abnormal results and none had Grade 4 abnormal results.

The use of laboratory abnormalities rather than AEs meant 14 patients (18% of the As Treated safety set) more than the use of MedDRA terms which define the TEAEs were reported including 5 more patients with Grade 3 events.

Comment:

1. Overall, the protocol-defined approach to recording adverse events has meant 20% of this Phase I/II study population who experienced an event of neutropenia including 6.3% (6/95) patients experiencing Grade 3 and 4 events were not captured by the MedDRA terms and are thus excluded from analyses that report TEAEs.
2. All the Grade 3 and 4 events were treatment-emergent but not recorded as such and add an additional 6/95 patients with severe neutropenia to the palbociclib and letrozole arm across this entire trial that is, 6.3% of the very small population in this trial.

Comments: The evaluator considers these laboratory-determined events to be more accurate as treatment-related events and that these figures should be used in any tables in the proposed draft PI for this usage when Study 1008 is submitted (PI Comments). Throughout the analyses, the evaluator considers there is underreporting of events of neutropenia against which to record the total number of actions taken as a result (dose reductions, discontinuations etc), and no classification of these as related to treatment. Reporting of these events is included in this subanalysis for events of special interest but not elsewhere in the CSR when neutropenia is discussed or presented.

Such data collection and underreporting is of concern, and particularly for less common or rare events - a specific request for clinical laboratory data abnormalities from all the trials where it is not explicitly stated, will be sought for renal function and hepatic function abnormalities.

Dose interruptions, reductions (by cluster NEUTROPENIA)

All 42 patients with Grade 3 NEUTROPENIA in the palbociclib plus letrozole arm had their dose reduced/interrupted or had their treatment cycle delayed, while 3 of the 5 patients with Grade 4 NEUTROPENIA had their dose reduced/interrupted or had their treatment cycle delayed. (The remaining 2 of the 5 patients with Grade 4 Neutropenia were permanently discontinued from treatment). Discontinuations due to clinical laboratory abnormality of neutropenia could not be located by the evaluator.

No baseline or demographic characteristics were predictive of who might develop neutropenia.

Comment: No information is presented regarding actions taken for those 5 additional patients who had Grade 3 abnormal neutrophil counts by laboratory findings. It would not be standard clinical practice not to respond to such events, especially in a clinical trial setting, and the sponsor is invited to comment.

Time to onset, median duration (clinical laboratory findings)

Based on clinical laboratory findings, the median time to first onset was 15 days (range: 13-141), but first Grade >3 episodes were recorded up to 798 days after starting and the longest time to develop the lowest neutrophil counts was 1066 days. The median duration of neutropenia of any grade was 292 days (range: 6-1440) for the palbociclib and letrozole arm but for Grade 3 was 43 days (range: 1-254) and for Grade 4 was 7 days (range 4-33). The median time to recovery (that is, >1500 absolute neutrophil count) from lowest neutrophil count among patients with Grade ≥ 3 neutropenia in that treatment arm was 99 days.

Comment: Essentially, neutropenia can occur at any time, tends to resolve quite slowly and the PI should include these figures to ensure this information is available to clinicians as this is different from cytotoxic-induced neutropenia. Dose reduction decreases the likelihood of further events but these still occur. The shorter duration for Grade 4 events is likely to be due to the strict withholding and dose reduction that occurs, whereas prolonged lower grade neutropenia is likely to be associated with continuation of the treatment.

Infections (based on Clinical laboratory findings)

As of January 2015, infections were reported more commonly in the palbociclib and letrozole arm (59% all grades; 6% Grade 3/4) compared with 33.8% in the letrozole alone arm (no Grade 3/4). These events included a range of bacterial, viral and fungal infections, none of which led to treatment discontinuation. The Phase II part of the study, 42.9% of patients with neutropenia (as defined by clinical laboratory abnormality) of any severity developed an infection or infestation, and 2.6% had a Grade 3/4 event. 26.9% with Grade 3/4 neutropenia developed an infection.

No TEAEs of febrile neutropenia, neutropenic sepsis, or neutropenic infection were reported in this Phase I/II study. Infections occurred in 7 patients, all Grade 1 or 2.

Comment: The use of concomitant granulocyte colony stimulating factor support in any of the studies to reduce the risk of infection has not been discussed and the sponsor is requested to present the proportion of patients in each study treated with colony stimulating factors, and any effect on the duration of neutropenia. It is important to include this information and to include a statement as to whether GCSF use is appropriate in the PI (Clinical Question), noting that absence of its use may be as informative of indicating how often it was used.

Study 1010

Phase I

Palbociclib as monotherapy (100 mg and 125 mg daily dosing) in patients with solid tumours was associated with neutropenia in 83.3% and 67.7% patients at the dose levels, respectively. Infections were observed but not considered related to palbociclib treatment. Given the limited relevance to the proposed usage, causality has not been evaluated further by the evaluator.

Phase I Part 2

Neutrophil count decreased was experienced by all 6 patients (100%) participating in this portion of the study as of 31 March 2015 (Grade 2 in severity in 1 patient, Grade 3 in 3 patients, and Grade 4 in 2 patients) by MedDRA term or clinical laboratory findings. All changes were considered treatment-related. 33.3% experienced infections but none was considered related to treatment by the sponsor.

Comment: Narratives were not available and the causality for these events was not evaluated. It is considered already established that patients receiving palbociclib are at an increased risk of infection (statement in the PI).

As with the Ph1P1 portion of the study, the sponsor indicates that no reports of febrile

neutropenia were received in the Ph1P2 portion of the study (90-day safety update).

The SCS summary of febrile neutropenia across studies in malignant disease is out of date and thus was not evaluated.[7]

8.4.5.5 Thrombocytopenia

Combination of palbociclib with fulvestrant Study 1023

This was presented in 2 ways: as laboratory findings or as TEAEs in Study 1023 as of 31 July 2015, based on a cluster term THROMBOCYTOPENIA comprising the MedDRA PTs of Thrombocytopenia and Platelet count decreased. TEAEs coding to PT Thrombocytopenia (13.0%) or PT Platelet count decreased (10.1%) were experienced by patients receiving palbociclib plus fulvestrant but not the comparator arm in this study. 8 patients (2.3%) experienced a Grade 3 (6 patients) or Grade 4 (2 patients) event and a single patient with Grade 3 toxicity discontinued permanently due to this AE, while 3 others with Grade 3 and 1 with a Grade 4 event had their dose reduced or treatment interrupted. The sponsor reports that '(based on Haemorrhage terms, excluding laboratory terms, within Standardized MedDRA Queries [Narrow])', there were no bleeding episodes.

Clinical laboratory findings indicated 210 patients (61.8%) in the palbociclib plus fulvestrant arm had abnormal platelet counts as of 31 July 2015, including 5 patients (1.5%) with Grade 3 decreases and 3 patients (0.9%) with Grade 4 decreases in these counts. In comparison, 17 patients (10.1%) in the placebo plus fulvestrant arm had abnormal platelet counts, all of Grade 1 severity. A shift in platelet counts from Grade ≤2 at baseline to Grade ≥ 3 post baseline was observed for 8/340 patients (2.4%) in the palbociclib plus fulvestrant arm No such shifts in platelet counts were observed in the placebo plus fulvestrant arm.

Comments:

1. The definition in the Protocol of an AE with respect to an abnormal test finding is the same as Study 1003 and has once more led to a level of under-reporting of the events for the population as a whole, especially for lower grade AEs of thrombocytopenia. The comparator arm provides the expected baseline rates and this is much higher in the experimental arm. The total number with Grade 3 or 4 TEAEs or laboratory abnormal results is the same although the distribution is different. The sponsor is requested to provide an explanation. Are the TEAEs a subset of the laboratory test abnormalities?
2. The rate of epistaxis is noted to be increased in Study 1008 for the palbociclib arm and sponsor is requested for Study 1023, to state whether searching using any other MedDRA terms that covers any event of bleeding that is, captures events including but not limited to haemorrhage, bleeding, epistaxis or bruising, yields any events absolutely, and whether these were associated with the events of thrombocytopenia. (Clinical Questions).

Combination with letrozole and palbociclib – Study 1008 top-line summary (no CSR available)

No specific data, analyses or discussion is presented and the CSR is required to evaluate this risk.

Combination with letrozole and palbociclib – Study 1003

The cluster term THROMBOCYTOPENIA used PTs coding to thrombocytopenia and platelet count decreased. The MedDRA PT of thrombocytopenia reported in the TEAE tables did not capture all the events of significant decrease in platelets related to treatment.

As of January 2 2015:

[7] For discussion see responses to Clinical safety questions 5 and 7.

Phase I

- 3 patients in the (25%) had developed thrombocytopenia – no events of platelet count decreased; 2 Grade 2, 1 Grade 1
- Based on clinical laboratory tests, 8/12 patients (66.7%) had abnormal platelet counts, although no Grade 3 or Grade 4 decreased counts were reported;

Phase II

- 19 patients (22.9%) in the part developed thrombocytopaenia/platelet count decreased with palbociclib and letrozole compared with 2 patients on letrozole alone (2.6%);
  - 2 were Grade 3 events, 0 Grade 4 events
    - 2 patients had a dose reduction/interruption/delay but none discontinued permanently;
- Based on clinical laboratory tests, 53/82 patients (64.6%) had abnormal platelet counts
  - 3 (3.7%) Grade 3 events, no Grade 4;
    - shift from Grade ≤2 to Grade ≥ 3 occurred in 3 patients;
    - 12/77 (15.6%) on letrozole alone had an abnormal result;
    - 1 Grade 3 events, no Grade 4 ;

The sponsor reports that there were no associated events of bleeding using the term 'haemorrhage'.

Comment: An appropriate statement should be included in the PI to reflect the nearly 4-fold and almost 50% absolute increase in rates of all grades of thrombocytopenia with palbociclib; these changes should be recorded as very common with a percentage in any ADR table of a draft PI when the CSR for Study 1008 is submitted (PI Comments).

There was an increased rate of epistaxis (6% versus 1.3%; all Grade 1 events in both arms) in the palbociclib and letrozole arm; whether these events or any other bleeding events were associated with thrombocytopenia/platelet count decreased is not discussed and the sponsor is requested to state the platelet count at the time of each event of epistaxis for these patients as well as for any patients in either treatment arm experiencing an event of bleeding or haemorrhage in any organ system (Clinical Questions).

Study 1010 in Japanese Patients with Advanced Malignant Solid Tumours, Including Breast Cancer, Receiving Palbociclib Alone (Phase I Part 1) or in Combination with Letrozole (Phase I Part 2 and Phase II)

Phase I

Two events: 1Grade 2 (100 mg QD) cohort and 2 events in the 125 mg cohort (1 Grade 1 and 1 Grade 4) events of thrombocytopenia by TEAE or laboratory finding were observed.

Comment: The report is inconsistent with the 125 mg cohort being stated to be Grade 1 and Grade 4 events in paragraph 1 (p196, SCS) then Grade 3 and Grade 4 in the second paragraph. The management was of temporary discontinuations and dose reduction, respectively.

Phase I Part 2

Grade 1 or 2 events were reported as TEAEs in 4/6 patients and 5/6 patients using laboratory findings. No action was required.

No report was included in the SCS for thrombocytopenia in the Phase II part of this Study

although the 90-day safety update refers to safety events for 32 patients being included in this SCS.

8.4.5.6 QT prolongation

A potential of palbociclib for QT prolongation and hemodynamic effects was identified from in vitro assays and/or in vivo cardiovascular dog studies. Palbociclib caused a small but statistically significant increase of action potential duration at 90% repolarization at 10 μM (4475 ng/mL) in the dog Purkinje fiber assay and had a concentration associated with 50% inhibition (IC50) at 3.2 μM (1432 ng/mL) in a human ether-à-go-go related gene assay.

Combination of palbociclib and fulvestrant Study 1023

As of 31 July 2015, evaluations of QTc were based on the data reported for 150 patients in the palbociclib plus fulvestrant arm and 109 patients in the placebo plus fulvestrant arm who had both baseline and postbaseline ECG data. Twelve-lead triplicate ECG recordings were performed in patients with advanced breast cancer receiving palbociclib plus fulvestrant or placebo plus fulvestrant in Study 1023 at screening and end of treatment.

Comment:

1. This approach lacks the rigour necessary to characterise ECG abnormalities or determine the potential for palbociclib to cause QT prolongation; as such, this study provides only very limited information regarding potential ECG abnormalities that may be observed while on treatment.
2. The denominator changed for this update (and therefore the rate of events recorded) from that reported in the SCS as more patients had completed the trial and had their final recording.

One patient in the palbociclib plus fulvestrant arm and 1 other patient in the placebo plus fulvestrant arm had a post baseline QTcF of ≥ 500 msec (90-day safety update). The proportion of patients with a post baseline QTcB of ≥ 500 msec was higher in the palbociclib plus fulvestrant arm (3.3%) than in the placebo plus fulvestrant arm (1.8%). The proportions of patients who had a >60 msec maximum increase from baseline in QTcF and QTcB were also higher in the palbociclib plus fulvestrant arm (2.0% and 2.7%, respectively) than in the placebo plus fulvestrant arm (0.9% for each QTc measurement).

One patient in the palbociclib plus fulvestrant arm of Study 1023 experienced an SAE of Grade 3 Electrocardiogram QT prolonged (resolved within 2 days) as of 31 July 2015, which coincided with a Grade 2 SAE of pericarditis. Palbociclib therapy was temporarily discontinued in response to these events and was subsequently restarted, although at a reduced dose of 100 mg QD; the events did not reoccur thereafter. No new SAEs of Electrocardiogram QT prolonged were reported in this study as of 31 July 2015.

Comment: After reviewing the details of this SAE, the evaluator agrees with the investigator who 'considered there was a reasonable possibility that the events pericarditis and QTc prolongation were related to the blinded therapy and not related to fulvestrant, to a concomitant medication or to a clinical trial procedure' and also with the sponsor that there is still uncertainty about attribution of causality to the treatment received given the clinical events surrounding the admission with pericarditis. A dose-reduction was made, and no further abnormalities were recorded on rechallenge. It is appropriate, given the preclinical findings and this case, that QT prolongation is investigated further and reported. It was a secondary endpoint of Study 1008, but not included in top line summary in this application so remains an important, outstanding issue needing evaluation. It is appropriately listed as an important potential risk in the safety specification of the RMP.

The following relevant TEAEs were experienced by patients in that treatment arm: Tachycardia

(9 patients [2.6%]), Presyncope (5 patients [1.4%]), Bradycardia and Palpitations (3 [0.9%] each), Atrial fibrillation and Sinus tachycardia (2 [0.6%] each), as well as Electrocardiogram QT prolonged, Extrasystoles, Syncope, Ventricular extrasystoles, and Ventricular tachycardia (1 [0.3%] each). Among these relevant TEAEs, Electrocardiogram QT prolonged (Grade 3 in severity) along with Atrial fibrillation, Bradycardia, Tachycardia, Ventricular extrasystoles, and Ventricular tachycardia (all 'Grade 1' in severity – see evaluator comment below) experienced by 1 patient each were considered to be related to treatment.

Comment: The Study protocol states that CTCAE v 4.0 was used to grade events. There is no classification of Grade 1 for ventricular tachycardia, as this arrhythmia necessarily requires medical attention and potentially intervention. Similarly, there are no CTCAE terms for 'bradycardia', 'tachycardia' or 'ventricular extrasystoles' to which the term Grade 1 could be attached. The sponsor is requested to comment on which grading system was used for these assessments and to provide updated details and classifications regarding these adverse events as per the protocol, and the clinical details surrounding the event of ventricular tachycardia (Clinical Question).

Combination with letrozole and palbociclib – Study 1008 top-line summary (no CSR available)

Although a secondary endpoint, no data were presented on the outcome of the ECG substudy in 60 patients in this study. An event of Grade 3 QT prolongation is included in the summary of Grade 3-5 TEAEs in the palbociclib and letrozole arm but no further information is provided.

Comment: The full CSR is required and no comment or recommendation can be made on the limited information provided.

Combination with letrozole and palbociclib Study 1003

One of 12 patients had a maximum increase from baseline in QTcF interval of ≥ 30 and <60 msec (Grade 2) in the Phase I part of this study and no patients had a QTcF value of >500 msec.

In the Phase II part, cardiac events were infrequent with 3 in the palbociclib and letrozole arm and 4 in the letrozole arm. There were no reports of the following preferred terms in the palbociclib and letrozole arm during the Phase II portion of the study: syncope, cardiac arrest, convulsion, electrocardiogram QT prolonged, sudden death, torsade de pointes, ventricular fibrillation, ventricular flutter, or ventricular tachycardia.

Comment: QT prolongation was noted in the preclinical studies, and there has been one case reported in Study 1023 and one in Study 1008. Other cardiac adverse events were infrequent in patients receiving palbociclib.

Study 1010

As of 31 March 2015 (SCS), none of the patients with ECG data available for evaluation had postbaseline QTc values of >500 msec in this portion of the study, and none had increases from baseline in QTc values of ≥ 30 msec (Study 1010). No data are provided for the Phase II part of the study in the SCS.

The 90-day safety update reports that as of 31 July 2015, no patients had an on-study post baseline QTcS, QTcF, and/or QTcB value longer than 500 msec in completed Studies 1003, 1010 Phase I, 1001, 1002, and 1004. A single patient in Study 1001 had a maximum baseline change >60 msec but was able to carry on treatment.

Comment: A review of the CSR for Study 1001 PK/safety study included a patient in the 'Summary of ECG outlier analysis' with a QTcB ≥ 500msec in the 75mg dose level group but no reports where QTcF≥ 500msec .

Summary: QT prolongation and VT were observed in Study 1023 in the experimental arm. QTcF prolongation from baseline >60msec occurred more commonly in the palbociclib and

fulvestrant arm compared with the placebo and fulvestrant arm. The responses to the clinical questions should provide some clarification surrounding the event of VT.

8.4.5.7 Eye disorders with a focus on cataracts

Combination of palbociclib and fulvestrant Study 1023

Eye disorders were more frequently experienced by patients in the palbociclib plus fulvestrant arm (TEAEs: 22.3%; treatment-related AEs: 10.7%) than in the placebo plus fulvestrant arm (TEAEs: 10.5%; treatment-related AEs: 2.9%).

Cataracts

3 patients developed cataracts in the palbociclib and fulvestrant arm compared with none in the comparator arm. For 2 of the cases reported and where the safety update/clinical summary include a brief review, the two respective investigators clearly considered the cataract development or rate of development to be related to palbociclib, and the sponsor disagreed and does not consider them treatment-related.

Clinical evaluator comments on cataracts:

1. The clinical evaluator was able to locate the CIOMS for [information redacted] and notes the investigator has remained adamant this is treatment-related.
2. No narrative was available for [information redacted], and for the first case reported, the reference hyperlink in the 90-day safety update (as with all but one tried by the evaluator), identified an unrelated table; therefore it is not possible to evaluate this adverse event.
3. This remains an important identified risk as it would appear both investigators consider this related. This should be listed as such in the RMP.

Overall, the frequencies of any TEAEs (22.3%) and any treatment-related AEs (10.7%) within the MedDRA SOC Eye disorders were reported more frequently in the palbociclib plus fulvestrant arm of Study 1023 as of 31 July 2015 were (90-day safety update). There was a substantial increase in these events reported between the previous cut-off date of 5 December 2014, of 5.2% more TEAEs and 3.2% more treatment-related events. No CTCAE grading is provided for these and there were no narratives to determine the severity or action required with respect to the study drugs.

These TEAEs and treatment-related TEAEs in the palbociclib arm include a more frequent occurrence of conditions which threaten visual acuity as well as events describing visual impairment:

- Vision blurred, visual impairment, visual acuity reduced, myopia;
- retinal degeneration, macular fibrosis, cataract, panophthalmitis;

Comments:

1. No narratives or supporting data was provided for evaluation of how relation to treatment was determined from the baseline TEAEs.
2. Nonetheless, the clinical evaluator notes the much higher rate of treatment-related events which will cause visual impairment, with consequent impairment of function and quality of life. This warrants a Precaution given:
    a. the frequency is high
    b. they have been designated as treatment-related
    c. some of the events described above are not reversible
    d. many are likely to cause significant local discomfort without threatening vision.

3. PI does not currently have up to date data on these events and the frequency and the reporting of 'vision blurred', 'lacrimation increased', 'dry eyes' does not accurately or adequately reflect the incidence nor the severity of the events observed in this latest safety update.
4. The CMI should clear identify these risks.
5. The RMP should include terms that capture visual impairment in addition to the specific adverse event of cataracts for targeted pharmacovigilance.
6. The sponsor is requested to characterise further the nature of the conditions leading to reports of visual impairment and provide a discussion about the increased rate of events affecting vision/visual acuity which would compromise vision in those receiving palbociclib, as seen in Study 1003 in the palbociclib and fulvestrant arm. Were there any preclinical data which identified visual impairment besides cataract development? The CIOMS and narrative for the patient with 'blindness' attributed to cerebral metastases are requested. This would require a significant metastasis or haemorrhage into such a lesion in the occipital region for such blindness to occur and be attributable to metastases.

Study 1008

No data, analyses and discussion as an event of special interest is provided from Study 1008, and the reported rates in the 'Adverse Drug Reaction' table cannot be evaluated due to there being no data or analyses provided.

Study 1003

In Phase II (Ph2P1+Ph2P2), a higher percentage of patients in the palbociclib plus letrozole arm (17 patients, 20.5% [treatment-related 10.8%]) had at least 1 TEAE in the SOC of Eye disorders compared with the letrozole alone arm (4 patients, 5.2% [treatment-related 1.3%]). Treatment emergent events of vision blurred, cataract (1).

Significant treatment-emergent adverse events, by MedDRA preferred term, which threaten vision in the palbociclib and letrozole arm and letrozole alone arm were:

- Cataract 1.2% versus 0
- Vision blurred 2.4% versus 0
- Visual acuity reduced 2.4% versus 0
- Visual impairment 3.6% versus 3.0%
- Blindness 1.2% versus 0% (this was due to cerebral metastases)

The narrative for the 83 year old who developed a cataract indicates this was considered age-related. The episode of blindness occurred with brain metastases so is central blindness rather than an eye disorder per se.

A further case of bilateral cataracts was reported in the Phase I population as of the 2 January 2015 cut-off (SCS). Events of lacrimation, visual impairment and dry eye were reported to be treatment-related in the SCS.

Study 1010

Phase I

No AEs of Cataracts was reported in the Phase I portion of Study 1010. In the Ph1P2 portion of the study, 1 patient (16.7%) experienced Grade 1 Conjunctival haemorrhage and the other patient experienced Grade 1 Vision blurred within the MedDRA SOC Eye disorders. These TEAE were considered to be unrelated to study treatment.

No information on the rates of visual disorders or cataracts could be located in the 90-day safety

update for the Phase II part of the study.

Study 1001

No information was provided about cataract formation or visual adverse events for Study 1001 and no events were located in a search of the CSR by the evaluator.

Comments:

1. Cataracts are diagnosed commonly in the older age group, who will form a significant proportion of patients in the proposed target population. An acceleration of the rate of cataract formation by palbociclib cannot be excluded and this needs to be a prespecified adverse event of interest in ongoing randomised clinical trial as routine pharmacovigilance will not be able to differentiate between background rates and a treatment effect.
2. Although there was a link postulated from the preclinical models between cataract formation and hyperglycaemia, this should not be presumed to be the mechanism and the absence of hyperglycaemia should not discount the risk of cataract formation.
3. The increased frequency of adverse events affecting vision by terms that are not actual diagnoses means the potential for cataracts to be the cause is not excluded. In any case, the excess of these events supports the need for a Precaution as above.

8.4.5.8 Hyperglycaemia-related events

As of 31 July 2015, a total of 5 patients (1.4%) in the palbociclib plus fulvestrant arm and 4 patients (2.3%) in the placebo plus fulvestrant arm experienced hyperglycaemia.

In each treatment arm, all but 1 of the TEAEs of Hyperglycaemia was of Grade 1 severity. The remaining patients (one in each treatment arm) experienced Grade 3 hyperglycaemia. In addition, diabetes mellitus (Grade 1) was experienced by 1 patient (0.3%) in the palbociclib plus fulvestrant arm and glycosylated haemoglobin increased (Grade 1) was experienced by 1 patient (0.6%) in the placebo plus fulvestrant arm. As stated earlier in this section, none of the 3 patients who experienced cataracts in the palbociclib plus fulvestrant arm of the study experienced any hyperglycemia-related events as of 31 July 2015.

No data were submitted on this for evaluation from Study 1008.

Comment: These rates appear to be very low, but given this was a significant signal in the preclinical studies, and it is also readily monitored as part of routine investigations, it is appropriate that it remains in the RMP as an important potential risk for palbociclib.

Study 1003

Phase I/II Study

One patient in the Phase I part had a TEAE of hyperglycaemia (Grade 2) and one patient in the palbociclib and letrozole arm had a TEAE of diabetes mellitus (Grade 2). Neither was considered treatment-related but it is not possible to evaluate causality for either as no details are provided.

Details of eye disorders were provided (as above) for consideration of hyperglycaemia-related events. Cataracts occurred in both parts of the study (1 patient in each Phase) but neither had hyperglycaemia-related events.

Comment: The sponsor is requested to provide details of clinical laboratory findings for glucose for the 2 patients with cataracts in this study any elevated HbA1c results as this is more likely to capture events of hyperglycaemia than isolated terms used to identify TEAEs. (Clinical Question)

No information from Study 1010 is provided but a review of the clinical chemistry tables did not reveal any events. A single case of hyperglycaemia is recorded in the Study 1001 CSR.

8.4.5.9 Interstitial lung disease and pneumonitis

Combination of palbociclib and fulvestrant Study 1023

A summary of TEAEs including those coding to PTs within the MedDRA SOC Respiratory, thoracic and mediastinal disorders and a TEAE of pneumonia within the SOC Infections and infestations experienced by at least 2 patients each in either treatment arm of Study 1023 as of 31 July 2015 is provided in the 90-day safety update. No TEAEs of interstitial lung disease or pneumonitis were reported in this study as of that data cutoff date.

A review of the data tables in this study indicate that one patient in the palbociclib and fulvestrant arm had a present medical history of interstitial lung disease and one in the comparator arm had pneumonitis - both these were listed as 'present' suggesting the patients were enrolled with this condition still active but these were not specific exclusion criteria. No new cases were reported using these specific terms.

Respiratory events were experienced more frequently by patients in the palbociclib plus fulvestrant arm (TEAEs: 44.9%; treatment-related AEs: 15.4%) than in the placebo plus fulvestrant arm (TEAEs: 30.2%; treatment-related AEs: 8.1%).

Study 1008

No specific discussion or analyses were provided in the top-line summary document for Study 1008. Review of the TEAE tables reveals a single case of Grade 3 pneumonitis in the palbociclib and letrozole arm, a single Grade 2 event of interstitial lung disease (reported as treatment-related but this remains blinded, and an SAE) and 2 deaths from 'respiratory failure' and 'pulmonary fibrosis'; there is a single, Grade 2 event in the comparator arm. No CIOMS or narratives were available unblinded to assess these events further.

Study 1003

No updated information was included in the 90-day safety update for Study 1003 or 1010. As of 2 January 2015, no cases of pneumonitis, interstitial lung disease, hypoxia or dyspnoea were reported using MedDRA preferred terms in the palbociclib and letrozole arm and a single case of Grade 2 pneumonitis was recorded in Study 1003 in a patient receiving letrozole alone.

Study 1010

No events of interstitial lung disease or pneumonitis were reported in the Phase I part and no details are provided for the Phase II part of this study. In the Ph1P2 portion of Study 1010, 2 patients (33.3%) experienced respiratory disorders, Grade 1 TEAEs of Dysphonia and Upper-airway cough syndrome, of which Dysphonia was considered to be related to study treatment.

Study 1001

A single case of 'allergic alveolitis' resulted in permanent discontinuation in a patient receiving 100 mg on a 21/28 days dosing schedule. No narrative or CIOMS could be located for this case.

Comment: The terms 'interstitial lung disease' and 'pneumonitis' are specific diagnostic terms and it is not possible to exclude that some of those with 'dyspnoea', 'cough', 'dyspnoea exertional', 'hypoxia', which are all reported with far higher frequencies in the palbociclib and fulvestrant arm do not have either of these 2 diagnoses. It is appropriately listed as an identified important risk in the RMP, and the Study 1008 CSR when submitted should provide narratives to permit evaluation and assessment of causality of the events in that trial.

The current PI does not adequately capture the increased rate of adverse events of cough, dyspnea and the presentation in the PI of only what the sponsor has determined to be adverse

drug reactions (which appear to be a subset of treatment-related AEs) has not been updated and therefore cannot be evaluated for the latest dataset. As such, it currently does not accurately or adequately represent the event rates in this trial.

8.4.5.10 Venous thromboembolic disorders

The evaluator has broadened the evaluation to include arterial thromboembolic events.

Combination of palbociclib and fulvestrant Study 1023 (as of 31 July 2015)

In table 14.3.1.8.6.1 from Study 1023, 7 events of pulmonary embolism were recorded: 1 Grade 1, 4 Grade 3, 1 Grade 4 and a death. 2 DVTs as well as a single case of subclavian vein thrombosis and vena cava thrombosis were reported in the palbociclib and fulvestrant arm.

As of 31 July 2015, a single case of a pelvic DVT was reported in the placebo and fulvestrant arm.

Combination of letrozole and palbociclib Study 1008 top-line summary (no CSR)

No specific discussion or analyses were provided in the top-line summary document for Study 1008, using terms likely to capture all events of thrombosis and embolism. For those events presented of pulmonary embolisms, treatment allocation was not unmasked and there were no accompanying unblinded narratives.

Comment: The full CSR is required for detailed evaluation and it is not possible to evaluate the data provided, nor provide comments on the serious, potentially life-threatening events.

8.4.5.11 Other studies

Combination of letrozole and palbociclib Study 1003 (Phase I/II)

As of 31 July 2015, in Study 1003, 2/12 patients in the Phase I part of the study and 5/83 patients in the Phase II part receiving palbociclib and letrozole had an adverse event recorded of pulmonary embolism; 2/83 had a DVT in the Phase II part. Six of these events were recorded as Grade 4. There was also a case in the Phase II part of ischaemic colitis (Grade 3), which was considered treatment-related and treatment was discontinued in a woman receiving palbociclib and letrozole (see SAEs Study 1003). No cases of DVT or PE were recorded in the letrozole alone arm.

In the investigator-initiated research using palbociclib monotherapy, there was a death on-study from ischaemic colitis which the investigator considered related to treatment but the sponsor does not. The narrative could not be located for evaluation and the sponsor is requested to provide a copy in their response (Clinical Questions).[8]

Study 1010

No venous thromboembolic events have been reported in this study in the SCS or 90-day safety update.

In Study 1001, a patient receiving palbociclib experienced a Grade 4 pulmonary embolism.

Study 1004 conducted in patients with myeloma; there was a report of a deep vein thrombosis.

Comments:

1. a Precaution with the heading' Thrombosis and thromboembolism' should be included in the PI, citing that there have been DVTs, pulmonary embolisms and arterial thromboembolic events including some that have been fatal, given the:
    a. 10 arterial or venous thromboembolic or thrombotic events occurring in those

[8] Sponsor correction: There was no case of fatal ischaemic colitis.

receiving palbociclib and letrozole compared with none in the letrozole alone arm in the small study population (95 patients received palbociclib and letrozole) in Study 1003;

b. 9 events (including 1 death) in Study 1023 in the palbociclib and fulvestrant compared with one Grade 2 event in the placebo and fulvestrant arm;

c. the Grade 4 pulmonary embolism in a patient in Study 1001;

2. The evaluator could not locate the narrative for the fatal event of ischaemic colitis in the investigator-initiated study due to the cross-referencing hyperlink being incorrect; given there have been 2 cases of this otherwise uncommon arterial thrombosis, these arterial events merit inclusion in the PI under the Precautions section 'Thrombosis and thromboembolism'[8].

3. In Study 1023, the pulmonary embolisms and two cases were listed as treatment-emergent SAEs. It is noted that in Study 1003, the events of pulmonary embolism are not recorded in the CIOMS or narrative as being considered related to the study drug. However, investigators as individuals and collectively, would not have much experience of palbociclib's adverse event profile and the growing body of evidence indicates that these events are more common in patients receiving palbociclib.

8.5 Evaluation of issues with possible regulatory impact

8.5.1 Liver function and liver toxicity

8.5.1.1 Integrated safety analyses

None provided.

8.5.1.2 Main/pivotal studies that assessed safety as the sole primary outcome

None.

8.5.1.3 Pivotal and/or main efficacy studies

Combination of palbociclib and fulvestrant Study 1023

The 90-day safety update provided a table of clinical chemistry test abnormalities for Study 1023 and the following information:

Rates of ALT, AST and bilirubin, the Grade 1-4 increases in the palbociclib and fulvestrant arm were similar.

A single case of 'liver failure' and 'disease progression' was reported as an SAE, and there was also a case of 'Drug-induced liver injury' reported that was not classified as meeting the criteria for an SAE. [9]These cases are discussed in detail in the SAE section of this report and the sponsor has been requested to provide additional comments and also make a change to the RMP as a result of the case of reported drug-induced liver injury.

Comment: Based on these data, no clear pattern emerges across the Grade 2, 3, and 4 events for each parameter to suggest liver toxicities are occurring at a substantially increased rate with palbociclib.

[9] Clarification: There was a case report of hepatic failure assessed by the sponsor to be unrelated to blinded therapy and fulvestrant and to any clinical trial procedure. For this case the investigator considered drug induced hepatitis could not be excluded and therefore two separate AEs were collected for this event. For further discussion see Response to Safety Question 18.

No information is provided about the case of increased bilirubin for the patient – details of this are requested (Clinical Question).

Combination of palbociclib and letrozole – Study 1008

No evaluable data provided – the full CSR is required.

8.5.1.4 Other studies

Combination of palbociclib and letrozole Study 1003

No patients in the Phase I/II study had liver test abnormalities meeting Hy's law for drug-induced liver injury. A review of the shifts in clinical chemistry findings in the Phase II part did not identify an imbalance between the palbociclib and letrozole compared with letrozole alone arms in liver enzymes or bilirubin levels.

Study 1010

The sponsor reported a single patient who had elevated liver enzymes (≥ 3xULN) for AST and ALT and at a different time, bilirubin ≥ 2xULN but on the background of progressing liver metastases, states this does not meet criteria for Hy's Law. Grade 3 increases in AST and ALT are included in table 98 (SCS) but it is not clear if these are from the aforementioned patient.

Comment: A review of the liver function tests does not reveal any consistent pattern or abnormalities to suggest a treatment-related effect.

8.5.2 Renal function and renal toxicity

8.5.2.1 Integrated safety analyses

None provided.

8.5.2.2 Main/pivotal studies that assessed safety as the sole primary outcome

None.

8.5.2.3 Pivotal and/or main efficacy studies

Combination of palbociclib and fulvestrant Study 1023

The 90-day safety update indicates that Grade 1-3 (no Grade 4) changes in creatinine were the most common abnormal chemistry value recorded, and experienced by 11.7% more patients in the palbociclib and fulvestrant arm compared with the comparator arm (94.2% versus 82.5%). Across all grades, there were more events in the palbociclib and fulvestrant arm including 2 patients with Grade 3 creatinine change compared with none in the comparator arm.

When examined by SOC MedDRA preferred terms, renal and urinary disorders were more common in the palbociclib and fulvestrant arm (5.5% versus 3.5%). None of these events exceeded Grade 2 in severity, and one patient in the experimental arm (with Grade 1 tubulointerstitial nephritis) experienced a temporary discontinuation.

Combination of palbociclib and letrozole – Study 1008

An AE leading to discontinuation was acute kidney injury but no detailed information on this or other clinical chemistry abnormalities is provided to evaluate – the full CSR is required.

8.5.2.4 Other studies-Other efficacy studies

Combination of palbociclib and letrozole Study 1003

In the palbociclib plus letrozole arm, changes in serum creatinine were experienced by 37.8%, (32.9% Grade 1, 3.7% Grade 2 and 1.2% Grade 4) compared with 26% in the letrozole alone arm (19.5% Grade 1, 6.5% Grade 2, no Grade 3 or 4 events). Hypermagnesaemia was more common and more severe in the palbociclib and letrozole arm: 19.8% (including 7.4% Grade 3)

compared with 14.3% (all Grade 1).

TEAEs of renal and urinary disorders in the Phase I and Phase II part of the study occurred in 12 % of patients, and included nephrolithiasis (Grade 3), nephropathy (Grade 1) and renal disorder (Grade 3) – the 2 Grade 3 events were reported as SAEs (Study 1003 CSR) as well as an event of urethral obstruction and all required temporary discontinuations. TEAEs in the letrozole alone arm occurred in 9.1% including nephrolithiasis, renal impairment.

Two SAEs were reported: 1 patient with 'acute renal failure' and one with Grade 3 'renal disorder'.

A draft CIOMS for an 84 year old with 'abdominal pain' and 'renal disorder' was found but had not been referenced by the sponsor. Notably, the patient had an elevated creatinine, hypotension and 'dizziness, fatigue, freezing' and was hospitalized.[10]

Comments:

1. The clinical evaluator notes the haemoglobin was reported as 6 mmol/l (normal 7.3 -9.9) which is equivalent to 96 g/l. No conclusions can be drawn regarding this event which does not provide a diagnosis for the presenting complaints.
2. The remaining CIOMS for the SAEs and Grade 3 events could not be located and should be provided by the sponsor (Clinical Questions).

On the limited information provided, there is an increase in serum creatinine in those receiving palbociclib, and hypermagnesaemia which could together suggest an element of treatment-related renal dysfunction. While these might be affected by concomitant medications (for example, bisphosphonates) the increase in creatinine is observed across two separate randomised trials (1023, 1003) suggesting a treatment effect of palbociclib on renal function which needs further investigation. The CSR for Study 1008 may address this further. Serum magnesium should be monitored periodically (PI Comments).

Study 1010

Grade 1 and 2 events of elevated creatinine, and a single Grade 1 event of hypermagnesaemia were in the source data tables for Phase I Parts 1 and 2. No Grade 3 or 4 events were recorded for either parameter.

8.5.3 Other clinical chemistry

8.5.3.1 Integrated safety analyses

None provided.

8.5.3.2 Main/pivotal studies that assessed safety as the sole primary outcome

None.

8.5.3.3 Pivotal and/or main efficacy studies

Combination of palbociclib and fulvestrant Study 1023

A review of the laboratory clinical chemistry did not reveal any significant issues with other clinical chemistry parameters.

[10] Sponsor clarification: The investigator considered the event was possibly related to clinical trial procedure: bone scan. Both the investigator and the sponsor considered there was not a reasonable possibility that the event of renal disorder was related to study medication or concomitant medication (resolved and did not recur following re-introduction of therapy).

Combination of palbociclib and letrozole Study 1008

No data, analyses or discussion provided for evaluation.

8.5.3.4 Other efficacy studies

Combination of palbociclib and letrozole Study 1003

A review of the laboratory clinical chemistry did not reveal any significant issues with other clinical chemistry parameters, other than those discussed above.

In the palbociclib plus letrozole arm, clinical chemistry shifts from Grade ≤2 at baseline to Grade ≥ 3postbaseline in hypermagnesaemia were observed for 6/81 patients (7.4%); in hypophosphatemia for 3/81 patients (3.7%); in AST and hyperkalemia for 2/82 patients (2.4%) each; and in ALT, hypocalcemia, hypokalemia, and hyponatremia for 1/82 patients (1.2%) each. In the letrozole alone arm, clinical chemistry shifts from Grade ≤2 at baseline to Grade ≥ 3 postbaseline in AP were observed for 4/77 patients (5.2%); in hypermagnesaemia, hyponatremia, and hypophosphatemia for 2/77 patients (2.6%) each; and in ALT, AST, and hypocalcemia for 1/77 patients (1.3%) each.

Study 1010

As of 31 March 2015, no prominent changes in clinical chemistry were evident in the Phase I Part 2 portion of the study, with a single event of Grade 3 hypophosphataemia. A review of the study tables for the Phase I Part 1 of this study did not reveal any new safety signals.

8.5.4 Haematology and haematological toxicity

The events of neutropenia and thrombocytopenia are discussed in detail above in the section on Adverse events of special interest.

8.5.4.1 Integrated safety analyses

None provided

8.5.4.2 Main/pivotal studies that assessed safety as the sole primary outcome

None.

8.5.4.3 Pivotal and/or main efficacy studies

Combination of palbociclib and fulvestrant – Study 1023

It is unclear whether the reporting is for the MedDRA preferred term of anaemia or for the clusters of preferred terms.

As of July 31 2015, anaemia occurred very commonly and was more severe in the palbociclib and fulvestrant arm: (78.3% versus 40% in the comparator arm), with 24.3% experiencing Grade 2 (Hb 80-100 g/l) and 3.2%, Grade 3 (Hb<80 g/l). No data are provided for Grade 4 events defined as 'Life-threatening consequences; urgent intervention indicated' (Clinical Question). Of the 40% experiencing anaemia in the palbociclib and fulvestrant arm, 7.1% were Grade 2, and 1.8%, Grade 3 events. There was an increase in reporting rates of 2.3% (no grades provided) between the 5 December 2014 and 31 July 2015 cut-off dates.

No information was provided about the number of transfusions, median time and range to development of Grade 3 anaemia to provide information about the speed of onset.

Comments:

1. 18.6% more patients had Grade 2 or 3 events of anaemia in the palbociclib and fulvestrant arm. Those with Grade 3 anaemia would be symptomatic and require transfusion, and many of those with Grade 2 would receive a transfusion especially where the haemoglobin was observed to be declining over time, or where there were comorbidities likely to be

exacerbated by anaemia for example, ischaemic heart disease.

2. The CTCAE grading system does not provide a numeric value for Grade 4 events, rather these are life threatening events requiring immediate action. The sponsor is requested to provide the number of, and clinical details for, any patients for whom transfusions were required in these circumstances (Clinical Question).[11]
3. Laboratory measurements provided more accurate information than the Cluster of MedDRA preferred terms for anaemia (any event having a preferred term that equals to Anaemia or Haematocrit decreased or Haemoglobin decreased) which primarily requires clinicians to nominate the event, or for it to require action or cause symptoms. The sponsor is requested to provide laboratory-based data for anaemia as the basis for inclusion in the PI for haematological and clinical abnormalities rather than using the cluster of MedDRA preferred terms.
4. Patients are being monitored closely due to the AE of significant neutropenia and any decline in haemoglobin levels will be detected also. The rates are considered significant but manageable as an adverse event.

Combination of letrozole and palbociclib Study 1008

Clusters of preferred terms for anaemia is any event having a preferred term that equals to Anaemia or Haematocrit decreased or Haemoglobin decreased.

Table 14.3.1.1.3 of TEAEs includes anaemia listed as occurring in 23.2%, including a Grade 4 frequency of 0.2%, Grade 3, 5.2%.

Table 14.3.1.8.6.1 lists the frequency of TEAEs of anaemia as 24.1%.

Comments: No specific data, analyses or discussion in the top-line summary were provided for evaluation – the full CSR is required. The reason for the different rates would appear to be the use of clustering of terms rather than laboratory abnormalities.

8.5.4.4 Other efficacy studies

Combination of letrozole and palbociclib Study 1003

Updated data were provided for anaemia rates in this study in the SCS (cut-off date 2 January 2015). Overall, anaemia (by laboratory values) was twice as common in the palbociclib and letrozole arm compared with the letrozole alone arm (84.1% versus 40.3%) and more severe: 4.9% were Grade 3 events versus 2.6% in the comparator arm, and there was a Grade 4 event in the experimental (Grade 4; CTCAE version 3 provides a Grade 4 classification for grading of laboratory values). All of these would be expected to need transfusion, as well as a proportion of those with Grade 2 events (30.5% versus 13% in the comparator arm).

Notably, lymphopenia was more prominent and severe in the palbociclib and letrozole arm (80.5% versus 35.1%) with Grade 3/4 events 18.3% versus 2.6%, with no Grade 4 events in the letrozole alone arm.

[11]For discussion see Response to Clinical Safety Question 17.

Table 32: Study A5481003 Summary of abnormal haematological laboratory findings by maximum severity grade, Phase II population as of 2 January 2015

Hematologic Test Treatment Arm	N	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Hemoglobin						
Palbociclib+letrozole	82	39 (47.6)	25 (30.5)	4 (4.9)	1 (1.2)	69 (84.1)
Letrozole alone	77	19 (24.7)	10 (13.0)	2 (2.6)	0 (0)	31 (40.3)
Lymphocytes (absolute)						
Palbociclib+letrozole	82	14 (17.1)	37 (45.1)	14 (17.1)	1 (1.2)	66 (80.5)
Letrozole alone	77	15 (19.5)	10 (13.0)	2 (2.6)	0 (0)	27 (35.1)
Neutrophils (absolute)						
Palbociclib+letrozole	82	6 (7.3)	19 (23.2)	47 (57.3)	5 (6.1)	77 (93.9)
Letrozole alone	77	6 (7.8)	5 (6.5)	2 (2.6)	0 (0)	13 (16.9)
Platelets						
Palbociclib+letrozole	82	43 (52.4)	7 (8.5)	3 (3.7)	0 (0)	53 (64.6)
Letrozole alone	77	11 (14.3)	0 (0)	1 (1.3)	0 (0)	12 (15.6)
White blood cells						
Palbociclib+letrozole	82	3 (3.7)	37 (45.1)	38 (46.3)	0 (0)	78 (95.1)
Letrozole alone	77	14 (18.2)	6 (7.8)	0 (0)	0 (0)	20 (26.0)

Data source: A5481003 SCS Table 14.3.4.1.5.1.b.
N=total number of patients with data available for evaluation; n=number of patients meeting prespecified criteria; SCS=Summary of Clinical Safety.
Note: Each patient is counted once in each row based on the highest severity grade reported for the event.

Study 1010

As of 31 March 2015 (SCS), the Phase I monotherapy with palbociclib 100 mg or 125 mg daily was associated with abnormal laboratory findings in all haematological parameters, with a Grade 4 event of neutropenia at each dose level plus a Grade 4 event of thrombocytopenia.

In the Phase I part 2, abnormal haematological laboratory findings observed for Japanese patients with advanced breast cancer who received palbociclib plus letrozole included neutropenia (83.3% Grade 3 or 4), anaemia (66.7% Grade 2) and 1 event of Grade 3 lymphopenia. Shifts in absolute neutrophil counts from Grade ≤2 at baseline to Grade ≥ 3 postbaseline occurred for 5 patients (83.3%), while shifts in white blood cell counts from Grade ≤2 at baseline to Grade ≥ 3 postbaseline were observed for 3 patients (50.0%).

Comments:

1. The broad bone marrow suppressive effects of palbociclib are clear from Studies 1010, 1003 and 1023, and preliminary data from Study 1008. Given the frequency of anaemia requiring supportive intervention including in an emergency setting (Study 1003), this should be presented in a Precaution with the overarching title of Haematological disorders, with Neutropenia, Thrombocytopenia and Anaemia as subheadings, populated with information from the clinical laboratory abnormalities not the TEAEs which underreport the observed effects. Overall, anaemia is manageable but requires significant supportive measures for at least of 6.1% of those on palbociclib. Appropriate information should be included in the PI and CMI (PI and CMI comments).
2. The rate and severity of the treatment-related lymphopenia raises concerns about risks with live vaccines, opportunistic infections, tuberculosis, viral reactivation, PML etc and a clinical question has been included to address this (Clinical Question).

8.5.5 Other laboratory tests

No other laboratory tests were reported.

8.5.6 Electrocardiograph findings and cardiovascular safety

8.5.6.1 Integrated safety analyses

None provided.

8.5.6.2 Main/pivotal studies that assessed safety as the sole primary outcome

None.

8.5.6.3 Pivotal and/or main efficacy studies

Combination of palbociclib and fulvestrant Study 1023

ECG abnormalities (QT prolongation) and cardiovascular AEs were discussed under Adverse events of special interest.

Combination of palbociclib and letrozole Study 1008

An ECG substudy in 60 patients was undertaken but no data were presented in the top-line summary or tables for evaluation and comment – the full CSR is required.

8.5.7 Vital signs and clinical examination findings

8.5.7.1 Integrated safety analyses

None provided for the studies submitted as pivotal.

8.5.7.2 Pivotal studies that assessed safety as the sole primary outcome

None.

8.5.7.3 Pivotal and/or main efficacy studies

Combination of palbociclib and fulvestrant Study 1023

TEAEs of hypertension occurred in 2.9% of patients on palbociclib and fulvestrant compared with 1.7% in the placebo and fulvestrant arm. 4/10 patients in the experimental arm developed Grade 3 hypertension, and the remainder were Grade 2, while 2/3 patients developed Grade 2 and, 1 Grade 3 in the placebo and fulvestrant arm.

Pyrexia occurred more commonly in the palbociclib and fulvestrant arm than in the placebo and fulvestrant arm (8.7% versus 4.1%).

Comment: Pyrexia is a very non-specific term and the increase in the experimental arm is not marked, and not of concern as an AE in its own right. It is considered consistent with the increase in infections, and neutropenia observed with palbociclib treatment.

Combination of palbociclib and letrozole Study 1008

No data are provided.

8.5.7.4 Other efficacy studies

Combination of palbociclib and letrozole Study 1003

No patients had SAEs reporting events consistent with clinically relevant changes in blood pressure, pulse rate, respiratory rate, or body temperature during the Phase I portion of the study.

Six events (7.2%) of hypertension, all Grade 2, were reported in the Phase II population compared with 6.5% in the letrozole alone alarm (Grade 1, 2 and 3 events reported).

Study 1010

A single case of Grade 2 hypertension was reported in the Phase I part of this study in a patient

taking palbociclib and letrozole.

8.5.8 Immunogenicity and immunological events

8.5.8.1 Integrated safety analyses

None provided.

8.5.8.2 Main/pivotal studies that assessed safety as the sole primary outcome

None.

8.5.8.3 Pivotal and/or main efficacy studies

This is not considered relevant to this application and there are no data provided which is considered acceptable.

8.5.8.4 Other studies

N/A

8.5.9 Serious skin reactions

8.5.9.1 Integrated safety analyses

None provided.

8.5.9.2 Pivotal studies that assessed safety as the sole primary outcome

None.

8.5.9.3 Pivotal and/or main efficacy studies

Combination of palbociclib and fulvestrant Study 1023

Rash was a more common TEAE in the palbociclib and fulvestrant arm (11% versus 5.2%) as of July 31 2015; of these, 7.8% in the palbociclib and fulvestrant arm and 2.9% in the placebo and fulvestrant arm were considered treatment-related. The majority were Grade 1 events, but 0.9% and 0.3% experienced a Grade 2 or a 3 event, respectively while all events in the comparator arm were Grade 1. Two events were reported as SAEs: rash and skin disorder.

The CIOMS for the skin disorder identified the skin disorder as due to injury and the CIOMS for the Grade 3 event of rash details a rapid onset of a maculopapular rash within 7 days of starting palbociclib and fulvestrant and was hospitalised with due to the rash, associated with stomatitis, fever, dyspnoea, nausea and vomiting and Grade 3 ECOG performance status. The dose of palbociclib was reduced to 100 mg and the rash did not recur on rechallenge.

Combination of palbociclib and letrozole Study 1008

Limited information is available but there were adverse events of rash leading to discontinuation but evaluation and comment by the evaluator are not possible due to the limited information available.

8.5.9.4 Other studies

Study 1003

Rash occurred more commonly in those on palbociclib and letrozole compared with letrozole alone in the Phase II part of the study (6% versus 1.2%). Most of these were Grade 1 or 2 events with no Grade 3 events.

Study 1010

Grade 1 rash was reported at a frequency of 16.7% in the Phase I Part 1 of the study, with no

cases in the Part 2 (no details provided for the Phase II population)

Study 1001

Rashes were common (9.5%) and considered related to treatment, none with a severity exceeding Grade 1 or 2 were observed in this study.

Comment: On the information provided to date, rash appears to be a common but generally mild adverse event.

8.5.10 Other safety parameters

None identified.

8.6 Other safety issues

8.6.1 Safety in special populations

8.6.1.1 Age

Combination of palbociclib and fulvestrant Study 1023

75.2% of patients in the palbociclib and fulvestrant arm and 75.3% in the placebo and fulvestrant arm were younger than 65 years of age at baseline. The rates of TEAEs, SAEs and discontinuations were similar.

Comments:

1. Given the proposed usage is in postmenopausal women and the frequency in older women, the sponsor is requested to provide a breakdown for the events reported in the 90-day safety update for those > 75 years of age and include this in the PI (PI Comments and Clinical Question).
2. Subgroup analyses of TEAEs by age were hampered by relatively small numbers and a lack of statistical power to determine a significant difference. It is thus not possible to provide information for the PI for these events, for example alopecia occurred more commonly in older women but there were only 22 in this arm.

8.6.1.2 Race

Combination of palbociclib and fulvestrant Study 1023

Most patients participating in either treatment arm of this study were White (72.6% in the palbociclib plus fulvestrant arm and 76.4% in the placebo plus fulvestrant arm [intent-to-treat population]). The second largest race group in this study was Asian (21.3% in the palbociclib plus fulvestrant arm and 17.8% in the placebo plus fulvestrant arm [intent-to-treat population]).

While TEAE frequencies were similar between the 2 race groups (98.4% for White patients and 100% for Asian patients, Grade 3/4 TEAE frequency was much higher in Asian patients (94.5%) than in White patients (71.3%), Similarly, there was a higher overall Grade 3/4 treatment-related AE frequency in Asian patients (94.5%) than in White patients (63.7%) along with a higher overall treatment-related SAE frequency in Asian patients (9.6%) than in White patients (4.4%) were observed in the palbociclib plus fulvestrant arm. These differences were not observed in the placebo plus fulvestrant arm.

No reliable observations could be made regarding the safety profile of palbociclib plus fulvestrant treatment in patients of Black race due to small numbers: 12 in the palbociclib plus fulvestrant arm and 8 in the placebo plus fulvestrant arm.

This information was corroborated by the increase in severe TEAEs (Grade 3/4), SAEs and treatment discontinuations in those from the Asia Pacific region compared with North America and Europe.

Comment:

1. The assessment of individual AEs to inform the PI is limited by small numbers but given the overall consistently higher risk profile observed in Asian patients particularly for severe events, a heading under Special Populations is warranted. Based on current information, there appears to be a predisposition to more severe adverse events which will require closer monitoring and potentially more dose adjustments (PI and CMI Comments).
2. Submission of the study reports for the following studies once completed may characterise this risk further: Study 1010 conducted in Japanese patients and Study 1027 in Asian (Chinese) patients may provide further information.

8.7 Post marketing experience

Study A5481034 was an expanded access study of palbociclib in combination with letrozole as treatment of postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer for whom letrozole therapy is deemed appropriate.

238 women received at least one dose of palbociclib and letrozole as of 31 July 2015. Palbociclib 125 mg QD was given according to Schedule 3/1 in combination with letrozole 2.5 mg QD continuously in this study. Study objectives were to collect additional safety and efficacy data for the combination of palbociclib and letrozole in postmenopausal women with HR-positive, HER2-negative advanced breast cancer. 40 patients (16.7%) completed the study, 197 patients (82.1%) were permanently discontinued from treatment, and 1 patient (0.4%) was ongoing as of that data cutoff date.

Comment: Efficacy data were not presented, and the data for safety was descriptive.

139 patients (58.0%) were younger than 65 years of age, while 99 patients (41.6%) were 65 years of age or older; the mean age was 61.6 years, ranging from 29 years to 89 years. The majority of patients (85.3%) were White. Approximately half of patients (50.8%) had ECOG PS 0 at baseline, and 8.8% had ECOG PS 2.

8 of the 238 patients (3.4%) died on study as of 31 July 2015. Disease progression was the most frequently reported SAE (n=5) in these death cases. A clinical outcome of pancytopenia experienced by Subject [information redacted] was reported in the safety database as not resolved rather than fatal. None of the SAEs associated with deaths in Study 1034 was considered by the sponsor to be related to treatment.

Treatment emergent SAEs include febrile neutropenia, acute kidney injury, pancytopenia and hepatic enzyme abnormal and DVT. One case each of peripheral motor neuropathy and asthenia were also included. Of these, the febrile neutropenia and pancytopenia were considered treatment-related.

Comment: The evaluator is in agreement with the attribution of most of these events to disease progression after reviewing the CIOMS for the SAEs. Several patients appear to have died within a short period of commencing treatment, suggesting their disease was at a much more advanced stage than was observed in those enrolled in the clinical trials. The non-randomised nature of the data and the lack of baseline information make assessment of causality difficult. One case of pancytopenia in an 89 year old woman appeared to be treatment related and resolved and was not reported as recurring after stopping temporarily and dose reduction. No new adverse events were identified.

8.7.1 Periodic Safety Update Report 03 February 2015-02 February 2016

8.7.1.1 Cumulative Subject Exposure in Clinical Trials

Cumulatively, it is estimated that 2,461 subjects have participated in the palbociclib clinical development programme as of the DLP: 410 subjects were exposed to palbociclib alone; 661 subjects received palbociclib in combination with other drugs; 1,313 subjects received blinded-therapy; and 77 subjects received comparator drugs (that is, letrozole).

8.7.1.2 Cumulative and Interval Patient Exposure from Marketing Experience

During this reporting interval, it is estimated that 22,532 patients were exposed to palbociclib worldwide since the product was first approved on 03 February 2015: 11,581 patients aged 17-65; 10,951 aged >65 years and 969 aged >75. The doses reported were 3470 patients receiving 100 mg and 18093 receiving 125 mg.

3,107 cases with 7,303 adverse events from post-marketing data sources, 65.0% of which were non-serious were reported. Of these 3,107 cases, 2,912 (93.7%) were reported from spontaneous sources and 193 (6.2%) were reported as compassionate use; the remaining 2 cases were reported from either the literature or a non-interventional study.

The most frequently reported serious and non-serious adverse events (≥ 40 events) from the marketing program cases included Product use issue (319), Fatigue (156), White blood cell count decreased (143), Disease progression (129), Nausea (85), Diarrhoea (54), Neutropenia (48), Breast cancer metastatic (46), and Death (40). Given these are all known side effects, only the cases of death will be evaluated in detail. The sponsor states there were no new, ongoing, or closed signals for palbociclib during the reporting interval.

8.7.1.3 Events noted

QT prolongation was noted in one patient (QTc 700msec) and put down to a drug interaction between the patient's medication (dofetilide) which is a CYP3A substrate and may also affect the QT interval.

Comments:

1. Direct potentiation of QT prolongation by palbociclib and dofetilide was not discussed in the narrative. This is plausible given the observed effects of palbociclib on QTc in the clinical trials.
2. The sponsor states as a preventability measure that '*Coadministration of palbociclib with concomitant medications known to prolong the QT interval should be avoided*.' (PSUR). This information should be included in the PI (PI Comments).

The sponsor presents data on venous thrombosis and thromboembolic events, with one fatality not able to be excluded as related to palbociclib. The sponsor indicates that the current information is adequate (in the US label) and does not warrant any changes.

Comment: This wording is not in the draft PI submitted with this application and should be, together with the changes recommended in the section of venous thromboembolism in the evaluation report.

Other events are not possible to evaluate and all are discounted by the sponsor as adding any further information to the identified risks with palbociclib.

8.7.1.4 Deaths

155 deaths were reported from postmarketing sources but were no data are presented for evaluation.

- 96 reported no cause (PT of 'death')
- 59 deaths was most likely attributable to:

- progression of the underlying malignancy (44) [32 due to breast cancer];
- hepatic events (9);
- infections/myelosuppression (8);
- cardiac events (4);
- thromboembolic events (3);
- haemorrhagic events (2);
- and 1 occurrence each of the following events: Circulatory collapse, Disseminated intravascular coagulation, Gastric ulcer, Haemolysis, Product use issue, and Renal failure.

8.7.1.5 Use in the Elderly

The PSUR did not provide information that could be evaluated, and no additional changes for the RMP or PI can be made.

8.8 Evaluator's overall conclusions on clinical safety

There was no integrated safety summary and no single document provided a comprehensive and clear picture of the safety profile for palbociclib.The 90-day safety provided updates for an SCS prepared for the FDA and not submitted with this application, but which appears likely to have been updated by the version provided.The sponsor has been requested to provide a single, up to date comprehensive summary integrating the safety data from all studies rather than this detailing each study individually (and partially) This information should capture exposure, median duration and adverse events for all populations receiving the same treatment, not study by study.

The addition of palbociclib to either fulvestrant or letrozole is associated with a substantial increase in toxicities, most of which are haematological and in particular, neutropenia. This occurs in the vast majority of patients and is often of a Grade 3 or 4 severity. However, it does not appear to be associated with a correspondingly high risk of neutropenic fever or sepsis, and was generally manageable with treatment interruption, delays and dose reductions. No information is provided about the use of granulocyte colony stimulating factors was included and to what extent this might have reduced the incidence, severity and sequelae of the observed events. There were relatively few permanent discontinuations required due to neutropenia. Of note, the observed neutropenia occurs very early (median time to first onset 14 days) but may occur at any time during treatment (although does not appear to be a cumulative toxicity), and persists for a lengthy period after withholding treatment. This would not necessarily be anticipated by medical oncologists used to managing chemotherapy-related neutropenia which is typically of a relatively short duration, and information in the PI about this should be included (PI Comments). Leukopenia was common and often prolonged, and the potential clinical impact (PML, viral reactivation, opportunistic infection, risks with live vaccines) is not currently addressed in the dossier (Clinical Question). If no information to reassure regarding this is available, this should be included as important missing information in the RMP. Infections, sometimes fatal, occurred more commonly in patients on palbociclib including a death from neutropenic sepsis that the evaluator considers treatment-related. Thrombocytopenia also occurred commonly, and the sponsor has been asked to correlate these events to determine whether this is associated with an increased risk of bruising or bleeding events. The high level of surveillance and frequent clinical and laboratory visits required to monitor these haematological parameters, offsets some of the convenience of an oral medication.

Of note, a review of some of the investigator initiated studies on clinicaltrials.gov indicates they appear to be investigating a lower dose as although generally manageable, the tolerability was

relatively low with 64.9%, 31% and 3.8% requiring temporary discontinuation, dose reduction or permanent discontinuation of palbociclib respectively, in Study 1023. These rates were similar to those reported for Study 1008, and in Study 1003, 15.7% discontinued permanently.

Other frequently reported TEAEs were fatigue, infections, nausea, arthralgia, stomatitis, vomiting, diarrhea and alopecia. Many of these were of Grade 1 or Grade 2 maximum severity except for neutropenia and leukopenia, which were most commonly reported as Grade 3 events. Alopecia was of both greater frequency and severity in patients receiving palbociclib in addition to fulvestrant or letrozole. The impact of these adverse events on quality of life has not been adequately assessed to date, although it was noted that palbociclib added to fulvestrant significantly delayed the time to development of pain which is an important benefit.

Of concern is the frequency of thrombotic and thromboembolic events, with one fatal pulmonary embolism reported and several Grade 4 events. Of note, there has been one case reported of ischaemic colitis in patients receiving palbociclib[8] .

Other events identified as of special interest by the sponsor were pneumonitis/interstitial lung disease, QT prolongation, liver dysfunction, hyperglycaemia and cataract and visual disturbance - as well as neutropenia, thrombocytopenia and venous thrombosis, which have already been discussed. The protocol-defined method for reporting TEAEs and the presentation of AEs that occurred in ≥ 5% of the study population makes identification of the rates of these less common but potentially severe events more difficult, and for many events the narrative or CIOMS was not found or was blinded to treatment allocation. This has led to multiple clinical questions, and the responses to these questions need to be evaluated before any comments can be made. QT prolongation was observed in the clinical studies to date and has been investigated in a substudy within Study 1008, but the results were not provided in the top-line summary. In addition, although liver function test abnormalities were not common, there were cases reported of drug-induced liver injury and further details have been requested (Clinical Question).

One area of uncertainty, but where there were more reports in the palbociclib and fulvestrant arm is the risk of suicidal behaviour. This was an exclusion criterion for Studies 1023 and 1008, but not 1003 which is the subject of a clinical question (Clinical Question).

In terms of special populations, there was a signal for increased severity of adverse events in Asian patients in Study 1023 with a higher rate reported for Grade 3 or 4 events compared with non-Asian patients. Patients with Asian ethnicity make up a significant proportion of the Australian population and information alerting to this should be included in the PI. Submission, once completed, of the studies conducted solely in Japanese patients (Study 1010) and solely in China (Study 1027) may provide further information once completed.

No special safety concerns were identified in those over the age of 65, but information about the numbers of women and a breakdown of adverse events in the elderly population >75 years is awaited (Clinical Question).

9 First round benefit-risk assessment

9.1 First round assessment of benefits

The statistically significant improvement in PFS of 4.9 months observed with palbociclib and fulvestrant is considered clinically meaningful, and sustained over the 3 efficacy reports. Within the statistical limitations imposed by only a small sample being reviewed by the limited blinded independent central review of the PFS as of 5 December 2014 (first cut-off date), there appeared to be a low likelihood of bias and within the sample population reviewed, the findings were supported by the BICR. Most of this benefit is derived from stable disease and no complete responses were observed at any of the 3 time points reported. The duration of response among

those who responded was not statistically significantly increased in the palbociclib and fulvestrant arm compared with those in the fulvestrant and placebo arm, but the baseline response rates were higher (that is, the treatment failure rate was lowered with the addition of palbociclib) which is clinically important. The study data are immature and no data are available for overall survival as yet. The delay in time to onset of pain in this study is also considered a clinical benefit, but no other quality of life measures were significantly improved.

Uncertainties with this proposed usage are related to whether 'hormone receptor-positive' describes the population treated, that is, whether there were any patients enrolled with ER- PR-positive metastatic breast cancer (Clinical Question). Similarly, the number of patients with locoregional or locally advanced inoperable disease requires clarification (Clinical Question).

The reported statistically significant improvement in PFS in Study 1003 is considered promising but due to the methodological issues, the evaluator believes no improvement in any of the reported outcomes can be asserted. Data from Study 1008 were selected for presentation for 5of the 12 planned study endpoints: PFS was reported to be statistically significantly improved by 10.3 months, but there were no data presented from the blinded independent central review in support of these findings. These were reported to be positive at a presentation in June 2016 at the American Society of Clinical Oncology annual meeting but are available in abstract form only. The overall response rate improvement was statistically significant but a relatively modest increase of 10.9%, and the level of clinical benefit rate was increased further slightly, due to additional patients having stable disease (CBR: 14.6%). These reported improvements are considered clinically significant.

There are many clinical questions arising from the evaluation of the limited information provided in the top-line data for Study 1008, with no data presented for 7/11 endpoints of the study nor the blinded independent review findings and analyses. The clinical questions address uncertainties about randomisation compared with CRF populations, and many surrounding adverse events. The clinical study report was not available at the time of this evaluation and is required to permit a full evaluation.

The convenience potentially offered by an oral medication as opposed to intravenous administration in an outpatient setting, is offset somewhat by the high level of monitoring required necessitating frequent and ongoing blood tests and clinic visits which is more akin to the monitoring level required for patients on chemotherapy than those on endocrine therapy.

9.2 First round assessment of risks

Haematological toxicities, often Grade 3 or 4 neutropenia, but also thrombocytopenia and leukopenia occurred in the vast majority of patients. Although generally considered manageable from a clinician's perspective, the high proportions of temporary discontinuations, dose reductions and discontinuations suggest that palbociclib as an add-on is not particularly well tolerated by patients.

Other concerns are the rates of thromboembolic events, which are currently not addressed in the PI. Overall, each of the studies except one very small trial (Study 1010) presented here had events of pulmonary embolism including one fatal event, with further reports of deep vein thrombosis and one event of ischaemic colitis. In Study 1008, there were 4 events which cannot be investigated further due to ongoing blinding.

Many more patients receiving palbociclib also experienced AEs associated with visual loss and impairment, the nature of which is not fully understood due to the non-specific nature of the terms used for reporting. These should be included in the PI (Clinical Question).

The extent of the risks cannot be fully established at this time without the sponsor's responses

to the clinical questions for Study 1023 which include queries/issues about cases of drug-induced liver injury[12], cataract formation, ischaemic colitis, as well as suicidal ideation and behaviours.

It is not known if the clinical benefit from palbociclib is proportional to the dose received, and whether those requiring a dose reduction have comparable clinical outcomes with those maintained on the starting dose (Clinical Question).

9.3 First round assessment of benefit-risk balance

The magnitude of the benefit on PFS is established and statistically significant and clinically relevant for the proposed usage in women with ER-positive metastatic breast cancer receiving palbociclib following progression on earlier endocrine therapy. There are a number of outstanding issues that prevent a benefit-risk assessment being made at this point, but satisfactory responses to the clinical questions may change this.

While the magnitude of the benefit in improving PFS appears promising in Study 1003, and the investigator assessed outcomes indicate a statistically significant improvement in the 4/12 study endpoints that were presented (PFS, ORR, CBR and DoR) in Study 1008, this could not be fully evaluated due to the very limited data presented. The blinded independent central review was not presented in the top-line summary. There are a number of serious adverse events including an increase in deaths on study in the palbociclib and letrozole arm that could not be evaluated due to ongoing blinding, with all CIOMS blinded to treatment allocation. Thus the risks of treatment cannot be fully established and the benefits could not be verified through evaluation of the full dataset and the blinded independent central review.

10 First round recommendation regarding authorisation

No recommendation regarding authorisation for the proposed combination of palbociclib and fulvestrant can be made at this time without the responses to the clinical questions, and evaluation of those responses in the second round of the clinical evaluation.

Study 1003 is not considered to satisfactorily demonstrate safety and efficacy for the proposed indication for palbociclib and letrozole as first line treatment for a very common cancer. There are many outstanding questions arising from evaluation of the limited data provided for Study 1008, which require addressing as well as significant endpoints which have not been submitted for evaluation in this dossier. It is not considered that responses to the clinical questions raised in this evaluation alone would be sufficient to allow the evaluator to make a benefit-risk assessment (missing efficacy and safety endpoints, ongoing blinding to treatment allocation would continue to be limitations). It is recommended that the future submission of the full CSR for Study 1008 address the issues and questions raised regarding the proposed usage (that is, for both Study 1003 and 1008), and that a Product Information reflecting those data be included. Given the extensive questions already asked and those envisaged upon review of the CSR, it is considered important that this should be submitted as a separate application. It is beyond the scope of a second round evaluation to review an entire CSR and the TGA does not accept rolling submissions.

11 Clinical questions

[12] Clarification: There was a case report of hepatic failure assessed by the sponsor to be unrelated to blinded therapy and fulvestrant and to any clinical trial procedure. For this case the investigator considered drug induced hepatitis could not be excluded and therefore two separate AEs were collected for this event. For further discussion see Response to Safety Question 18.

The following questions about efficacy and safety are to address uncertainties or provide clarification on the study data submitted. Some require responses only if the sponsor is pursuing inclusion of a statement in the PI. In such instances, if not pursuing inclusion of that information, it would be acceptable to state that and the question would no longer require an answer. Other questions pertaining to Studies 1003 and 1008 are included in this report but it is recommended by the evaluator that responses to be these be provided (if not already in the CSR for Study 1008 for those pertaining to that study) as part of a separate application for the first line indication with the full CSR for Study 1008 as the responses to these questions alone will not be sufficient to overcome the reasons for not recommending approval for the first line indication. These particular questions are included at this juncture to reflect the uncertainties about the data provided to date, but responses to them could be deferred to a subsequent application if the first line indication is no longer pursued in this application.

11.1 Clinical questions

11.1.1 Efficacy

1. Many patients required a dose reduction or delay. It is not discussed whether the clinical benefit for those on a lower dose is comparable with those who manage to stay on the starting dose. The sponsor is requested to provide an analysis of the efficacy outcomes and a forest plot of PFS and ORR to demonstrate the effect by dose received for Study 1023 (with the lowest dose received to be used for any who have had dose reductions).
2. Study 1003: Please provide the breakdown of the operations as to whether they were breast versus non-breast surgery for each treatment arm. For those who underwent breast surgery, please state the number and percentage going on to receive adjuvant therapy, by treatment arm.
3. Study 1003: Please provide a breakdown of the numbers of the 17.9 % patients for each arm who received no endocrine therapy following an earlier ER-positive breast cancer diagnosis.
4. Study 1003: The data presented in [Tables 27 and 28] of the CSR for investigator and BICR censoring respectively, differ from those data presented for the BICR censoring in Table 26 and Table 27 of the FDA report (publicly available on the website) for Study A5481003. The sponsor is requested to provide an explanation for all differences in the data presented in the dossier versus the tables in the FDA report, including but not limited to, the higher AE rates, clinical progression, withdrawal of consent reported in the FDA report- noting that the FDA table was generated in response to an FDA query on 28 Feb 2014.
5. For Study 1003, the sponsor is requested to provide a breakdown for both the control and experimental arms of the numbers and percentage where BICR was performed prospectively versus retrospectively.
6. For Study 1003, the sponsor is requested to provide concordance rates between the investigator and BICR by imaging modality eg bone scan, CT, MRI for each lesion type that is, bone lesions, visceral, other.
7. For Study A5481008, the sponsor is requested to state whether the CRF or Impala data was used to define populations for the primary efficacy analysis of the data, and how such discrepancies are handled in the statistical analysis. Noting that the 2016 ASCO meeting presentation of the latest results for Study 1008 (including BICR-reviewed data) by Dr Richard Finn used the CRF data, the sponsor is requested to provide a comment on the choice of this dataset over that presented for the primary analyses in this top-line summary.

8. For Study A5481008, what subgroups were prespecified for efficacy analyses?
9. How many patients 'in follow up for progression' in Study A5481008 were still on study drug in each arm?
10. When submitting the CSR for Study A5481008, the sponsor is requested to provide details of the deaths of each patient who died without evidence of disease progression if not already included in that document. This is recommended to be done as a second NCE application.
11. Uncertainty exists as to whether there is a benefit for those with de novo metastatic disease. Whether this represents an increased responsiveness to the control arm which generally did better than in other subgroup analyses cannot be checked against the group who had received no prior systemic treatment for their disease (irrespective of stage of presentation) as these data could not be located in the Tables or Topline summary. Provision of these data is requested to be included when the CSR is lodged with the TGA (second NCE application recommended).
12. For Study 1023, the anticipated dropout rate was high at 25%, particularly for those with metastatic disease and a high degree of motivation to continue treatment if their disease is not progressing. The sponsor is requested to provide a rationale for this high rate. Was this to anticipate side effects related to the use of fulvestrant, the administration of which is associated with significant discomfort?
13. In the update report using an earlier cut-off date of 16 March 2015, discontinuations due to withdrawal of consent occurred in 1.2 % (4 patients) in the palbociclib and fulvestrant arm but are now reported as 0.9% (3 patients) with a later cut-off date - the sponsor is requested to explain why there are now fewer presented (Clinical Questions).
14. The sponsor included an updated PFS analysis for Study 1023, which also included updated OR, DoR and clinical benefit rate. None of these analyses were supported by BICR-derived analyses; the sponsor is requested to provide the BICR analyses for these endpoints for evaluation or state that none was done.
15. CSR for Study A5481023 includes data about the recurrence type. This includes 'newly diagnosed' as a significant category (17.7% of total population) amongst breakdown by anatomical site which makes it difficult to establish how many in the study had local or locoregional disease only. The sponsor is requested to provide:
    a. A breakdown of numbers in each arm this is a population identified in the indication;
    b. The following efficacy outcomes for those in each arm with local or locoregional disease: median PFS, OR, DoR, CBR.
16. This question only needs to be addressed in the response if the sponsor wishes to retain the PI statements about quality of life in the Clinical trials section:
    a. a justification of the clinical significance of the presented results against the prespecified criteria in the SAP;
    b. to indicate meaningful completion rates, please provide the number and percentage of patients who completed all questions of the EORTC-QLQ-C30 out of the PRO analysis in each arm;
    c. please provide the number / percentage of patients for whom pro-rating was undertaken due to missing data in each arm.
17. In Study A5481023, no information was found by the evaluator as to how many of the biopsy samples used in the central testing were from a biopsy sample taken following their most recent episode of progression to determine ER/PR/HER2 status – the sponsor is requested to provide this information as it has been shown that a discordant rate between

primary and secondary breast cancers has been reported to be as high as 25-30%.

18. Study 1023: The sponsor is requested to provide 3 additional sensitivity analyses, presented as a forest plot with accompanying HRs comparing the ITT PFS:
    a. A sensitivity analysis, removing all those who were ineligible for enrolment due to subsequently determined ER-/PR- or HER2+ disease by central testing, to determine whether there was any effect on the ITT PFS analysis;
    b. A second sensitivity analysis excluding those 118 patients whose data were missing or inadequate for central laboratory testing of ER,PR or HER2 status as well as those who were deemed ineligible by central laboratory testing, is also requested to determine whether there was any effect on the ITT PFS analysis;
    c. A subgroup analysis of those whose results were discordant that is, not ER-positive or they were HER2-positive.
19. The sponsor is requested to provide the number of patients in each arm whose tumour was ER-negative/PR-positive and the results (PFS, OR, DoR, and CBR) for these patients.
20. Study A5481023: The change to a different schedule (2 weeks on/2 weeks off) was not described in the Protocol and the benefits of this dose in the 3.8% who switched to this regimen cannot be assured. It is not clear what palbociclib dose was taken in this regimen (please provide this information). It would be apparent to the investigator that the patient was receiving palbociclib due to the AE profile, and this may have introduced a bias in wanting to continue if there was a clinical benefit observed but problematic toxicities. That so many changed to this regimen indicates a degree of unmasking. The sponsor is requested to provide an explanation of whether these non prespecified alterations were included in the protocol deviations and also whether these patients' outcomes were included in the efficacy analyses, and whether any subgroup efficacy analyses were performed for those on this regimen. (Clinical Questions).
21. Study A5481023 the sponsor is requested to state whether searching using any other MedDRA terms that might capture events of haemorrhage, bleeding or bruising, yields any events associated with the adverse events of thrombocytopenia. (Clinical Questions).
22. Study A5481008: Within the study, there was some discordance between the baseline information provided at randomisation which affected the stratification and has had an impact on the efficacy analyses, particularly on the subgroup analyses, depending which dataset is used for the ITT population. The full impact of these cannot be understood and contextualised without presentation of the study protocol deviations. It is not sufficient to provide the analyses for these groups according to the differing information source (that is, randomisation versus CRF). A more rigorous approach should include:
    a. Presentation of the number of patients for whom there was any discordance between the randomisation information and CRF;
    b. Whether these patients were from a single or limited number of investigation centres - it is noted that in Study 1003, the FDA clinical site audit identified a single site as having a significant number of protocol deviations but that analyses with these patients censored were not reported to significantly affect the outcomes;
    c. Presentation of sensitivity analyses for the efficacy outcomes censoring the data from these patients incorrectly classified.

11.1.1.1 Safety

1. Clinical evaluator comment: the sponsor is requested to provide a table which integrates from all clinical studies (referencing the source studies) and presents:
    a. the total number of patients treated to date:

i. at the proposed dose level and regimen (palbociclib 125 md QD 3/1)

- in combination with fulvestrant
- in combination with letrozole at the proposed dose
- in combination with letrozole at any dose level

ii. ii. as monotherapy

- at the proposed dose and schedule
- at any other dose

b. the median duration of treatment for all those patients and an interquartile range

i. in combination with fulvestrant

ii. in combination with letrozole at the proposed dose

iii. in combination with letrozole at any dose level

2. The sponsor is requested to explain the rationale behind the exclusion from Study A5481008 of patients with recent or active suicidal ideation or behaviour. In particular, the sponsor is requested to provide case details where palbociclib might have been implicated in patients committing suicide or becoming suicidal that is, while taking or after recently stopping palbociclib. And further to the results in Study A5481023, where 4 patients were reported to have a psychosis, depression or suicide attempts, the sponsor is requested to discuss the potential role of palbociclib in these events.
3. The sponsor is requested to provide with a future provision of the CSR for Study 1008, an integrated safety summary for the 2 studies 1003 and 1008, and an updated PI to reflect these data.
4. For Study A5481023, the remaining events accounting for the 3.5% of Grade 3 or 4 TEAEs for the palbociclib and fulvestrant arm and 1.7% in the comparator arm (90-day safety update) are not presented. The sponsor is requested to provide this information.
5. An update infection rate/febrile neutropenic rate has not been presented in this safety update for Study 1023 and this is needed, to ensure the figure quoted in the PI is accurate.
6. Bone marrow suppression occurs resulting in leukopenia and neutropenia. The sponsor is requested to provide the following information, and where cases have occurred, provide the details.

a. What were the rates of opportunistic infections reported for each of the arms for Study 1003, 1023 and 1008?

b. Were any cases of Hepatitis B reactivation identified?

c. Has PML ever been reported in the palbociclib development program? Please provide details of any cases reported.

7. There needs to be a heading and discussion of the rates of infection and febrile neutropenia (0.6% of patients receiving palbociclib and fulvestrant reported at 5 December 2014 cut-off – but what is it now with the later dataset?) An updated infection rate/febrile neutropenic rate has not been presented in this safety update for Study 1023 and this is needed, to ensure the figure quoted in the PI is accurate (Clinical Questions and PI comments).
8. Table 5 of the draft PI presents out of date data for Adverse Drug Reactions which is in the SOC format which needs to be updated with the 90-day safety update. Where there are clinical laboratory findings (eg for biochemical and haematological events), these should be included in any data presented as these are more accurate than TEAEs. It must be shown clearly how the figures used in the ADR table were reached and why any treatment-related

events were discounted. This is required in the response (clearly indicating how these figures were reached) and to be inserted in the PI (see PI comments and Clinical Questions).

9. Study A5481023: Without a table providing side-by-side comparison of the adverse events of lower frequency, presented with similar terms collapsed to provide a single figure (as in the SOC presentation with like MedDRA terms collated, it is very difficult to determine whether there have been additional clinically significant adverse events occurring more commonly in the experimental arm. Given the importance of understanding these for both clinicians and patients, the sponsor is requested to present all the adverse events, (including all grades frequency, as well as Grade 3 and Grade 4) that occurred more often in the palbociclib and fulvestrant arm than the placebo and fulvestrant arm (Clinical Questions). These adverse events' preferred terms should be clustered to capture the same event being classified by a range of different terms.
10. For Study A5481023: It is difficult to determine whether the difference between the rates of thrombocytopenia from laboratory findings compared with the TEAEs of thrombocytopenia indicates a level of under-reporting of the events for the population as a whole for lower grade AEs of thrombocytopenia as it would be unusual for such a high percentage of patients who have received endocrine therapy as their last treatment to be thrombocytopenic (even Grade 1 or 2) at baseline; however, the reporting of TEAEs appears to match the total number with Grade 3 or 4 TEAEs although the distribution is different (one patient more is reported to be Grade 4 not Grade 3). The sponsor is requested to provide an explanation.
11. Study A5481023 The rates of epistaxis and thrombocytopenia are both noted to be increased in Study 1008 for the palbociclib arm and sponsor is requested for Study 1023, to state the rates for bleeding events by:
    a. Broadening the search criteria beyond 'Haemorrhage' and to use all MedDRA terms that are designed to cover the event of bruising, bleeding in any organ (including petechiae)
    b. How many of these were associated with the events of thrombocytopenia in Study 1023?
12. Study A5481003: the sponsor is requested to provide the platelet count for the patient at the time of requiring a dose reduction for petechiae.
13. Study A5481008: 'Summary of all-causality treatment-related adverse events' states that 6.1% and 5.0% of patients permanently discontinued letrozole due to an AE in the experimental and comparator arms, respectively. This figure exceeds that for those permanently discontinuing the study due to an AE for those arms (2.5% and 1.8%, respectively). The sponsor is requested to provide explicit details regarding how these patients were treated and followed up from this point of discontinuation.
    a. Was palbociclib or placebo continued as monotherapy in any patients? If so, how many in each arm?
    b. If both letrozole and the placebo or palbociclib were discontinued, what is the difference between the group who permanently discontinuing the study and those labeled as permanently discontinuing letrozole?
14. Study A5481008: Events rates for TEAEs of thrombocytopenia were not reported as occurring below 10% in Study 1008. This is an artefact of the high cut-off threshold of ≥ 10% in either arm and use of separate MedDRA terms for TEAE reporting; the combination of treatment-related thrombocytopenia/platelet count decreased was 14.9% in the experimental arm and 1.4% in the comparator that is, a 10-fold increase in risk, with the lower cut-off of 5% reporting the treatment-related AEs. Furthermore with the lower

threshold in the treatment-related events table, the adverse event of epistaxis also emerges which could be linked to the low platelets (any correlation of these 2 adverse events should be addressed in the clinical overview and safety section when providing the CSR for Study 1008). When submitting the CSR for Study 1008, the sponsor is requested to include a table of TEAEs with a cut-off of 1% in either arm, treatment-related AEs with a cut-off of 1% in either arm to be consistent with the Grade 3/4/5 TEAE reporting provided. This will assist in identification of events that may require inclusion in the PI to inform clinicians and patients. The assessment of attribution of AEs considered treatment-related cannot be made without knowing the baseline percentage listed as treatment-emergent. (Clinical Questions).

15. Study A5481008: Top-line summary provide frequencies for treatment-related adverse events by frequency of at least 5% in either arm. Given, rare events will be missed by presentation this way, the sponsor is requested to provide a table where the cut-off is 1% in either arm when submitting the CSR for Study 1008. The same threshold should be used for the TEAEs – it would be acceptable to add in a table to capture this rate of events. It is recommended that these issues be addressed when submitting the Study 1008 to facilitate any evaluation.
16. Investigator-initiated research death on study: The narrative could not be located for evaluation of the case of ischaemic colitis on palbociclib monotherapy, and the sponsor is requested to provide a copy of it in the response.
17. Study A5481023: The CTCAE grading system does not provide a numeric value for Grade 4 events of anaemia but defines this as 'Life-threatening consequences; urgent intervention indicated'. The sponsor is requested to provide the number of patients for whom transfusions were required in these circumstances and clinical details for such patients (Clinical Question).
18. Study A5481023: Study 1023 the CIOMS indicates that for the patient with 'drug-induced liver injury' (Subject [information redacted]) there was a substantial improvement in the liver function tests after discontinuing the study drugs, even though there is a background of progressive disease from which she died subsequently just over 2 months after the last dose of palbociclib. The evaluator agrees with the investigator and disagrees entirely with the conclusion of the sponsor who cite a 'progressive marked deterioration of hepatic function after discontinuation after study drugs' discontinuation' as a reason for this not being study related, when quite clearly, there was an improvement in liver function that would not be anticipated if this were solely progressive disease. The sponsor is requested to comment upon the quite dramatic improvement in liver function tests, the imaging results that suggest a new appearance to the liver contour, as these appear to have been overlooked in the causality assessment.
19. Study A5481023: no information is provided about the case of Grade 4 increase in bilirubin – please provide the clinical details for this patient surrounding this event, including details of all the liver function tests that were performed, any diagnostic imaging, whether the study drug dose was reduced, delayed or discontinued and comment on these.
20. Study 1003: the remaining CIOMS for the SAEs (acute renal failure) and 2 Grade 3 events (nephropathy and nephrolithiasis) of renal and urinary disorders could not be located and should be provided by the sponsor.
21. Study 1023: the Study protocol states that CTCAE v 4.0 was used. A review of this reveals no such classification of Grade 1 for ventricular tachycardia (as this necessarily requires medical attention). Similarly, there are no CTCAE terms for 'bradycardia', 'tachycardia' or 'ventricular extrasystoles.' The sponsor is requested to comment and provide updated details and classifications regarding these adverse events, and to provide clinical details surrounding the event of ventricular tachycardia (Clinical Question).

22. Given the proposed usage is in postmenopausal women and the frequency in older women, the sponsor is requested to provide a breakdown for the events reported in the 90-day safety update for those > 75 years of age and include this in the PI.
23. Study 1003: The sponsor is requested to explain the unusual dose levels in the range accompanying the median daily dose included in the Phase II part of Study 1003 (stated range: 79.6 mg to 266.7 mg).
24. Thrombocytopenia/platelet count decreased was more common (19.3%) with palbociclib and letrozole compared with letrozole alone (1.3%), including Grade 3 events. There was an increased rate of epistaxis (6% versus 1.3%; all Grade 1 events in both arms) in the palbociclib and letrozole arm. Whether these were associated with thrombocytopenia is not discussed and the sponsor is requested to state:
    a. The platelet count at the time of each event of epistaxis for these patients
    b. Provide a breakdown of the events by MedDRA PT of any haemorrhage or bleeding in any organ, by treatment arm with the platelet count at that time for each patient experiencing an event.
25. Study 1003: The sponsor states: 'Both patients (2.4%) with Grade 3 Thrombocytopenia in the palbociclib plus letrozole arm had their dose reduced, interrupted or their cycle delayed (due to Grade 3 or lower Thrombocytopenia). No patients in either treatment arm were permanently discontinued due to a TEAE of Grade 3 Thrombocytopenia. No patients in either treatment arm had a TEAE of Grade 4 Thrombocytopenia. None of the events of Thrombocytopenia were serious or led to death' on page 261 of Study 1003 CSR. The sponsor is requested to provide the same information regarding any adverse events or dose level and schedule adjustments for the 2 cases with Grade 3 platelet count decreased adverse events (Clinical Questions).
26. Study 1003: No update of Table 68 from the CSR Overview of treatment-emergent adverse events Phase II As treated set, Study A5481003 CSR, cut-off date November 29 2013 was provided, nor text to update this information – the sponsor is requested to provide an updated table containing the latest data.
27. Investigator-initiated research: the safety update report states that detailed narratives are available in Appendix 2 for all 4 patients where the events were considered treatment-related. The evaluator could not locate them in Appendix 2 and the sponsor is requested to provide these in the response for the two patients:
    1. the patient (Case Number [information redacted]) with dyspnoea and pneumonia who was discontinued from palbociclib on day 232 (why?) and then developed dyspnoea and a nosocomial infection on day 257. Pneumonitis or interstitial lung disease need to be considered.
28. Investigator-initiated research palbociclib monotherapy for non-breast cancer patients: The 90-day report cites as including 2 patients with fatal SAEs considered treatment-related but the clinical evaluator notes 3 cases are listed here – no detailed narratives could be located for any of these 3 patients are the sponsor is requested to provide these.
29. Study 1023: Was a single patient able to be recorded as having both neutrophil count decreased and neutropenia by MedDRA PT (that is, 2 terms for the same clinical event)? If so, the sponsor is requested to provide the number of patients with an event of NEUTROPENIA (cluster term) without such double reporting (that is, individual patients should be presented as having only one event recorded).
30. Study 1023: following on from the question immediately before this one, the figures do not appear to tally for the number of patients reported to have Grade 3/4 events as defined by the cluster term NEUTROPENIA. 287 patients were reported to have NEUTROPENIA events

of any severity), with the text following stating 240 of these patients had Grade 3/4 severity. However, demonstrates that the number with maximum grade of 3 was 191 patients and of maximum Grade 4 was 37 and this equals 228 patients. The sponsor is requested to state which are the correct figures and explain why these differences occurred.

31. Study 1023: The TEAEs should be a subset of the clinical laboratory abnormalities, as this AE grading is based on a blood test. The sponsor is requested to explain how there are discrepancies between the clinical laboratory abnormalities and the MedDRA PT reported AEs including:
    a. More patients are reported to have Grade 3/4 neutropenia or neutrophil count decreased by MedDRA PT compared with those determined by clinical laboratory abnormalities (228 or 240 versus 225);
    b. 2 patients in the comparator arm had Grade 4 events on blood tests which were not recorded as TEAEs. In a blinded study, any Grade 4 events of neutropenia should be reported as AEs but the 2 events in the placebo and fulvestrant arm were not recorded as AEs. (Clinical Question).
32. The sponsor is requested to provide details of clinical laboratory findings for glucose for the 2 patients with cataracts and any elevated HbA1c results as this is more likely to capture events of hyperglycaemia than isolated terms used to identify TEAEs.
33. The sponsor is requested to characterise further the nature of the conditions leading to reports of visual impairment and provide a discussion about the increased rate of events affecting vision/visual acuity which would compromise vision in those receiving palbociclib, as seen in Study 1003. Were there any preclinical data which identified visual impairment besides cataract development? The CIOMS and narrative for the patient with 'blindness' attributed to cerebral metastases are requested. This would require a significant metastasis or haemorrhage into such a lesion in the occipital region for such blindness to occur and be attributable to metastases.

12 Second round evaluation

12.1 Second round clinical evaluator introductory comments

From review of the first round CER and the response including errata documentation, it is clear that there are significant process-related problems highlighted by this submission. These may be attributable, in part, to the growing complexity of (particularly oncology) clinical trial design and data, and the changing regulatory environment around 'early approvals'.

Whilst a small number of previous submissions have been recently approved on the basis of early data, it is important to note that the approval of a medicine for a last-line usage in a rare indication on the basis of surrogate markers or uncontrolled data, with caveats in the PI regarding the limited nature of the evidence (and with conditions of approval that include submission of full CSRs for Phase III confirmatory studies when available) is a very different thing to the approval of a medicine for a first-line usage in a very common indication on the basis of a top-level summary document. Whilst summaries are valuable overviews, the review of low-level data and systemic examination of investigative processes is the critical responsibility of a regulator. The TGA is a distinct entity to other regulators, and whilst their stances and reasoning provide collegiate support, their decisions do not dictate those of the Australian government.

The sponsor have submitted an application for first-line use of a first-in-class new chemical entity on the basis of a 'Topline Summary' (that is, not a complete CSR) from a Phase III RCT,

and supported by data from a study not adequately designed to support a first-line indication. The evaluation of this submission resulted in extensive questions to the sponsor from the first round clinical evaluator.

At this late stage in the application process, in order to support the efficacy and safety claims and ostensibly in answer to questions, the full CSR from the Phase III RCT (Study 1008) has been submitted. It was available months ago, but due to the nature of the current process and the fact that the sponsor had specifically been told not to submit 'rolling data', it was not submitted at that time. The second round evaluation therefore involves the review of a large number of responses, in addition to the review of an entire CSR for the pivotal trial supporting first-line registration.

Due to these unusual circumstances, the second round evaluation will focus entirely on the answers to questions posed by the first round clinical evaluator, and review of the PI/CMI documentation, while the CSR for Study 1008 will be reviewed separately by the Delegate. Where findings from Study 1008 are referred to in answers to questions or cited in PI text, this will be taken at face value and cross referenced for review by the Delegate.

Second round evaluator comments will be highlighted in the same formatting as this grey comment box throughout the second round CER.

12.2 First round evaluation errata

12.2.1 Errors of fact

An extensive listing of errors of fact that the sponsor has identified in the first round CER is included with the submission. This listing will be considered by the Delegate in constructing their overview.

12.3 Review of responses to clinical and PK/PD questions

12.3.1 Pharmacokinetics (PK) questions/responses

12.3.1.1 PK question 1

QUESTION 1

Although Study A5481032[13] examined dose proportionality between 4 single dose levels of palbociclib (75mg, 100 mg, 125 mg or 150 – 200 mg final Phase III capsule), no studies have been provided that examine the BE of these 3 dosage strengths nor has the sponsor applied for a waiver for the required studies. Can the sponsor please comment?

Sponsor Response

> *The bioequivalence strategy, including the justification supporting the equivalence of the different capsule strengths, was presented in Module 3, Section 3.2.P.2.2 Drug Product, as well as Module 2, Section 2.7.1 Summary of Biopharmaceutics. Palbociclib final Phase III/commercial free base capsules are available in 75mg, 100 mg, and 125mg dose strengths. These three capsule strengths have the same qualitative composition, are quantitatively proportional formulations (ie they derive from a 'common blend'), and are produced following the same manufacturing processes.*
>
> *To support the equivalence of the different capsule strength formulations, a statistical*

[13] Table 4.9 of the pharmacology evaluation report.

> *analysis was conducted on the palbociclib dose-normalized exposure parameters of AUC_{inf} and C_{max} following administration of the 75, 100, and 125 mg capsules under fed conditions to healthy Japanese volunteers in Cohort 1 of Study A5481032 (see Module 2, 1023 SCP, Section 2.7.2.1.3.3) following the recommended methodology described in Section 4.1.6 of the EMEA Guideline on the Investigation of Bioequivalence (BE). The results of this analysis indicated that the 90% CIs for the ratios of each comparison were all within the 80% to 125% BE range (see Module 2, 1023 SCP, Section 2.7.2.2.3.1.7.3). Since it has been established previously that palbociclib exhibits linear PK (see Module 2, 1023 SCP, Sections 2.7.2.3.1.2 and 2.7.2.3.1.3) across the dose range of 25 to 225 mg, the bioequivalence between the three capsule strengths indicates the capsule strength equivalence of the final Phase III/commercial free base capsules. The sponsor's position is that this analysis from Study A5481032 provides the same information as and obviates the need for a dedicated BE study.*
>
> *Based on the discussion above, the sponsor believes that the information included in the current submission provides adequate support to the dose strengths equivalence and no additional BE study is needed.*

'Common blend' refers to 'a batch of final blend that can be packed in different amounts providing various strengths of the capsule product'.[14]

The question posed by the PK reviewer relates to the difference between bioequivalence (equivalent rate and extent of absorption after administration of the same molar dose) and dose proportionality, which as stated has been shown in Study A5481032.

Per section 4.1.6 of the EMA guideline on bioequivalence:[15]

> *If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the different strengths and other product related issues described below. The strength(s) to evaluate depends on the linearity in pharmacokinetics of the active substance. In the context of this guideline, pharmacokinetics is considered to be linear if the difference in dose-adjusted mean AUCs is no more than 25% when comparing the studied strength (or strength in the planned bioequivalence study) and the strength(s) for which a waiver is considered.*
>
> *…*
>
> *If bioequivalence has been demonstrated at the strength(s) that are most sensitive to detect a potential difference between products, in vivo bioequivalence studies for the other strength(s) can be waived.*

A sufficient number of subjects were included in Study A5481032 per the EMA guideline (13 were studied in these dosage groups, and the guideline specifies not less than 12 should be included) and under the correct conditions – that is, fed conditions per the dosing recommendations.

Dose proportionality has been shown in Study A5481032, as described, and the PK shown to be linear across the relevant dose range, so dedicated BE studies are not required.

Evaluator comment:

The sponsor's response is accepted.

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[14] Anand, O., Yu, L. X., Conner, D. P., & Davit, B. M. (2011). Dissolution Testing for Generic Drugs: An FDA Perspective. The AAPS Journal, 13(3), 328. http://doi.org/10.1208/s12248-011-9272-y

[15] EMA guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), effective from 01/08/2010.

12.3.2 PK question 2

QUESTION 2

As M22 is the most abundant circulating metabolite (responsible for 14.8% of circulating radioactivity), does the sponsor have information regarding its activity?

Sponsor Response

> *In humans, the glucuronide conjugate of palbociclib (M22) accounted for 14.8% of plasma total radioactivity AUC, but constituted for only 1.5% of dose in urine (PD-0332991_15Oct13_113146). The small amount of this metabolite recovered in urine limited the feasibility of its isolation and further structural elucidation. In addition, the position of the glucuronide conjugate on the parent molecule could not be identified based on mass spectral analysis, hence the definitive structure of M22 could not be ascertained. As such, the pharmacological activity of M22 for CDK4/6 cannot be predicted by the known structure-activity-relationship. Moreover, it is anticipated that the polar nature of this metabolite will likely impede its ability to distribute into cells, thus attenuating its cellular potency towards the intended target of CDK4/6.*

Evaluator comment:

The sponsor's response is accepted.

12.3.3 PK question 3

QUESTION 3

Can the sponsor please provide the complete clinical trial report for Study A5481013, which examined the effects of hepatic impairment on palbociclib PKs?

Sponsor Response

> *The sponsor has initiated Study A5481013 to investigate the effect of varying degrees of hepatic impairment on single dose palbociclib pharmacokinetics, in otherwise healthy subjects. Upon completion of the study the sponsor will generate and submit the clinical study report (CSR) for this study to TGA. Pending sufficient results, the sponsor will also submit palbociclib treatment recommendations for patients with moderate and severe hepatic impairment at that time. Based on current enrollment projections, it is expected the CSR for Study A5481013 will be available by December 2017.*

Evaluator comment:

The PI reflects the current knowledge around hepatic impairment. The sponsor's response is accepted.

12.4 Pharmacodynamics (PD) questions/responses

12.4.1 PD question 1

QUESTION 1

Given that at the mean and median c following QD dosing with 125 mg palbociclib the upper bounds of the 90%CIs for QTcS range from +8.72 to +9.16 msec and therefore are relatively close to the 10 msec threshold,[16] ***is it possible that co-***

[16] Table 5.5.1 of the pharmacology evaluation report

administered drugs that increase palbociclib exposure even by as little as 20% to 30% will possibly result in major safety concerns?

Sponsor Response

In a Phase I dose-escalation trial in 74 patients with advanced solid malignant tumors (Study A5481001), palbociclib daily doses ranging from 25 mg QD to 225 mg QD were investigated with 2 dosing schedules, Schedule 3/1 (palbociclib taken orally QD for 3 weeks followed by 1 week off treatment) and Schedule 2/1 (palbociclib taken orally QD for 2 weeks followed by 1 week off treatment). The recommended Phase II doses (RP2Ds) were determined to be 125 mg QD on Schedule 3/1 and 200 mg QD on Schedule 2/1. As described in Section 2.7.2.3.1.3 of the Summary of Clinical Pharmacology (SCP) and detailed in Table 1 of this response, the exposure as assessed by plasma AUC0-10 and C_{max} increased in a dose-proportional manner over the entire dose range following single dose (Day 1) and multiple doses (Day 8) of palbociclib. Relative to 125 mg with Schedule 3/1, the exposure levels at steady state for 200 and 225 mg with Schedule 2/1 were generally consistent with the 60% and 80% higher daily doses, respectively. The ECG and PK data collected in these two cohorts of patients should provide sufficient coverage for assessing the potential for palbociclib-induced QTc prolongation in high exposure level in special populations (for example, elderly patients with low body weight, patients on concomitant moderate CYP3A inhibitor) under the current clinical dosing regimen of 125 mg with Schedule 3/1. Analysis of the QTcF (Fridericia's correction) and QTcB (Bazett's correction) versus RR plots revealed that Fridericia's was the more appropriate correction method, and QTcS (study-specific correction) was also calculated for evaluations. The ECG results demonstrated no patients had a maximum QTcF or QTcS >500 msec on study. Two patients, one in the 75 mg QD Schedule 3/1 dosing cohort and one in the 125 mg QD Schedule 3/1 dosing cohort, had maximum changes from baseline in QTcF or QTcS values of >60 msec. The categorical summaries of QTcF and QTcS are presented across all dosing cohorts in Table 2 and Table 3, respectively [1, 2]. There is no trend of more patients falling into categories of higher absolute QTc values or higher increase from baseline values with higher dose levels. Similar observations were also found in the summary of mean QTc change from baseline by nominal time for each dosing cohort [3].

In a substudy from Study A5481008 that was conducted as the definitive QT interval prolongation evaluation for the palbociclib program, triplicate ECG data were collected at clock time-matched baselines and at 5 time points (pre-dose and 2, 4, 6, and 8 hours postdose) on Day 14 after palbociclib had reached steady-state concentrations following a therapeutic dosing schedule (125 mg QD on Schedule 3/1 in combination with letrozole). Based on these ECG data and time-matched PK data a PK-pharmacodynamic analysis was performed to characterize the relationship between palbociclib exposure and ECG endpoints (RR and QTc intervals) using linear mixed effects model (PMAR-EQDD-A548b-sNDA- 611). While a slight positive linear relationship was observed between palbociclib concentration and QTcS, at the mean steady-state palbociclib C_{max} the mean QTcS increase from baseline was 4.04 msec, with the upper bound of the 1-sided 95% CI at 6.67 msec. As seen in Table 4, based on this model the predicted upper bound of the 1-sided 95% CIs for QTcS at 20% and 30% higher than the mean or median steady-state palbociclib C_{max} are both less than 10 msec. Similar results were obtained with QTcF and QTcB. Therefore, based on currently available data, there is no expectation of clinically relevant effects of palbociclib on the QT interval in patient populations with higher palbociclib exposure.

Evaluator comment:

The sponsor's response is accepted.

12.5 Efficacy questions/responses

12.5.1 Efficacy clinical question 1

QUESTION 1

Many patients required a dose reduction or delay. It is not discussed whether the clinical benefit for those on a lower dose is comparable with those who manage to stay on the starting dose. The sponsor is requested to provide an analysis of the efficacy outcomes and a forest plot of PFS and ORR to demonstrate the effect by dose received for Study 1023 (with the lowest dose received to be used for any who have had dose reductions).

Sponsor Response

As requested, the sponsor provides Progression-free survival (PFS) and best overall tumor response for three subsets of patients; those who had at least one palbociclib dose reduction during the Study A5481023, those who had a dose reduction to 100 mg/day, and those who had a dose reduction to 75 mg/day. Comparisons cannot be made to the control arm because <5 double-blind placebo-treated patients had a dose reduction of placebo. Thus, a forest plot cannot be generated.

As of 23 October 2015, 132 patients in the palbociclib plus fulvestrant arm had at least one palbociclib dose reduction. Palbociclib dose was reduced from 125 mg/day to 100 mg/day in 89 patients and to 75 mg/day in 43 patients (Table 1).

The requested PFS analyses were conducted in the 3 subsets of patients identified above and are presented in Table 2. A summary of best overall tumor response is also reported for the 3 subsets of patients in Table 3.

As shown in Table 2, the PFS medians of the 3 subsets of patients are comparable. The same conclusion can be drawn from the Objective Response Rate (ORR) results of the 3 subsets of patients (Table 3). The 95% Confidence Intervals (CIs) of the Kaplan-Meier estimates of median PFS and the 95% CIs of ORR for the 3 subgroups overlap indicating a lack of evidence to conclude that they are different.

In conclusion, the sponsor considers that the clinical benefit of patients treated with palbociclib plus fulvestrant was maintained although palbociclib was administered at a reduced dose.

Evaluator comment:

The sponsor's response is accepted.

12.5.2 Efficacy clinical question 2

QUESTION 2

Study 1003: Please provide the breakdown of the operations as to whether they were breast versus non-breast surgery for each treatment arm. For those who underwent breast surgery, please state the number and percentage going on to receive adjuvant therapy, by treatment arm.

The first round clinical evaluator comments relevant to this question were:

49.1% of patients had de novo metastatic disease which is a much higher figure than the 5-10% that would be expected with Stage IV disease at presentation in Australia.

the 'prior surgeries' rate is 81% in both arms, although it is not clear whether this is breast surgery; it would not be usual practice in Australia to perform breast surgery on a woman presenting with metastatic disease and this rate appears very high for palliative procedures. Similarly rates of radiation are 54.8% which may have been adjuvant or palliative.

Sponsor Response

The breakdown of breast vs. non-breast surgery for each treatment arm from Study A5481003 are summarised below:

Table 33: Breast versus non-breast surgery for each treatment arm from Study A5481003

Patients with Prior Surgery	Palbociclib + Letrozole (n=68)	Letrozole (n=66)
	n (%)	n (%)
Prior breast cancer surgery	56 (82.4)	51 (77.3)
Prior non-breast cancer surgery*	34 (50.0)	33 (50.0)

*Includes biopsies performed for breast cancer
Table 1003.313.1

The number and percentage of patients who received adjuvant therapy post breast cancer-related surgery by treatment arm are summarised below:

Table 34: Number and percentage of patients who received adjuvant therapy post breast cancer-related surgery by treatment arm

Patients with Prior Breast Cancer-Related Surgery	Palbociclib + Letrozole (n=56)	Letrozole (n=51)
	n (%)	n (%)
Adjuvant Therapy		
Yes	36 (64.3)	34 (66.7)
No	20 (35.7)	17 (33.3)

Table 1003.313.3

Evaluator comment:

As the prior non-breast cancer surgery category includes biopsies for breast cancer, it is not surprising that this rate is around half in each arm. The rate of breast cancer surgery is high compared to what the first round evaluator would have expected, it would seem, but is even between arms. Perhaps this high rate was related to the high rate of de novo metastatic disease in this study population as a whole (almost half).

Radiation therapy appears to have been predominantly adjuvant (though it isn't entirely clear that adjuvant therapy as it is included in the second table refers to adjuvant *radiation* therapy only).

The sponsor's response is accepted.

12.5.3 Efficacy clinical question 3

QUESTION 3

Study 1003: Please provide a breakdown of the numbers of the 17.9 % patients for each arm who received no endocrine therapy following an earlier ER-positive breast cancer diagnosis.

The first round clinical evaluator comments relevant to this question were:

66.7% had either relapsed within 12 months of completion of adjuvant treatment or had de novo disease, and these two groups have been put together for stratification purposes.

The latter (49.1%) would be expected to have a better prognosis than those relapsing after treatment, which makes this stratification factor likely to lead to prognostic factor imbalances – indeed this did happen with more patients with de novo disease in the palbociclib and letrozole arm;

The rates of prior antihormonal therapy (Table 22, CSR) indicate that 110/165 patients (67%) in the Phase II study received no prior hormonal therapy that is, 17.9% did not receive endocrine therapy following a diagnosis of ER-positive breast cancer – it is standard practice in Australia to offer endocrine therapy to women with ER-positive breast cancer, and may influence baseline response rates to any endocrine therapy commenced in the metastatic setting;

Sponsor Response

The sponsor would like to clarify the number of patients with no prior endocrine therapy is not 17.9% and cannot be derived as described by the evaluator in the Clinical Evaluation Report (page 44) by 'subtracting the 49.1% de novo group from 67% of the total population with no hormonal therapy' as 67% represents a subset of patients distinct from those who received prior systemic therapy as displayed in Table 22 of the Study A5481003 CSR. Table 22 is included below for reference.

In Study 1003, there were 57 patients (67.9%) in the palbociclib plus letrozole arm and 53 (65.4%) patients in the letrozole arm who received no prior endocrine therapy.

The number of patients who received no prior endocrine therapy is derived by subtracting the subset of patients who received 'Antihormonal' therapy in Table 22 of the CSR from the total number of patients in each arm (n=27 subtracted from N=84 is 57 patients and n=28 subtracted from N=81 is 53 patients).

Of the 57 patients from the palbociclib plus letrozole arm and 53 patients from the letrozole arm with no prior endocrine therapy, there were 13 patients and 16 patients, respectively, who received other systemic therapy. The numbers are summarised below:

Table 35: Patients with no prior systemic therapy and patients who received other systemic therapy

Patients with No Prior Endocrine Therapy	Palbociclib + Letrozole (n=57)	Letrozole (n=53)
	n (%)	n (%)
Received no prior systemic therapy	44 (77.2)	37 (69.8)
Received other systemic therapy	13 (22.8)	16 (30.2)

Table 1003.321.1

Evaluator comment:

The sponsor's clarification is accepted.

There were a total of 110 out of 165 subjects (~67%) in the Phase II ITT population for this study who had not been treated with prior hormonal therapy. They made up 67.9% (57/84) of the active arm and 65.4% (53/81) of the comparator arm.

Table 36: Rate of previous or endocrine systemic therapy

	Palbociclib + Letrozole (n=84)	Letrozole (n=81)
Prior endocrine therapy	27 (32.1%)	28 (34.6%)
Prior systemic therapy other than endocrine	13 (15.5%)	16 (19.8%)
Prior systemic therapy of any kind (total)	40 (47.6%)	44 (54.3%)

Derived from the sponsor's response, as tabulated above, the rate of previous systemic therapy was higher in the comparator arm by approximately 6.7%. The imbalance of de novo metastatic disease (a confounder also associated with better outcomes) between the arms was identical to the imbalance in previous systemic therapy between arms; these were likely the same individuals.

In the context of the efficacy outcomes reported, where investigator results were borderline and BIRC results gave a hazard ratio crossing 1, such an imbalance in a key prognostic factor introduces further uncertainty about the validity of the findings of trial 1003.

The findings of trial 1003 are not pivotal to registration, nor involved in the information presented in the PI, and thus its flaws are not further relevant.

12.5.4 Efficacy clinical question 4

QUESTION 4

Study 1003: The data presented in the CSR for investigator and BICR censoring respectively, differ from those data presented for the BICR censoring in Table 26, p69 and Table 27, p70 of the FDA report (publicly available on the website) for Study A5481003. The sponsor is requested to provide an explanation for all differences in the data presented in the dossier versus the tables in the FDA report, including but not limited to, the higher AE rates, clinical progression, withdrawal of consent reported in the FDA report noting that the FDA table was generated in response to an FDA query on 28 Feb 2014.

Sponsor Response

> *The differences between the sponsor and FDA classifications for some of the reasons for censoring in the PFS analyses are highlighted in Table 1 and Table 2. Twelve patients (highlighted in red) were classified as 'No on-study disease assessments' as the censoring reason by the sponsor in the PFS analysis based on investigator assessment (Table 1), but were classified as other reasons by the FDA. Similarly, 10 patients (highlighted in red) were classified as 'No on-study disease assessments' by the sponsor in the PFS analysis based on BICR data (Table 2), but were classified as other reasons by the FDA.*
>
> *A patient's objective disease progression time can be censored for multiple reasons in the PFS analysis depending on what happens to the patient in the study. Sometimes, there can be multiple reasons for censoring. In the programming algorithm for censoring reasons, the sponsor assigns 'No on-study disease assessments' with a higher priority if there are multiple reasons for censoring. Patients with 'No on-study disease assessments' as the censoring reason are those patients who permanently withdrew from the study for various reasons (for example, adverse event, consent withdrawn) prior to the first scheduled tumour assessment, and their PFS times is censored at Day 1. Patients classified as 'No on-study disease assessments' in both PFS analyses (investigator assessment and BICR) had*

their PFS times all censored at Day 1. In the FDA analysis, these patients were classified with the specific reason for withdrawal as described in Tables 3 and 4 below.

In both the sponsor and FDA analyses, patients were censored at Day 1, and more importantly, both analyses showed the same number of patients with PFS events and censoring; therefore, any differences between the sponsor and FDA classifications for the reasons for censoring had no impact on the PFS analyses and the results were consistent.

Evaluator comment:

The sponsor's response is accepted.

12.5.5 Efficacy clinical question 5

QUESTION 5

For Study 1003, the sponsor is requested to provide a breakdown for both the control and experimental arms of the numbers and percentage where BICR was performed prospectively versus retrospectively.

Sponsor Response

The Blinded Independent Central Review (BICR) evaluation was incorporated in the Protocol Amendment 6 (dated 08Nov2012) for Study A5481003 after discussion with the US FDA in September 2012. At this time, the protocol had fully accrued all 165 randomised patients. There were tumor assessment imaging scans collected in a retrospective manner upon the implementation of the protocol amendment and prospectively for the assessments performed after the implementation of the protocol amendment at each participating site. The breakdown of numbers and percentage of the visits/time points for which BICR was performed retrospectively (on or prior to 08Nov2012) vs. prospectively (after 08Nov2012) are summarised below:

Table 37: Numbers and percentage of the visits/time points for which BICR was performed retrospectively (on or prior to 08Nov2012) vs. prospectively (after 08Nov2012)

	Palbociclib + Letrozole (N=945)	Letrozole (N=661)
	n (%)	n (%)
Visits performed on or prior to 08Nov2012	708 (74.9)	525 (79.4)
Visits performed after 08Nov2012	237 (25.1)	136 (20.6)

Table 1003.317.3
N=number of visits/timepoints

Evaluator comment:

The reason for asking this and the following clinical question was that the first round evaluator identified investigator assessment as a significant potential source of bias in an open-label study such as this, and BICR was not undertaken from the outset of the study.

This response shows that there was a slightly higher rate of retrospective BICR sampling in the control arm. Whether this is of any significance is not clear, as one would expect BICR to remain unbiased whether images were collected before or after the decision was made that these should be reviewed centrally, as it is not in the taking of the image but in its review that the bias might be expected to manifest.

The sponsor's response is accepted.

12.5.6 Efficacy clinical question 6

QUESTION 6

For Study 1003, the sponsor is requested to provide concordance rates between the investigator and BICR by imaging modality eg bonescan, CT, MRI for each lesion type that is, bone lesions, visceral, other.

Sponsor Response

> *A patient can have more than one lesion types and multiple lesions of the same type. The investigator and BICR may observe different lesion types for a patient. Even if they observed the same lesion type, they may look at the different lesions.*
>
> *The concordance rates between the investigator and BICR for bone lesions, visceral, other are 88.7%, 76.1%, and 81.1%, respectively.*
>
> *The concordance rate is defined as*

The total number of patients with the same lesion type either observed or not observed by both investigator and BICR divided by the total number of patients who had tumour assessment by both investigator and BICR

Evaluator comment:

The reason for asking this and the previous clinical question was that the first round evaluator identified investigator assessment as a significant potential source of bias in an open-label study such as this.

This response shows the rates of concordance were consistently between 75 and 90%. These rates are not unexpected, given the fraction of cases requiring adjudication for the central reviewers (that is, the rate of discordance between blinded reviewers) has been shown to be around 40%.[17]

The sponsor's response is accepted.

12.5.7 Efficacy clinical question 7

QUESTION 7

For Study A5481008, the sponsor is requested to state whether the CRF or Impala data was used to define populations for the primary efficacy analysis of the data, and how such discrepancies are handled in the statistical analysis. Noting that the 2016 ASCO meeting presentation of the latest results for Study 1008 (including BICR-reviewed data) by Dr Richard Finn used the CRF data, the sponsor is requested to provide a comment on the choice of this dataset over that presented for the primary analyses in this top-line summary.

Sponsor Response

> *Results provided in the top-line summary previously submitted in the registration application were stratified based on data from the study interactive randomisation technology (called 'IMPALA'). As the randomisation in IMPALA occurred prior to the data being source verified by the sponsor, there were minor discrepancies in the distribution of patients by the stratification factors following data cleaning activities based on the CRF data. For this reason, the CRF source document verified data were considered more accurate and were used in all subsequent submission reports. The distribution of patients by the 3 stratification factors assessed based on investigator chosen-strata reported in IMPALA as well as derived from the data entered on the appropriate CRFs are summarised in Table 1 below.*

[17]Ford RR, O' Neal M, Moskowitz SC, Fraunberger J (2016) Adjudication Rates between Readers in Blinded Independent Central Review of Oncology Studies. J Clin Trials 6:289. doi: 10.4172/2167-0870.1000289

As specified in the statistical analysis plan, the primary PFS analysis was performed using Disease Site (Visceral, non-visceral) recorded on IMPALA as the stratification factor to estimate the Hazard Ratio and to calculate the p-value. While Disease Free Interval and Prior Hormonal Therapy were also stratification factors for patient randomisation, they were not used for the primary PFS analysis.

A sensitivity analysis was performed to evaluate whether there was a difference when using CRF data for Disease Site as the stratification factor (see sensitivity analysis #4 in the Study A5481008 CSR provided). For sensitivity analysis #4, the results showed a HR of 0.572 with 95% CI (0.459, 0.713) similar to the primary PFS analysis which showed a HR of 0.576 with 95% CI (0.463, 0.718).

In conclusion, the minor discrepancies between the IMPALA data and CRF data on stratification factors did not have an impact to the primary PFS analysis.

Evaluator comment:

The sponsor's response is accepted.

12.5.8 Efficacy clinical question 8

QUESTION 8

For Study A5481008, what subgroups were prespecified for efficacy analyses?

Sponsor Response

The Study A5481008 Statistical Analysis Plan (SAP) version 2.0 was submitted in the initial registration application in Module 5.3.5.1 for Study A5481008. Version 3.0 was updated for study Protocol amendment 7 and is provided herein.

The SAP specified that the potential influences of baseline patient characteristics such as age, ethnic origin, ECOG performance status, geographical region, selected biomarkers, and stratification factors on the primary PFS, OS, and OR endpoints may be evaluated. In addition, to assess the impact of the concomitant use of proton pump inhibitors and the impact of palbociclib administered under fasting conditions, PFS was also evaluated in the population excluding patients who took proton-pump inhibitors and/or any other antacid medications concomitantly with study drug under fasting conditions during the active treatment phase.

Evaluator comment:

The sponsor's response is accepted.

12.5.9 Efficacy clinical question 9

QUESTION 9

How many patients 'in follow up for progression' in Study A5481008 were still on study drug in each arm?

The first round clinical evaluator comments relevant to this question were:

The censoring rates indicate similar absolute differences in discontinuations without disease progression across both arms. It is unclear how many patients 'in follow up for progression' were still on study drug (Clinical Questions) as this could include some where progression had not been established radiologically yet.

Clinical worsening in the absence of objective radiologically confirmed progression was handled differently in this study compared with Study 1003 and was required to be declared as PD only once there was radiological confirmation; clinical progression and

discontinuation due to suspected progress was to be declared due to global deterioration and the numbers are even in both arms

Sponsor Response

As of the data cutoff date 26 February 2016 a total of 257 patients were still on study drug: 199 patients in the palbociclib + letrozole arm and 58 in the placebo + letrozole arm.

Evaluator comment:

This question pertains to one of the categories which tabulates the reasons for censorship in each arm, as it relates to the Kaplan-Meier curve of PFS in Study 1008.

The numbers cited by the sponsor are identical to the totals cited [table not in this report] under the category 'in follow up for progression'. Therefore it appears that this is an error of communication, whereby the first round evaluator thought that 'in follow up for progression' referred to subjects in whom progression *had occurred*, and they were being followed up regardless. However, it appears the meaning of this category is actually 'in follow up/not yet progressed' that is, *waiting* to see progression which had not yet occurred.

This meaning should be confirmed by the formal review of Study 108. See section 13.

12.5.10 Efficacy clinical question 10

QUESTION 10

When submitting the CSR for Study A5481008, the sponsor is requested to provide details of the deaths of each patient who died without evidence of disease progression if not already included in that document. This is recommended to be done as a second NCE application.

Sponsor Response

Study A5481008 Clinical Study Report (CSR) is provided to address the request for details of the deaths of patients who died without evidence of disease progression.

Deaths on study (that is, on treatment, included up to 28 days after the last dose of blinded therapy) as well as deaths that occurred during the follow-up period (that is, more than 28 days after the last dose of blinded therapy) as of the data cutoff date of 26 February 2016, are reported in Section 12.3.1.1 Study A5481008 CSR.

There were 7 (1.6%) patients in the palbociclib plus letrozole group and 2 (0.9%) patients in the placebo plus letrozole group who died on study without evidence of disease progression and were considered by the Investigator to be due to other/unknown causes (Table 49 Study A5481008 CSR).

During the post-treatment follow-up period, 7 (1.6%) patients died in the palbociclib plus letrozole arm for reasons other than progression and 2 (0.9%) patients in the placebo plus letrozole arm (Table 49 Study A5481008 CSR). Details and causality of deaths that were not due to disease progression are summarised in Tables 50 and 51 Study A5481008 CSR.

CIOMS narratives for these patients are provided in Section 14.3.3.1 Study A5481008 CSR.

Of note, none of the deaths without documented progression occurring in the palbociclib plus letrozole arm either on study or during the follow-up period was considered to be treatment – related by the Investigator (Table 50 Study A5481008 CSR).

Evaluator comment:

The sponsor indicates that the details of the deaths of each patient who died without evidence of disease progression have been included in the CSR document for Study 1008.

The sponsor's response is accepted.

12.5.11 Efficacy clinical question 11

QUESTION 11

Uncertainty exists as to whether there is a benefit for those with de novo metastatic disease. Whether this represents an increased responsiveness to the control arm which generally did better than in other subgroup analyses cannot be checked against the group who had received no prior systemic treatment for their disease (irrespective of stage of presentation) as these data could not be located in the Tables or Top-line summary. Provision of these data is requested to be included when the CSR is lodged with the TGA (second NCE application recommended).

Sponsor Response

An updated forest plot of subgroup analyses of PFS based on the CRF data is provided in Figure 1 for Study A5481008.

Prolongation of PFS in the palbociclib plus letrozole arm was demonstrated in all prespecified subgroups based on the stratification factors derived from the data recorded on the CRFs and baseline characteristics (Figure 1).

A reduction in the risk of disease progression or death in the palbociclib plus letrozole arm compared with the placebo plus letrozole arm was observed in all individual patient subgroups regardless of age, race, prior treatment, length of disease-free interval (see below for additional details), type of disease, and ECOG performance status at baseline.

This reduction in the risk was evident for all 3 disease-free interval subgroups: de novo metastatic disease (HR of 0.674 [95% CI: 0.457, 0.993]), disease-free interval ≤12 months since completion of prior (neo) adjuvant therapy (HR of 0.501 [95% CI: 0.329, 0.761]), and disease-free interval >12 months (HR of 0.516 [95% CI: 0.365, 0.731]).

Of note, using the data from the study interactive randomisation technology as previously provided in Figure 3 Study A5481008 Top Line Summary (submitted in the initial registration application), the upper bound of the 95% CI for patients with de novo metastatic disease was slightly above 1.0.

However, using the more accurate CRF-derived data (see Efficacy Question 7), the upper bound of the 95% confidence interval of HR for patients with de novo metastatic disease was <1.0 (Figure 1). Therefore the results from all 3 disease-free interval subgroup analyses were statistically significant.

The sponsor reviewed a number of the potential factors that may have influenced the HR estimate of the subgroup of patients with de novo metastatic disease. A comparison of patient key demographic and baseline disease characteristics across the disease-free interval (DFI) patient subgroups are summarised in Table 2.

All baseline patient demographic and disease characteristics are generally well-balanced between both treatment arms for each of the DFI subgroup. One notable exception is the proportion of patients with and without measurable disease in the de novo metastatic disease subgroup compared to the other 2 DFI subgroups. Patients with measurable disease represented approximately 90% of the de novo metastatic disease subgroup but approximately 70% in each of the other 2 DFI subgroups (Table 2). While a reduction in the risk of disease progression or death in the palbociclib plus letrozole arm compared with the placebo plus letrozole arm was observed regardless of the presence of measurable disease or not, the observed HR was higher for patients with measurable disease (HR of 0.663 [95% CI: 0.517, 0.849]) than for patients with no measurable disease (HR of 0.350 [95% CI: 0.215, 0.568]) at baseline. This observed HR for patients with measurable disease was similar to that observed for patients with de novo metastases of which 90% had measurable disease. Additionally, 151 out of the 157 patients with no measurable disease

were patients with bone-only disease for whom a statistically significant reduction in the risk of disease progression or death in the palbociclib plus letrozole arm compared with the placebo plus letrozole arm was observed (HR of 0.363 [95% CI: 0.221, 0.594]) (Figure 1).

Additionally, as of the data cut off (26 Feb 2016), in the de novo metastatic subgroup the percentage of patients with events in the palbociclib plus letrozole arm versus placebo plus letrozole was 39.5% vs.51.9%, respectively. By comparison, the percentage of patients with events in each treatment arms in the ≤ 12 months and > 12 months DFI subgroups were 53.6% versus 77.1% and 40.4% versus 61.3 %, respectively. It is important to note that a smaller percentage of patients with de novo metastatic disease had a PFS event in the placebo plus letrozole arm (51.9%) compared to the other two DFI subgroups where greater percentages of patients with events were observed (77.1% and 61.3%, respectively) suggesting that placebo plus letrozole data for the de novo metastatic subgroup may not be as mature as the data from the other two DFI subgroups to determine the median PFS for patients with de novo metastatic disease. As there were patients still on treatment at the time of data cutoff, additional PFS events will occur and thus, a future PFS analysis may provide further confirmation of the clinical benefit of palbociclib plus letrozole in this subgroup of patients.

Results of the prespecified subgroups analyses based on stratification factors derived from the data recorded on the CRFs and baseline demographics and disease characteristics, supporting the consistency of PFS benefit findings within the study population are detailed in the A5481008 CSR.

In conclusion, the higher percentage of patients with measurable disease in the de novo subgroup and the maturity of the data at the time of the data cutoff, offer possible explanations for the higher observed HR for this subgroup than that observed for the other 2 DFI subgroups.

Evaluator comment:

The HR for the subgroup of patients with metastatic disease at diagnosis (de novo) for the active versus placebo arm falls just inside nominal statistical significance (0.674 [95% CI: 0.457, 0.993]), when the stratification is performed using data that has been cleaned based on CRF information rather than unaltered data from an interactive response technology (IRT) system 'IMPALA' (see Question 7 and response). With the IMPALA-based stratification, the result was HR 0.729 (95% CI: 0.486, 1.093; p=0.063).

In terms of the meaning of this for statistical significance, even with the cleaned data this result is only just borderline significant.

However, it is agreed that the rate of PFS events in the placebo arm for the de novo metastatic subgroup is lower than those in the placebo arms whose disease was recurrent after remission (for whatever duration). It is possible that the data is not yet fully mature and additional evidence of PFS benefit in the de novo group may accrue with further follow up.

The relevance of measurable disease and bone-only disease are not clear from this analysis – these may be confounders if on the same causal pathway as de novo disease, but that subgroup analyses for them were significant does not change the borderline significance of the de novo subgroup analysis.

Whilst there is not strong evidence that palbociclib adds to efficacy of letrozole in de novo metastatic disease, there is some, and there is no biological reason to suspect that de novo metastatic disease should be expected to respond any differently to those in the other categories of duration since remission.

Given that the data cut-off date was ten months ago, a reanalysis for efficacy in the de novo subgroup may be valuable but is not necessary to support registration. The submission of

further data to this point when available could be made a condition of registration.

12.5.12 Efficacy clinical question 12

QUESTION 12

For Study 1023, the anticipated dropout rate was high at 25%, particularly for those with metastatic disease and a high degree of motivation to continue treatment if their disease is not progressing. The sponsor is requested to provide a rationale for this high rate. Was this to anticipate side effects related to the use of fulvestrant, the administration of which is associated with significant discomfort?

Sponsor Response

> *The 25% anticipated dropout rate was an estimation and was only used at the study design stage for planning purposes. For a given Hazard Ratio (HR) of PFS to be detected in the study, a higher dropout rate would not increase the number of PFS events but would extend the follow-up time for cumulating events. This would result in the enrollment of more patients in order to shorten the follow-up time. In fact, for the analysis of PFS only about 11% of patients' had PFS times that were censored for various reasons that could be considered as drop out (see yellow highlighted rows in Table 1 below). This rate was much lower than the estimated rate of 25% used for planning purposes.*

Evaluator comment:

The sponsor's response is accepted.

12.5.13 Efficacy clinical question 13

QUESTION 13

In the update report using an earlier cut-off date of 16 March 2015, discontinuations due to withdrawal of consent occurred in 1.2 % (4 patients) in the palbociclib and fulvestrant arm but are now reported as 0.9% (3 patients) with a later cut-off date - the sponsor is requested to explain why there are now fewer presented (Clinical Questions).

Sponsor Response

> *The review and cleaning of data is an ongoing process which is active until all the patients complete their treatment and their survival status is reported. In particular, at the time of the data cutoff date of 05 December 2014 which was used for data reporting in the CSR, most patients were still on treatment and site visits for data review were conducted very frequently. Therefore, some data modifications may have occurred due to query resolution, source data verification or additional information that may become available to the investigators after the data snapshot for data reporting.*
>
> *During subsequent data reviews, it was identified that the investigator reported 'withdrew consent' as reason for treatment discontinuation for Patient [information redacted] (Table 1023.683.1; data cutoff date 16 March 2015), but this patient refused to continue treatment and accepted to proceed with the follow-up visits, thus making the reason for treatment discontinuation* ***(that is,*** *'withdrew consent') inappropriate. A query was raised and the investigator changed the reason for treatment discontinuation to 'subject refused continued treatment for reason other than adverse event', which was the reason for treatment discontinuation in the clinical database as of the data cutoff date of 23 October 2015 (Tables 1023.683.2 and 1023.683.3).*

Evaluator comment:

The sponsor's response is accepted.

12.5.14 Efficacy clinical question 14

QUESTION 14

The sponsor included an updated PFS analysis for Study 1023, which also included updated OR, DoR and clinical benefit rate. None of these analyses were supported by BICR-derived analyses; the sponsor is requested to provide the BICR analyses for these endpoints for evaluation or state that none was done.

Sponsor Response

In Study A5481023 a sample-based Blinded Independent Central Review (BICR) approach was to be implemented as an auditing tool for PFS as per the protocol and the Statistical Analysis Plan (SAP). The objective of this approach was to corroborate the results of the primary investigator-assessed PFS analysis and to evaluate for any potential bias. The BICR audit approach was not intended to provide an alternative means of definitive analysis. Of note, this approach was discussed with and agreed upon by both the US FDA and EU EMA.

The External-Data Monitoring Committee met on April 2015 to review the results of the prespecified interim analysis (data cutoff date 05 December 2014) and concluded that the study met its primary objective of prolonging the investigator-assessed PFS in the palbociclib plus fulvestrant arm compared to the placebo plus fulvestrant arm. This interim analysis was therefore considered the primary analysis of PFS and a PFS analysis based on BICR data from the randomly sampled audit subset (n=211) was then conducted. Although not required by protocol and SAP, the PFS analysis based on the BICR audit approach was again performed at the time of the first PFS update (data cutoff date 16 March 2015) to further corroborate the investigator–assessed PFS analysis on a more mature dataset. The results of updated PFS analysis based on BICR audit approach (n=211) at the data cutoff date of 16 March 2015 are presented in Table 1 and the results of secondary efficacy analyses of Objective Response and Clinical Benefit Rate in Table 2 and Duration of Response in Table 3.

The results of the updated PFS analysis based on BICR audit approach as of the data cutoff date of 16 March 2015 were consistent with the primary and updated analyses of the ITT population and with the BICR data at the data cutoff date of 05 December 2014. The HR was 0.375 (95% CI: 0.233, 0.604; stratified 1-sided p-value 0.000015) in favor of palbociclib plus fulvestrant. The median PFS was not reached (NR) (95% CI: 10.9, NR) for the palbociclib plus fulvestrant arm and was 3.8 months (95% CI: 3.4, 9.3) for the placebo plus fulvestrant arm (Table 1023.412.3).

Also, based on data as of the cutoff date of 16 March 2015, the differential discordance, as determined by the Early and Late Disagreement Rates (20.05% and -21.43%, respectively), was not suggestive of any investigator bias in favor of the palbociclib plus fulvestrant arm (Table 1023.412.9).

Based on the above findings which confirmed the consistency between the investigator-assessed PFS with the BICR-based audit approach, an additional BICR assessment of the second updated PFS analysis from the 23 October 2015 cutoff date was not considered necessary by the sponsor.

Evaluator comment:

The sponsor's response is accepted.

12.5.15 Efficacy clinical question 15

QUESTION 15

Table 16, CSR for Study A5481023 includes data about the recurrence type. This includes 'newly diagnosed' as a significant category (17.7% of total population) amongst breakdown by anatomical site which makes it difficult to establish how many in the study had local or locoregional disease only. The sponsor is requested to provide:

a. A breakdown of numbers in each arm this is a population identified in the indication;

b. The following efficacy outcomes for those in each arm with local or locoregional disease: median PFS, OR, DoR, CBR.

Sponsor Response

The sponsor has provided a listing reporting sites of disease for each patient categorized as 'newly diagnosed' by the investigators (Table 1023.679.1).

Most patients in both the palbociclib plus fulvestrant arm and in the placebo plus fulvestrant arm had a distant recurrence (for example, bone involvement in the disease). One patient in the palbociclib plus fulvestrant arm was found to meet the definition of 'locoregional recurrence' ([information redacted]). This patient had a recurrence in the chest wall with only 2 superficial lesions that were followed during the study through physical examinations. This patient was added to the other patients with Local recurrence and Locoregional recurrence to provide the requested efficacy outcomes of the subset of patients with local/locoregional recurrence.

The analyses presented in this response were conducted on the dataset corresponding to the data cutoff date of 23 October 2015. Some minor differences in the number of patients with local/locoregional recurrence reported in the CSR (data cutoff date 05 December 2014) and those reported in the present analyses (data cutoff date 23 October 2015) were due to the data review and cleaning process. This process is ongoing because there are patients in the study who are still on treatment.

Progression-free survival (PFS) of patients with local/locoregional recurrence is presented in Table 1, and objective response rate (ORR), duration of response (DoR) and clinical benefit response rate (CBRR) in Table 2.

As shown in Table 1 the benefit of palbociclib plus fulvestrant versus placebo plus fulvestrant in significantly prolonging PFS is also apparent in patients with local/locoregional recurrence. A numerically higher ORR which did not reach statistical significance was demonstrated for palbociclib plus fulvestrant versus placebo plus fulvestrant (Table 2). This is very likely due to the small number of patients with tumor response in the subset of patients with local/locoregional recurrence. Median DoR was similar for the 10 patients in the palbociclib plus fulvestrant arm and the 3 patients in the placebo plus fulvestrant arm who had a tumor response. The analysis of CBR (CR, PR and SD≥ 24 weeks) in the subset of patients with local/locoregional recurrence demonstrated a numerically higher CBR for palbociclib plus fulvestrant compared with placebo plus fulvestrant (Table 2), which did not reach statistical significance.

In conclusion, a clinically and statistically significant improvement in PFS of palbociclib plus fulvestrant over placebo plus fulvestrant was observed also in the subset of patients with local/locoregional recurrence, benefit that was also maintained in ORR and CBR.

Evaluator comment:

Table 1023.679.1 is not reproduced in this CER but has been reviewed. As described by the sponsor, there was only one subject in this listing (subject [information redacted]) who had only local disease recurrence.

The sponsor's response is accepted.

12.5.16 Efficacy clinical question 16

QUESTION 16

This question only needs to be addressed in the s31 response if the sponsor wishes to retain the PI statements about quality of life in the Clinical trials section:

1. a justification of the clinical significance of the presented results against the prespecified criteria in the SAP;
2. to indicate meaningful completion rates, please provide the number and percentage of patients who completed all questions of the EORTC-QLQ-C30 out of the PRO analysis in each arm;
3. please provide the number / percentage of patients for whom pro-rating was undertaken due to missing data in each arm.

Sponsor Response

> *The sponsor has acknowledged the TGA comments and agreed to remove the quality of life claims made based on Global Health Status/QoL and emotional functioning, requested in PI Question 19.*
>
> *The sponsor proposes to replace the above mentioned information with a prespecified time to event analysis for deterioration in pain (TTD), defined as first occurrence of an increase of at least 10 points in pain symptom scores.. Statistically convincing and plausible results were achieved with a difference in median time to deterioration of 8.0 versus 2.8 months, HR 0.6, p <0.001.*
>
> *The TTD statement proposed in the PI aligns with the approved SmPC. The sponsor considers this useful information for prescribers and hence proposes it be included in the Product Information:*
>
> *'Time to Deterioration (TTD) was prespecified as time between baseline and first occurrence of ≥ 10-point increase from baseline in pain symptom scores. Addition of palbociclib to fulvestrant resulted in a symptom benefit by significantly delaying TTD in pain symptom scores compared with placebo plus fulvestrant (median 8.0 months versus 2.8 months; HR of 0.64 [95% CI: 0.49, 0.85]; p<0.001).'*

Evaluator comment:

The evaluator referred to the answer to a question raised regarding the PI.[18]

[18]Sponsor Response to the relevant PI question: The sponsor acknowledges the evaluator's position regarding the claims of Global Health Status/QoL and emotional functioning in the Product Information and recognises that the change from baseline does not exceed the 10 point threshold that has been established as a minimum to reach clinical significance. As such the sponsor has removed the claims from the PI.
Instead the sponsor proposes to include information on a prespecified time-to-event analysis for deterioration in pain (TTD), defined as first occurrence of an increase of at least 10 points in pain symptom scores. 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.
"Time to Deterioration (TTD) was prespecified as time between baseline and first occurrence of ≥10-point increase from baseline in pain symptom scores. Addition of palbociclib to fulvestrant resulted in a symptom benefit by significantly delaying TTD in pain symptom scores compared with placebo plus fulvestrant (median 8.0 months versus 2.8 months; HR of 0.64 [95% CI: 0.49, 0.85]; p<0.001)."
The sponsor considers this useful information for prescribers and the TTD statement proposed is approved in the SmPC.

12.5.17 Efficacy clinical question 17

QUESTION 17

In Study A5481023, no information was found by the evaluator as to how many of the biopsy samples used in the central testing were from a biopsy sample taken following their most recent episode of progression to determine ER/PR/HER2 status – the sponsor is requested to provide this information as it has been shown that a discordant rate between primary and secondary breast cancers has been reported to be as high as 25-30%.

Sponsor Response

Study A5481023 required eligible patients to provide a tissue biopsy sample taken at the time of presentation with recurrent or metastatic disease. A de novo biopsy was required only if no archived tissue of metastatic disease was available at study initiation. Archival tissue of primary disease was acceptable only for patients with bone only disease and for those patients who entered the study just after disease progression while receiving adjuvant therapy.

The protocol did not require the collection of the exact tumor biopsy site information including whether it was a recent metastatic site or not.

The time between the date of patient tumor biopsy and the date of randomisation was less than 1 month for 19% of tissue samples, between 1 and 2 months for 11% of samples, and between 2 and 6 months for 8% of samples. Twelve percent of tissue samples were biopsied more than 6 months and within 12 months before randomisation. There were 50% tissue samples biopsied more than 12 months before randomisation.

The sponsor would like to comment that while it is recognized that discordance in human epidermal growth factor receptor 2 (HER2) status and hormonal receptors status between the primary breast tumor and the corresponding metastatic lesion is frequent, mainly when adjuvant chemotherapy was the treatment of choice, it is not demonstrated that additional modifications of hormonal and HER2 receptors status occur when the disease is already metastatic (1).

Current best practice is to check receptor status from the most accessible metastatic lesion before selecting the treatment for a patient with metastatic disease. For these reasons, and also considering the objective difficulties to biopsy all the metastatic lesions of a patient, the sponsor adopted the current best practice to rigorously select patients to be eligible for the study.

References

1) Curtit E, Nerich V, Mansi, L et al. Discordances in Estrogen Receptor Status, Progesterone Receptor Status, and HER2 Status Between Primary Breast Cancer and Metastasis. Oncologist. 2013 Jun;18(6): 667–674

Evaluator comment:

- Site of biopsy for the sample that was used to identify hormone receptor status was not required to be recorded per protocol.
- Proportion of biopsies that were de novo at study entry versus archived metastatic tissue versus archived primary tissue has not been provided.
- In Study 1003, a large proportion of subjects (22.7% of the ITT population) had bone-only disease at diagnosis of metastatic disease.
- For half of the samples the biopsy that was used was at least a year old prior to randomisation, suggesting a high proportion of samples were archival tissue. Whether these were of secondary or primary disease is not clear.

- On the subject of discordance:
  - A 2016 study of tumour expression profiles found 'primary tumors and metastases were highly concordant for HER2 (84 %, p = 1.13E-08), ER (90 %, p = 3.26E-10) and PR (83 %, p = 2.09E-09) and ER-and PR-positive metastases were significantly found to be of visceral origin (p = 0.03, p = 0.02).'[19]
  - A literature review on the topic in 2015 found that PR varied more than ER, at a rate of 10% to 30% for ER and 20% to 50% for PR.[20] Loss of PR co-expression, that is, ER-positive/PR- is often seen in subjects who have developed resistance to an endocrine agent like tamoxifen.[21]
  - A 2014 meta-analysis notes that 'clinical management of breast cancer metastasis has been based largely on the initial assessment of the primary tumor.'[22] In this study, a large proportion of discordance in hormone receptor status was attributed to the 'limited accuracy of receptor assays'. They state 'The corrected discordance in ER between primary tumors and recurrent or metastatic lesions was 12.4%, and there were more positive-to-negative changes (10.1%) than negative-to-positive changes (2.3%). Similar patterns were observed for progesterone receptor (PR), although the overall discordance in PR was higher.'
- In the worst case scenario, if all of the tumour samples that were at least a year old by time of randomisation (~50%) were archival primary tissue, then it is likely that 5% to 15% of the total study population could have had discordant HR profiling.
- Subjects more likely to have discrepancy would be those who'd had prior chemotherapy or endocrine therapy.
- The ASCO guidelines on the use of biomarkers to guide decisions on systemic therapy for women with metastatic breast cancer (published April 2015)[23] state that 'if discordances are found, evidence is lacking to determine whether outcomes are better with treatment regimens based on receptor status in the metastases or the primary tumor.'
- The biopsy sources in Study 1008 likely to be reflective of real-world practice and give reasonable external validity to the findings. It is also more likely that changes in receptor status went from HR+ to HR- than the other way around, making a type 2 error more likely than a type 1 error, so it is unlikely that this has led to an overestimation of effect.

[19] Aktas, B., Kasimir-Bauer, S., Müller, V., Janni, W., Fehm, T., Wallwiener, D., … on behalf of the DETECT Study Group. (2016). Comparison of the HER2, estrogen and progesterone receptor expression profile of primary tumor, metastases and circulating tumor cells in metastatic breast cancer patients. BMC Cancer, 16, 522. http://doi.org/10.1186/s12885-016-2587-4

[20] Rossi S, Basso M, Strippoli A, Dadduzio V, Cerchiaro E, Barile R, D'Argento E, Cassano A, Schinzari G, Barone C. Hormone Receptor Status and HER2 Expression in Primary Breast Cancer Compared With Synchronous Axillary Metastases or Recurrent Metastatic Disease. Clin Breast Cancer. 2015 Oct;15(5):307-12. doi:10.1016/j.clbc.2015.03.010. Review. PubMed PMID: 25922284.

[21] Yau, HSC. (2008) Oxidation Sensitive ER Transcriptional Regulation in Hormone-dependent Breast Cancer. Joint Doctor of Philosophy dissertation with the University of California, San Francisco.

[22] Sighoko, D., Liu, J., Hou, N., Gustafson, P., & Huo, D. (2014). Discordance in Hormone Receptor Status Among Primary, Metastatic, and Second Primary Breast Cancers: Biological Difference or Misclassification? The Oncologist, 19(6), 592–601. http://doi.org/10.1634/theoncologist.2013-0427

[23] Van Poznak, C, Harris, LN and Somerfield, MR. Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline (2015). doi: 10.1200/JOP.2015.005215. Available: http://ascopubs.org/doi/abs/10.1200/JOP.2015.005215

Conclusions:

It is unlikely that then lack of certainty around origin of biopsy has significantly biased the efficacy results of this study, although it does introduce some additional uncertainty.

The sponsor's response is accepted.

12.5.18 Efficacy clinical question 18

QUESTION 18

Study 1023: The sponsor is requested to provide 3 additional sensitivity analyses, presented as a forest plot with accompanying HRs comparing the ITT PFS:

a. A sensitivity analysis, removing all those who were ineligible for enrolment due to subsequently determined ER-/PR- or HER2+ disease by central testing, to determine whether there was any effect on the ITT PFS analysis;

b. A second sensitivity analysis excluding those 118 patients whose data were missing or inadequate for central laboratory testing of ER,PR or HER2 status as well as those who were deemed ineligible by central laboratory testing, is also requested to determine whether there was any effect on the ITT PFS analysis;

c. A subgroup analysis of those whose results were discordant, that is not ER-positive or was HER2-positive.

Sponsor Response

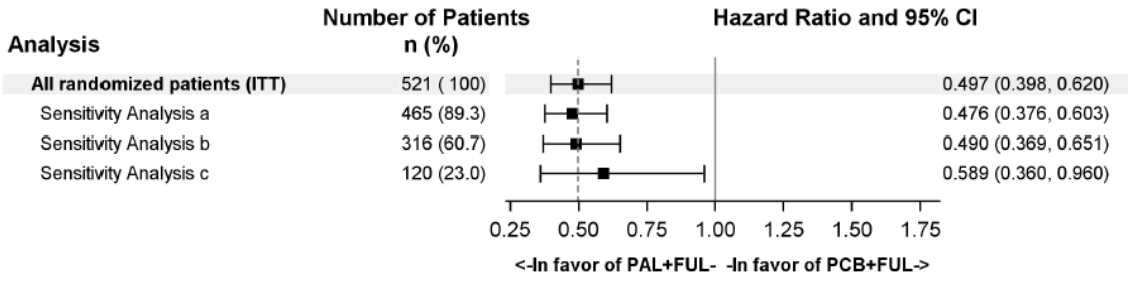
As requested, the sponsor provides the forest plot of the primary Progression-free survival (PFS) and 3 sensitivity analyses (Figure 13) based on the data cutoff date of 23 October 2015.

Sensitivity Analysis a. Excluding patients who do not meet the criteria of HR+ (ER-positive or PR-positive) and HER2- categorized by central laboratory.

Sensitivity Analysis b. Excluding patients who do not meet the criteria of HR+ (ER-positive or PR-positive) and HER2- categorized by central laboratory and patients whose data were missing or inadequate for central laboratory testing of ER,PR or HER2 status.

Sensitivity Analysis c. Patients with at least one discordant ER, PR, and HER2 status between local and central laboratories.

Figure 13: Forest plot of the primary and sensitivity analyses



Summaries of the 3 sensitivity analyses are provided in Tables 1 to 3.

In conclusion, the sensitivity analyses associated with exclusion of patients with differences in ER/PR/HER2 receptor status between local laboratories and central laboratory confirmed the benefit of palbociclib plus fulvestrant versus placebo plus fulvestrant in significantly prolonging PFS. The results of these sensitivity analyses further support the robustness of the primary PFS analysis.

Evaluator comment:

The sponsor's response is accepted.

12.5.19 Efficacy clinical question 19

QUESTION 19

The sponsor is requested to provide the number of patients in each arm whose tumour was ER-/PR-positive and the results (PFS, OR, DoR, and CBR) for these patients.

The round 1 clinical evaluator comments relevant to this question were:

The sponsor has also been requested to provide a breakdown of the numbers and outcomes for those with ER-/PR-positive disease as this population is currently encompassed by the proposed indication, but no efficacy outcomes are provided specifically for this group. Until this information is provided, any potential recommendation may require that the indication is restricted to those with ER-positive disease only.

Sponsor Response

> *Study entry testing for eligibility criteria of ER, PR, and HER2 was based on local laboratory results utilising assays consistent with local standards for the reporting of the efficacy endpoints. Central assessment of ER, PR, and HER2 on tumor samples with adequate quality and quantity were performed retrospectively at the central laboratory Clairent diagnostic services, Inc. The efficacy results for patients who were identified as ER-/PR-positive by local testing is provided in Table 1 and by central laboratory testing in Table 2.*

Evaluator comment:

In this study (Study 1023), there were 3 subjects by local laboratory testing and 13 subjects by central laboratory testing who had ER-/PR-positive baseline disease. Only one of these subjects had an objective response, which lasted 3.71 months. This subject was in the placebo arm. This trial (Study 1023) does not provide any evidence of efficacy in subjects with ER-negative/PR-positive disease however the very small population in whom ER was negative precludes drawing statistically significant conclusions. Study 1003 had ER positivity as an inclusion criterion, and so wouldn't include any ER-/PR-positive disease.

On this basis alone, it may appear that restriction of the indication to 'ER-positive' rather than 'HR+' disease would be appropriate if there is no evidence of efficacy in ER-negative/PR-positive disease seen Study 1008. However, the following information suggests that this might not be appropriate:

- The PR is an estrogen-regulated gene – so PR activity is modulated by ER activity rather than the other way around.[24]
- PR positivity in the absence of ER positivity is rare – approximately 2% of breast cancers,[25] and these patients tend to be treated the same as ER-positive/PR-positive patients,[26] that is, the NCCN guidelines refer only to 'hormone receptor' positive or negative, not specifying ER/PR status separately.[27]

[24] Edmonds CE and Mankoff DA (2016) "Progesterone Receptor Imaging" in Molecular Pathology of Breast Cancer (Badve S and Gokmen-Polar Y [eds]). Ch 13.3.2; p 194
[25] http://www.breastcancer.org/symptoms/diagnosis/hormone_status/read_results
[26] Yazici O, Erdem GU, Aksoy S at el. (2016) Comparison of clinical outcomes in patients with early stage ER-/PR+, HER2- breast cancer patients with triple negatives. J Clin Oncol 34, 2016 (suppl; abstr e12556)
[27] NCCN Quick Guide Stage IV breast cancer

- Receptor status can change during the course of disease and at any one time may not be uniform throughout the body as tumour clonal lines continue to evolve, so receptor status may not be consistent between one biopsy and another. This is more common for PR (20-50% differences between locoregional and distant metastases) than for ER (10-30%), whilst on the contrary, HER2 status tends to show high concordance.[20]
- Some authors argue that ER-/PR-positive breast cancer is not a reproducible subtype, and the value of PR testing is questionable, with no association seen between PR status and prognostic value in multivariate modelling.[28]
- There appears to be poor concordance of testing between peripheral and central laboratories as evidenced by the complete disagreement between central and local laboratory results in this group (there were zero subjects identified as ER-/PR-positive by both laboratories in agreement). This supports that there is variability between laboratory testing sites as well as between biopsies or due to clonal evolution with time.
- ER-/PR-positive/HER- patients tend to have more aggressive tumours (hypothesised to have similar to clinical outcomes in triple negative patients),[26] so the difference between the efficacy rate in ER-positive/PR-positive and ER-/PR-positive subjects in this study may reflect the natural history of the disease rather than lack of efficacy in the latter group.
- The sponsor's response is accepted.

12.5.20 Efficacy clinical question 20

QUESTION 20

Study A5481023: The change to a different schedule (2 weeks on/2 weeks off) was not described in the Protocol and the benefits of this dose in the 3.8% who switched to this regimen cannot be assured. It is not clear what palbociclib dose was taken in this regimen (please provide this information). It would be apparent to the investigator that the patient was receiving palbociclib due to the AE profile, and this may have introduced a bias in wanting to continue if there was a clinical benefit observed but problematic toxicities. That so many changed to this regimen indicates a degree of unmasking. The sponsor is requested to provide an explanation of whether these non prespecified alterations were included in the protocol deviations and also whether these patients' outcomes were included in the efficacy analyses, and whether any subgroup efficacy analyses were performed for those on this regimen.

Sponsor Response

> *The sponsor would like to clarify that the palbociclib dose 75 mg/day schedule 2 weeks on/2 weeks off is allowed by the Protocol of Study A5481023. In protocol Section 5.3.4.2.3 (Dose Reductions), Table 3 reports the guidelines to modify the dose of palbociclib/placebo when treatment-related toxicities occurred. Table 3 with related footnotes is provided in this document.*
>
> *In Table 3 one of the footnotes indicates that when a patient was already receiving palbociclib at 75 mg/day (or placebo equivalent) according to schedule 3 weeks on/1 week off, it was possible to consider changing the schedule to 75 mg/day schedule 2 weeks on/2 weeks off.*
>
> *In this clinical trial, eligible patients may have received several prior anti-tumor agents,*

https://www.nccn.org/patients/guidelines/quick_guides/breast/stage_iv/index.html#2

[28] Hefti MM, Hu R, Knoblauch NW et al. (2013) Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype. Breast Cancer Research 2013. 15:R68. DOI 10.1186/bcr3462

including chemotherapy, thus increasing the propensity to develop toxicities during a subsequent anti-tumor therapy (that is, study treatment). For this reason, the protocol provided oncologists and patients with an additional possibility to adapt the palbociclib/placebo dosing in order to continue with the study therapy when an objective clinical benefit was observed (for example, tumor response or stabilization).

Study A5481023 results demonstrated that adding palbociclib to fulvestrant a clinically meaningful and statistically significant benefit in Progression-free survival (PFS) was obtained for patients with estrogen receptor -positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer.

At the data cutoff date of 23 October 2016, a total of 14 patients in the palbociclib plus fulvestrant arm had the palbociclib dose reduced to 75 mg/day schedule 2 weeks on/2 weeks off (Table 1023.565.14). Of these patients, 5 were still ongoing as of 31 October 2016 with >2 years of treatment and 9 patients had discontinued study treatment, most of whom were due to disease progression. Overall, the 75 mg/day schedule 2 weeks on/2 weeks off dosing regimen was administered for <6 months in 5 patients, for approximately 10 months in 3 patients and for ≥ 1 year in 6 patients.

A specific PFS analysis of those patients who received 75 mg/day schedule 2 weeks on/2 weeks off was not conducted.

However, the PFS analysis of the subgroup of patients who had the dose of palbociclib decreased to 75 mg/day, which includes also patients with a dose decreased to 75 mg/day schedule 2 weeks on/2 weeks off, was conducted and is provided in Table 1 together with the PFS analysis of patients who had at least one palbociclib dose reduction and those who had a dose reduction to 100 mg/day. As shown in Table 1, the PFS of the 3 subgroups of patients is comparable.

In conclusion, the sponsor considers that the possibility of continuing treatment, although at a reduced total number of mg of palbociclib over a treatment cycle compared to the 3 weeks on/1 week off regimen, still represented a clinical benefit for patients in this setting.

Comment: The PFS analysis for the smaller dose subgroups given by the sponsor is outlined in Table 38 below, with updated PFS results in the ITT placebo and active groups, which was provided by the sponsor in the response) for comparison.

Table 38: PFS in reduced dose subgroups and ITT population, from Study 1023 (data cut-off: 23Oct2015)

Group	N =	Objective progression	Death without progression	K-M estimate of median PFS in months (9% CI)
Placebo + fulvestrant (ITT population of Study 1023)	174	130 (74.7%)	3 (1.7%)	4.6 (3.5, 5.6)
Palbociclib + fulvestrant (ITT population of Study 1023)	347	198 (57.1%)	2 (0.6%)	11.2 (9.5, 12.9)
Palbociclib + fulvestrant **subgroup**: patients with at least	132	66 (50.0%)	0	14.1 (11.1, 16.7)

Group	N =	Objective progression	Death without progression	K-M estimate of median PFS in months (9% CI)
one dose reduction				
Palbociclib + fulvestrant **subgroup**: Patients with dose reduction to 100 mg/day	89	46 (51.7%)	0	11.3 (9.2, N.E.)
Palbociclib + fulvestrant **subgroup**: Patients with dose reduction to 75 mg/day	43	20 (46.5%)	0	16.7 (11.2, N.E.)

The efficacy results in the subgroups with reduced doses are in keeping with those of the active arm generally, and do not overlap in confidence interval with the placebo arm. The dose reduction for management of adverse events was pre-specified, and blinding appears to have been maintained as dose reduction could have been undertaken for placebo also.

The sponsor's response is accepted.

12.5.21 Efficacy clinical question 21

Evaluator comment: this question is more related to safety than efficacy but the nomenclature of 'efficacy' question 21 is kept for continuity between documents.

QUESTION 21

Study A5481023 the sponsor is requested to state whether searching using any other MedDRA terms that might capture events of haemorrhage, bleeding or bruising, yields any events associated with the adverse events of thrombocytopenia.

Sponsor Response

The sponsor performed a search for the following Preferred Terms (PTs) that capture events of hemorrhage: Haemorrhage, Petechiae, Menorrhagia, Haematochezia, Haematuria, Epistaxis, Haemorrhoidal haemorrhage, Haemorrhage intracranial. A review of data from patients treated on the palbociclib and fulvestrant arm with adverse events of hemorrhage as captured by the above listed PTs and with laboratory findings of thrombocytopenia was performed.

Two cases of Grade 1 Epistaxis and Grade 1 Thrombocytopenia were identified. In one of the cases, the event Epistaxis did not have temporal plausible relationship with the event Thrombocytopenia, since the events occurred 3 months apart. In the other case, intermittent Grade 1 thrombocytopenia started in Cycle 2. The patient had 2 episodes of Epistaxis; the first occurred on Cycle 1 Day 22, lasted for one day and was assessed as related to study medication. No action was taken with study medication. The second event occurred on Cycle 5 Day 26; the event lasted one day and was considered unrelated to study medication but related to other illness. No action was taken with study medication. The patient was concomitantly taking ibuprofen.

Additionally, this search identified 35 adverse events (AE) reported in 31 patients. There were 29 cases of Epistaxis, 2 cases of Menorrhagia (2 events in 1 patient), 1 case of

Haematochezia, 1 case of Haematuria, 2 cases Haemorrhoidal haemorrhage and no cases for the remaining PTs listed above.

Please see Table 39 for a listing of pertinent adverse events by treatment arm.

Table 39: Adverse events by treatment arm

Event	Palbociclib/Fulvestrant	Placebo/Fulvestrant	Total
Epistaxis	25	4	29
Haemorrhoidal haemorrhage	1	1	2
Haematuria	0	1	1
Haematochezia	0	1	1
Menorrhagia	2	0	2
Petechiae	0	0	0
Haemorrhage intracranial	0	0	0

An analysis of the platelet counts was also performed for all patients in Study 1023. This analysis focused on 3 cycles: the cycle in which the adverse event occurred, as well as the preceding and subsequent cycle.

The review also included an analysis of concomitant medications, specifically aspirin, NSAIDs, and COX-2 inhibitors. 12/31 of patients with bleeding events were taking one or more of these concomitant drugs.

A review of the 35 cases of AEs of hemorrhage identified only 1 case in which a laboratory abnormality was not reported as an AE. This was a Grade 2 decrease in platelets that occurred 6 days after a Grade 1 Epistaxis was reported. This patient was concomitantly taking aspirin.

It is the responsibility of the investigator to determine when a laboratory test abnormality is to be considered an AE. As discussed in Safety Question 10, during the data review/cleaning process queries were generated for laboratory test abnormalities that were not reported as AEs. In some instances, investigators did not consider laboratory test abnormalities with a severity of Grade ≤2 as medically relevant and thus these may not have been reported as an AE.

In conclusion, a search for the above specified PTs pertinent for bleeding events and concurrent laboratory tests indicative of thrombocytopenia identified only a single case in which there was an association between the event (Epistaxis) and thrombocytopenia.

Evaluator comment:

The sponsor's response is accepted.

12.5.22 Efficacy clinical question 22

QUESTION 22

Study A5481008: Within the study, there was some discordance between the baseline information provided at randomisation which affected the stratification and has had an impact on the efficacy analyses, particularly on the subgroup analyses, depending which dataset is used for the ITT population. The full impact of these cannot be understood and contextualised without presentation of the study protocol deviations. It is not sufficient to provide the analyses for these groups according to the differing information source (that is, randomisation versus CRF). A more rigorous approach should include:

d. Presentation of the number of patients for whom there was any discordance between the randomisation information and CRF;

e. Whether these patients were from a single or limited number of investigation centres - it is noted that in Study 1003, the FDA clinical site audit identified a single site as having a significant number of protocol deviations but that analyses with these patients censored were not reported to significantly affect the outcomes;

f. Presentation of sensitivity analyses for the efficacy outcomes censoring the data from these patients incorrectly classified.

Sponsor Response

The sponsor refers the TGA to response to Efficacy Question 7 which clarified that because randomisation in IMPALA occurred prior to the CRF data being source verified, there were minor discrepancies in the distribution of patients by stratification factors for one or more of the investigator-chosen strata not matching the data recorded on the applicable CRFs. For this reason, the CRF source document verified data were considered more accurate and were used in all subsequent submission reports. The data based on the CRF were similar to those based on randomisation and the distribution of patients by the 3 stratification factors (Disease Site, Disease Free Interval, Prior Hormonal Therapy) was similar between the 2 treatment arms and did not have an impact on the primary PFS analysis.

Question a):

A summary of the concordance of patient by stratification factor is presented in Table 1 (disease site), Table 2 (disease free interval), and Table 3 (prior hormonal therapy). Disagreements between IMPALA and the CRF data were identified in 30 patients (23 in the palbociclib + letrozole arm and 17 in the placebo + letrozole arm) for the 'disease site' stratum, 59 patients (41 and 18, respectively) for the 'disease free interval' stratum and in 7 patients (4 and 3, respectively) for the 'prior hormonal therapy' stratum. Patients with more than one stratification disagreement are counted in each group. Geographic distribution of these disagreements and evaluation of their impact on the PFS primary analysis are summarised below in responses 22b and 22c, respectively.

Question b):

A total of 86 (12.9%) patients from 67 sites across 16 countries were randomised in IMPALA with one or more stratification factors not matching the data recorded on the applicable CRFs. A summary of the distribution of the stratification disagreements by country and by sites per treatment arm is provided in Table 4. Not one specific site was identified as an outlier with a large number of stratification-related protocol deviations.

Question c):

As clarified in Efficacy Question 7, while Disease site, Disease Free Interval and Prior Hormonal Therapy were all stratification factors for patient randomisation, the primary PFS analysis was performed using only Disease Site (Visceral, non-visceral) as the stratification factor to estimate the Hazard Ratio and to calculate the p-value. Consequently, the sponsor conducted a sensitivity analysis of PFS excluding only patients whose Disease Site (Visceral, non-Visceral) was assigned differently in IMPALA compared to the CRF data. A total of 30 patients (23 patients in the palbociclib-letrozole arm, 7 patients in the placebo-letrozole arm) were excluded from this sensitivity analysis.

A comparison of the PFS analysis results from the sensitivity analysis and the primary analysis is summarised in Table 5.

Results from the sensitivity analysis presented in Table 5, as well as from the sensitivity analysis #4 reported in the A5481008 CSR (summarised in Efficacy Question 7), demonstrate that the discrepancy between the IMPALA data and CRF data on the

stratification factor used for the primary PFS analysis did not significantly impact the results of the primary PFS analysis.

Evaluator comment:

The largest discrepancies between the IMPALA and the CRF data appear to be in the disease-free interval assignment of category. The category of metastatic disease with onset longer than 12 months after adjuvant therapy finished had the highest rate of misclassified subjects, with redistribution of 7% of the active arm and 5.9% of the placebo arm from this category to another (de novo metastatic or up to 12 months post adjuvant therapy).

There was also a slightly higher percentage of the active arm misclassified as visceral versus nonvisceral (both directions), with total 5.2% of the active and 3.2% of the placebo arm changed category. In both arms, slightly more patients were reclassified to non-visceral from visceral.

Prior hormonal therapy differed the least of the three strata investigated for CRS/IMPALA concordance.

The overall disagreement rate was 13.5% in the active and 11.7% in the control arm, and no one site was a particular culprit for misclassification – instances were sparsely distributed amongst the study centres.

The primary PFS analysis was stratified only by disease site, not the other randomisation factors. A sensitivity analysis of the primary outcome excluding patients whose disease site had been reclassified (23 patients in the active and 7 in the comparator arm) yields a very similar result to the primary analysis (HR 0.572 versus 0.576).

The sponsor's response is accepted.

12.6 Safety questions/responses

12.6.1 Safety clinical question 1

QUESTION 1

The sponsor is requested to provide a table which integrates from all clinical studies (referencing the source studies) and presents:

a. the total number of patients treated to date:

i. at the proposed dose level and regimen (palbociclib 125 md QD 3/1)

4. 1. in combination with fulvestrant

2. in combination with letrozole at the proposed dose

3. in combination with letrozole at any dose level

ii. as monotherapy

1. at the proposed dose and schedule

2. at any other dose

a. b. the median duration of treatment for all those patients and an interquartile range

i. in combination with fulvestrant

ii. in combination with letrozole at the proposed dose

iii. in combination with letrozole at any dose level

Sponsor Response

Table 40 summarises the number of patients treated from clinical studies as requested:

Table 40: Number of patients treated from clinical studies

	Number of Patients Treated
Number of patients treated at the proposed dose level and regimen (palbociclib 125 mg QD 3/1)	
In combination with fulvestrant (A5481023)	**345**
In combination with letrozole at the proposed dose	**587**
A5481003 (Phase 1 and Phase 2)	95
A5481008	444
A5481010 (Phase 1 Part 2 + Phase 2)	48
In combination with letrozole at any dose level	**317**
A5481027*	317
Number of patients treated at the proposed dose level and regimen (palbociclib 125 mg QD 3/1) as monotherapy	
At the proposed dose and schedule	**44**
A5481001 (only those treated at 125 mg QD 3/1)	22
A5481002	16
A5481010 (Phase 1 Part 1 only treated at 125 mg QD 3/1)	6
At any other dose	**58**
A5481001 (those treated at other doses/schedule)	52
A5481010 (Phase 1 Part 1 only treated at other dose)	6

*A5481027=combined two arms as this is an ongoing double-blind, placebo-controlled study

Table 41 summarises the median duration of treatment for the patients treated including an interquartile range as requested:

Table 41: Median duration of treatment

	Number of Patients Treated	Median Duration of Treatment in Months (interquartile ranges)
In combination with fulvestrant	345	10.8 (3.9, 12.9)
In combination with letrozole at the proposed dose	587	17.1 (8.7, 23.2)
In combination with letrozole at any dose level*	317	4.9 (2.5, 8.5)

*A5481027=combined two arms as this is an ongoing double-blind, placebo-controlled study

Evaluator comment:

It is presumed that 'Table' in the response refers to 'Table Median Duration of Treatment'.

The sponsor's response is accepted.

12.6.2 Safety clinical question 2

QUESTION 2

The sponsor is requested to explain the rationale behind the exclusion from Study A5481008 of patients with recent or active suicidal ideation or behaviour. In particular, the sponsor is requested to provide case details where palbociclib might have been implicated in patients committing suicide or becoming suicidal that is, while taking or after recently stopping palbociclib. And further to the results in Study A5481023, where 4 patients were reported to have a psychosis, depression or suicide attempts, the sponsor is requested to discuss the potential role of palbociclib in these events.

Sponsor Response

The exclusion of patients with recent or active suicidal ideation or behaviour from the A5481008 study protocol is consistent with standard protocol language included in all Pfizer protocol templates. Current Pfizer template language provides the rationale for

excluding patients with mental health related diagnosis as follows:

'acute or chronic medical or psychiatric conditions including recent (within the past year) or active suicidal ideation or behaviour 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 subject inappropriate for entry into the study'.

No cases of suicide attempts are reported in either Study A5481003 or Study A5481008 studies, while in Study A5481023, as this question indicated, 4 patients (3 in the palbociclib plus fulvestrant treatment group and 1 in the placebo plus fulvestrant treatment group) were reported to have serious (Grade 3 or 4) psychiatric disorders adverse events (that is, Psychotic disorder, Depression or Suicide attempts) as follows (Table 14.3.1.3.1 and 14.3.1.3.2 of A5481023 90 Day Safety Update):

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2 patients (0.6%) were reported to have experienced a suicidal attempt: Grade 3 (Patient 11031005) and Grade 4 Suicide attempt (Patient 11481004) respectively.

1 patient (0.3%) was reported to have one episode of Grade 4 Psychotic disorder (Patient 10731014)

1 (0.3%) patient was reported to have experienced Grade 3 Depression (Patient 11661005)

Additional details on these 4 adverse events are provided in Table 1.

The 4 above mentioned adverse events were associated with hospitalization and 1 adverse event (attempted suicide of Patient 11481004) led to permanent discontinuation of palbociclib. Three out of these 4 adverse events occurred while the patient was on study treatment, whereas Patient 11031005 attempted suicide 10 days after study treatment was permanently discontinued due to disease progression.

Of note, these events were all considered to be unrelated to study drug by the Investigators. The reported 4 psychiatric adverse events occurred in patients with concurrent depression, which in itself may lead to suicidal ideation or behaviour. In addition one patient (Patient [information redacted]) also had a relevant medical history for psychiatric disorders, had experienced previous episodes of psychosis and was under antipsychotic medical treatment at study entry. The psychotic episode for this patient that occurred on study was attributed by the Investigator to the permanent withdrawal of a concomitant antidepressive drug (quetiapine fumarate) three days before the first dose (Cycle 1 Day 1). The reported adverse event occurred approximately 3 months later (Cycle 4 of study treatment) and fully recovered with quetiapine fumarate re-introduction in patient's therapy.

Patients enrolled in Study A5481023 have experienced the challenges of disease progression and the limitations of existing therapeutic options available to them. The underlying advanced malignancy and associated psychological impact on the patient must also be considered as factors that may favor the development of or the worsening of pre-existing depression. In Study A5481023 there were alternative explanations for each of the 4 cases and these events were assessed by the Investigators as being unrelated to study drug.

The sponsor believes that there is insufficient evidence to consider palbociclib to be causally related to the development of psychiatric disorders.

Evaluator comment:

The inclusion of the following exclusion criterion in Study 1023 supports the sponsor's response that this criterion was not specific to Study 1008. The reasoning for including this specification in protocols may stem from its inclusion in trials of medications for depression.

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 judgement of the investigator, would have made the patient inappropriate for entry into this study.

The wording of the same criterion is less specific in the CSR for Study 1003 however it is noted that this may be a difference between Phase I/II and Phase III trial protocol templates.

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.

Given the circumstances they are in, I would be surprised if the rate of observed events (1.2%) was higher than the background rates of depression and suicide ideation, given their circumstances.

For points of comparison: rates of completed suicide in breast cancer survivors in the USA and Scandinavia have been reported to be between 0.07% and 0.99%.[29] Rates of major and minor depression in a sample of 200 mostly Australian metastatic breast cancer patients were reported to be 6.5% and 24.5% respectively.[30]

Table 42: Rates of completed suicide in various breast cancer registry studies (Source data: Guth *et al.*[29])

Source registry and timeframe	Completed suicides	Study population	Incidence (%)
Schairer et al[31]: 1953-2001	836	723810	0.12
US SEER Program: 1973–2001	245	375797	0.07
Sweden: 1958–2001	241	153902	0.16
Denmark: 1971–1999	166	68045	0.24
Finland: 1953–2001	125	71099	0.18
Norway: 1961–2000	59	5967	0.99
Basel Breast Cancer Database: 1990-2006	6	1165	0.52

[29] Guth U, Myrick ME, Reisch T, Bosshard G and Schmid SM (2011) Suicide in breast cancer patients: An individual-centered approach provides insight beyond epidemiology. Acta Oncologica. 50(7), 1037-1044. http://dx.doi.org/10.3109/0284186X.2011.602112

[30] Kissane DW, Grabsch B, Love A, Clarke DM, Bloch S and Smith GC (2004). Psychiatric disorder in women with early stage and advanced breast cancer: a comparative analysis. Australian and New Zealand Journal of Psychiatry 2004; 38:320–326

[31] Schairer C, Brown LM, Chen BE, Howard R, Lynch CF, Hall P, Storm H, Pukkala E, Anderson A, Kaijser M, Andersson M, Joensuu H, Fosså SD, Ganz PA, Travis LB. Suicide after breast cancer: an international population-based study of 723,810

Although there was an imbalance seen between active and comparator arms in Study 1023 with regard to psychiatric disorders, statistically this is likely to have been by chance, as the absolute numbers are small. Whether this is a pattern that has been noted in the safety data of confirmatory trial 1008 is not clear from the s31 responses, and should be checked on review of that study.

The sponsor's response is accepted.

12.6.3 Safety clinical question 3

QUESTION 3

The sponsor is requested to provide with a future provision of the CSR for Study 1008, an integrated safety summary for the 2 studies 1003 and 1008, and an updated PI to reflect these data.

Sponsor Response

The sponsor holds the evidence to which this Section 31 request refers. The sponsor has therefore appended the Clinical Study Report for Study A5481008 in its entirety as the source document for the Section 31 request for information questions relating to Study A5481008. The sponsor believes the provision of Study A5481008 CSR and the corresponding Summary of Clinical Safety (SCS) addresses the request for an integrated safety summary for Studies A5481003 and A5481008, for the following reasons:

Study A5481008 was a large randomised, double –blind phase 3 study designed to be a confirmatory trial of Study A5481003. Study A5481008 was conducted in a similar population of postmenopausal women with ER-positive HER2-negative advanced breast cancer as Study A5481003 but with a much larger sample size than Study A5481003 (N=666 for Study A5481008 versus N=165 for Study A5481003, with 444 patients in Study A5481008 and 83 patients in Study A5481003 treated with palbociclib, respectively).

The results described in the Study A5481008 CSR and SCS clearly confirm the clinical benefit of palbociclib and letrozole with a statistically significant, robust and clinically meaningful 10-month improvement in median PFS and also demonstrate that the safety profile of the combination of palbociclib plus letrozole was very similar in both studies.

The sponsor has also conducted an analysis of the frequency and severity of treatment-emergent adverse events in a pooled dataset of Studies A5481003 and A5481008. The frequency and severity of treatment-emergent adverse events were generally comparable to those observed in Studies A5481003 and A5481008 when analysed individually.

To support the above considerations, the following pooled safety tables are provided:

- Summary of treatment-emergent adverse events by MedDRA System Organ Class, Preferred Term (including clusters) and maximum CTCAE grade (all causality) – Tables 295.1, 295.2
- Summary of treatment-emergent adverse events associated with permanent discontinuation, dose reduction or temporary discontinuation (all causality) – Tables 279.1 to 279.6
- Summary of time to first onset of neutropenia and summary of duration of neutropenia (based on laboratory test data) – Tables 322.1 and 322.2

For neutropenia, the most common palbociclib-related adverse event, it is important to note the median time from first dose to first episode onset is exactly the same (15 days) in the integrated analysis (pooled data from Studies A5481003 and A5481008) as in Study A5481008 alone results (Table 322.1 and Table 51 of SCS). The median duration of any grade neutropenia is also similar between the pooled dataset of Studies A5481003 and

A5481008 and Study A5481008 alone analysis (316 versus 321 days respectively: Tables 322.2 and Table 52 of SCS).

The sponsor believes that the information provided in the CSR for Study A5481008 confirms the information already provided in the registration application. Thus, an integrated safety summary of Studies A5481003 and A5481008 would not be expected to provide relevant additional information on the safety of the palbociclib plus letrozole combination.

It is noted, that an integrated safety summary for A5481003 and A5481008 has not been requested by any other major regulator, including the EMA for which a full approval was granted based on the same data set provided in the initial registration application to the TGA. The EMA also received the 90 Day Safety Update from the sNDA for Study A5481023. An updated PI presenting the combined adverse drug reactions for Studies A5481003 and A5481008 for the treatment and comparator arms is provided as part of the Section 31Response for this application.

Evaluator comment:

The tables referred to by the sponsor have not been appended to this CER due to their length. Bone marrow suppression, primarily manifested by Grade 3-4 neutropenia, is the predominant feature of the AE profile for the active compared to the placebo arm.

Study 1003 is of lower phase than Study 1008 and had a number of issues around imbalanced randomisation (see evaluator comments following Efficacy question 3). Study 1008 is a much more robust demonstration of both efficacy and safety, and the safety data submitted with the full CSR will be reviewed in the context of the study.

The sponsor's response is accepted.

12.6.4 Safety clinical question 4

QUESTION 4

For Study A5481023, the remaining events accounting for the 3.5% of Grade 3 or 4 TEAEs for the palbociclib and fulvestrant arm and 1.7% in the comparator arm (90-day safety update) are not presented. The sponsor is requested to provide this information.

Sponsor Response

The sponsor would like to clarify that in the in-text Table 7 (Summary of All-Causality, Treatment-Emergent Adverse Events (All Cycles) Experienced by at Least 10% of Patients in Either Treatment Arm of Study A5481023 as of 31 July 2015 by MedDRA PT and Maximum Severity Grade Sorted by Decreasing Frequency (All Severity Grades) for Patients Receiving Palbociclib Plus Fulvestrant – All Treated Patients) of the 90 Day Safety Update document all the TEAEs experienced by at least 10% of patients in either treatment arm were reported as indicated in the table title.

In the footnote of Table 7 the number of the source table from which Table 7 was derived is provided (Table 14.3.1.1.3). This table was included together with all other source tables at the time the Study A5481023 90 Day Safety Update (data cutoff 31 July 2015) was submitted to the TGA. Table 14.3.1.1.3 includes all the TEAEs of any frequency that were reported by the defined data cutoff date by patients in the 2 treatment arms.

This table is linked directly to this response for convenience.

Evaluator comment:

Table 14.3.1.1.3 contains a listing of all TEAEs in both arms in Study 1023.

The Grade 3 and 4 events have been reviewed (see Table 43) and do not reveal any new safety

signals. The size of the study is not large enough to draw significant comparisons between arms where there are isolated cases. Additionally, multiple preferred terms (for example, fracture femur fracture, humerus fracture and road traffic accident) may have been reported for one case.

Neutropenia and Grade 3 and 4 infections were reported more frequently in the active arm. Additionally, there were 7 reports of 'breast mass' in the active arm: an AE term which is clearly related to underlying disease. It is very possible that a reporting bias is present, in that the presence of neutropenia could have resulted in partial unmasking of treatment. The other notable imbalance is in the SOC psychotic disorders. Although, like road traffic accident related fractures and a pathological fracture this is likely a reflection of chance rather than ascribable risk, this aspect of safety should be given particular consideration in review of Study 1008 data (see section 13).

Table 43: Grade 3 and 4 TEAEs in Study 1023, by treatment and System Organ Class (SOC)

	Active		Comparator	
MedDRA SOC	GRADE 3	GRADE 4	GRADE 3	GRADE 4
Blood and lymphatic system	• 2 x febrile neutropenia • 3 x neutropenia	• neutropenia		
Cardiac disorders	• pericarditis			
Endocrine disorders	• hyperthyroidism • hypothyroidism			
GI disorders	• abdominal pain • GORD • hiatus hernia • intestinal obstructive • nausea • small intestinal obstruction • vomiting		• 2 x ascites • diarrhoea • nausea • pancreas • vomiting	
General disorders and administration site conditions	• general physical health deterioration • pain • pyrexia	• asthenia	• pain	
Hepatobiliary	• bile duct stone • cholelithiasis • hepatic failure		• cholecystitis	

	Active		Comparator	
Infections and infestations	• bacteramia • erysipelas • escherichia sepsis • LRTI • meningitis aseptic • pharyngitis • pneumonia • sinusitis • URTI • viral infection	• 2 x cellulitis • urosepsis	• atypical pneumonia • gastrointestinal infection • pneumonia • viral upper respiratory tract infection	
Injury, poisoning and procedural complications			• femur fracture • fracture • humerus fracture • road traffic accident	
Investigations	• ALT increased • ECG QT prolonged	• neutrophil count decreased • troponin increased		
Metabolism and nutrition	• dehydration			
Musculoskeletal and connective tissue disorders	• back pain		• back pain • osteonecrosis of jaw • pathological fracture	• pathological fracture
Neoplasms	• endometrial cancer • rectal cancer		• adenocarcinoma gastric	
Nervous system	• carotid artery stenosis • cauda equina syndrome • drug withdrawal convulsions • migraine • paraesthesia • TIA	• sedation	• cerebrovascular accident	
Psychiatric	• depression • suicide attempt	• psychotic disorder • suicide attempt		
Reproductive and breast	• 6 x breast mass	• breast mass		

Active		Comparator		
Respiratory, thoracic and mediastinal	• 3 x PE • COPD • dyspnoea • pleural effusion	• dyspneoa	• COPD • Dyspnoea • pleural effusion • pulmonary hypertension	
Skin and subcutaneous tissue	• rash maculopapular			
Vascular	• DVT			

The sponsor's response is accepted.

12.6.5 Safety clinical question 5

QUESTION 5

An update infection rate/febrile neutropenic rate has not been presented in this safety update for Study 1023 and this is needed, to ensure the figure quoted in the PI is accurate.

Sponsor Response

Please refer to the sponsor's response to PI Question 23 and PI Question 26 which duplicate this query Safety Question 5.

Evaluator comment:

The sponsor's response is accepted.

12.6.6 Safety clinical question 6

QUESTION 6

Bone marrow suppression occurs resulting in leukopenia and neutropenia. The sponsor is requested to provide the following information, and where cases have occurred, provide the details.

a. What were the rates of opportunistic infections reported for each of the arms for Study 1003, 1023 and 1008?

b. Were any cases of Hepatitis B reactivation identified?

c. Has PML ever been reported in the palbociclib development program?

Please provide details of any cases reported.

Sponsor Response

Response to Query 6a:

In order to evaluate the frequency of opportunistic infections in Studies A5481003, A5481008, and A5481023, a search was performed for the following reported Preferred Terms (PTs) through January 02, 2015 (A5481003), 26 February 2016 (A5481008), and July 31, 2015 (A5481023):

Aspergillus infection, Bronchopulmonary aspergillosis, Aspergillus test positive, Oesophageal candidiasis, Anal candidiasis, Vulvovaginal candidiasis, Skin candida, Otitis externa candida, Candida pneumonia, Biliary tract infection fungal, Clostridium difficile

infection, Clostridium difficile colitis, Clostridium bacteraemia, Coccidioidomycosis, Coccidioides encephalitis, Meningitis coccidioides, Systemic mycosis, Cryptococcus test positive, Pneumonia cryptococcal, Fungal test positive, Cryptococcosis, Meningitis cryptococcal, Myocarditis mycotic, Cryptosporidiosis infection, Gastroenteritis cryptosporidial, Cytomegalovirus infection, Acute cytomegalovirus hepatitis, Cytomegalovirus chorioretinitis, Cytomegalovirus test positive, Isosporiasis, Endocarditis histoplasma, Histoplasmosis disseminated, Meningitis histoplasma Histoplasmosis, Pericarditis histoplasma, Acute pulmonary histoplasmosis, Chronic pulmonary histoplasmosis, Retinitis histoplasma, Polyomavirus-associated nephropathy, BK virus infection, Human polyomavirus infection, Urinary tract infection viral, Viraemia, JC virus test positive, JC virus infection, Kaposi sarcoma, Human herpes virus 8 test positive, Legionella test positive, Pneumonia legionella, Legionella infection, Microsporidia infection, Mycobacterium avium complex infection, Atypical mycobacterial infection, Atypical mycobacterial lymphadenitis, Lymph node tuberculosis, Disseminated tuberculosis, Tuberculosis, Mycobacterium tuberculosis complex test positive, Cutaneous tuberculosis, Epididymitis tuberculous, Pneumocystis jirovecii pneumonia, Pneumocystis jirovecii infection, Pneumocystis test positive, Meningitis bacterial, Lung infection pseudomonal, Pseudomonal bacteraemia, Pseudomonal sepsis, Pseudomonas test positive, Pseudomonas infection, Keratitis bacterial, Gastroenteritis salmonella, Aortitis salmonella, Arthritis salmonella, Salmonella bacteraemia, Salmonella test positive, Bacterial diarrhoea, Enterocolitis bacterial, Staphylococcal infection, Staphylococcal sepsis, Cellulitis staphylococcal, Staphylococcal abscess, Pneumonia streptococcal, Pneumococcal sepsis, Pneumonia pneumococcal, Meningitis pneumococcal, Streptococcal bacteraemia, Streptococcal infection, Bronchitis pneumococcal, Pneumococcal infection, Streptococcal abscess, Cellulitis streptococcal, Staphylococcal skin infection, Toxic shock syndrome streptococcal, Cerebral toxoplasmosis, Toxoplasmosis, Toxoplasma serology positive, Eye infection toxoplasma, Opportunistic infection, Respiratory monoliasis, Pneumonia fungal.

The following cases of interest were identified:

A. Palbociclib treated patients [N=884]

- A 72 year old obese (99 kg) female ([information redacted]) with non-insulin dependent diabetes mellitus, treated with palbociclib plus letrozole in Study A5481003, developed Grade 2 **Vulvovaginal candidiasis** on Study Day 161. The event resolved on Study Day 168. No action was taken with study medications.
- A 70 year old obese (107 kg) female ([information redacted]) treated with palbociclib plus letrozole in Study A5481008 developed Grade 1 **Skin candida** on Study Day 44. The event resolved on Study Day 59. No action was taken with study medications.
- A 66 year old obese (121 kg) female ([information redacted]) treated with palbociclib plus letrozole in Study A5481008 developed Grade 1 **Staphylococcal skin infection** on Study Day 157. The event resolved on Study Day 168. No action was taken with study medications.
- A 70 year old (51 kg) female ([information redacted]) treated with palbociclib plus letrozole in Study A5481008 developed Grade 2 **Staphylococcal infection** ('Staph infection left arm') on Study Day 220. The event resolved on Study Day 231. No action was taken with study medications.
- A 67 year old (61 kg) female ([information redacted]) with a history of hyperlipidaemia, treated with palbociclib plus letrozole in Study A5481008 for recurrent metastatic (sacrum, spine, ribs, bilateral iliac, sternum) breast cancer, developed Grade 2 Clostridium difficile infection on Study Day 90. She was treated with metronidazole and the event resolved 10 days later. Of note, the patient was treated with palliative radiation to the pelvis on Study Days 19 through 29 and was treated with methadone

and dexamethasone for bone pain. She was diagnosed with radiation enteritis (PT = Gastroenteritis radiation, Case number [information redacted]) on Study Day 38 and was hospitalized. The event resolved 8 days later. The patient finally developed Grade 3 pneumonitis on Study Day 76 at which time study medications were permanently discontinued. Thus, the patient had not received palbociclib for 2 weeks at the time she developed **Clostridium difficile infection**. The event was not causally attributed to study medications by the investigator.

- A 54 year old (77 kg) female ([information redacted]) with no relevant medical history treated with palbociclib plus letrozole in Study A5481008 for metastatic breast cancer, developed non-serious Grade 3 neutropenia on Study Day 16 and palbociclib was temporarily held. On Study Day 30, palliative radiotherapy was initiated, lasting through Study Day 45. Two days later, on Study Day 47, the patient developed nausea, vomiting, as well as deterioration of her general status, and was hospitalized ([information redacted]) and diagnosed with **Clostridium difficile infection**. At this time her laboratory values were as follows: haemoglobin: 10.5 g/dL (11.5 to 15g/dL); white blood cell count: 3.5/nL (3.5 to 10/nL). She was discharged 4 days later and considered recovered 8 days after diagnosis, upon which study medications were restarted. The event was not causally attributed to study medications by the investigator.
- A 39 year old (65 kg) female ([information redacted]) treated with palbociclib plus fulvestrant in Study A5481023 developed Grade 2 **Vulvovaginal candidiasis** on Study Day 92. The event resolved on Study Day 294. No action was taken with study medications.

B. Patients treated in comparator arms [N=471]

- A 63 year old (57 kg) female ([information redacted]) treated with placebo plus letrozole in Study A5481008 developed Grade 2 Staphylococcal infection on Study Day 162. The event resolved on Study Day 197. No action was taken with study medications. A 70 year old (77 kg) female (Patient ID [information redacted]) treated with placebo plus letrozole in Study A5481008 developed Grade 1 Skin candida on Study Day 420. The event has not resolved as of Study Day 504 and is ongoing. No action was taken with study medications.

Summary and Conclusion:

In summary, among 884 patients treated in the palbociclib arms, 3 candida skin infections and 2 staphylococcal skin infections, and 2 Clostridium difficile infections were observed (rate of 0.8%). Among 471 patients treated in comparator arms, 1 Staphylococcal infection and 1 candida skin infection were observed (rate of 0.4%). Of note, the adverse event analysis was not adjusted for the significantly longer study treatment duration in the palbociclib-treated arms compared to the treatment duration in the comparator arms (Study 1003: 420 days vs. 231 days; Study 1008: 603 days vs. 413 days; Study 1023: 330 days vs. 137 days, respectively).

Skin infections, particularly vulvovaginal candidiasis, as well as staphylococcal skin infections, but also clostridia infections (or carriage) may occur in patients without obvious immunocompromise. Diabetes (present in patient [information redacted]) as well as obesity (present in 3/7 palbociclib treated patients), cancer, and recurrent hospitalizations, as well as treatment with antibiotics are risk factors for these infections. Cutaneous and/or systemic candida or staphylococcal infections occur with much higher frequency and severity in immunocompromised patients and are therefore also considered under opportunistic infections. However, they are not exclusively or necessarily classic opportunistic infections, and thus their occasional occurrence at low severity grades in palbociclib treated patients does not justify the conclusion that palbociclib increases patients' risk of developing opportunistic infections. When diagnosing clostridia infections,

it is important to distinguish a positive carrier status from actual infection. No clinical details are provided for Patient ID [information redacted], thus it is not clear what, if any, symptoms were present. Patient [information redacted] did have gastrointestinal symptomatology and required hospitalization. Both patients had preceding radiotherapy, which may have caused or exacerbated gastrointestinal symptoms.

In patient [information redacted] palbociclib had not been administered for 30 days prior to the diagnosis of Clostridium difficile infection, while in patient [information redacted], palbociclib had not been administered for 2 weeks at the time Clostridium difficile infection was diagnosed.

Overall, this analysis does not support the conclusion that palbociclib increases a patient's risk of developing opportunistic infections.

Response to Query 6b:

In order to evaluate the reporting frequency of reported cases of Hepatitis B reactivation, a search of the clinical database was performed for the following Preferred Terms:

a. Hepatitis B (corresponds to Lower Level Term of Hepatitis B reactivation)
b. Chronic hepatitis B (corresponds to Lower Level Term of Chronic hepatitis B reactivation)

The search did not reveal any cases. In addition, a search was performed of any post-marketing cases of Hepatitis B or Chronic hepatitis B received on the Safety Database through November 15, 2016. This search also did not identify any cases.

Summary and Conclusion:

Testing for hepatitis B infection was not mandated at Study entry and a history of hepatitis B infection was not an exclusion criterion in any of the pivotal breast cancer trials. Since no cases of hepatitis B reactivation were reported in 884 palbociclib treated patients, or in any of the over 40,000 patients treated outside of company sponsored clinical trials, there is currently no evidence that treatment with palbociclib is causally associated with hepatitis B reactivation.

Response to Query 6c:

In order to evaluate the reporting frequency of Progressive multifocal leukoencephalopathy (PML), a search of the clinical database was performed for the following Preferred Terms: Progressive multifocal leukoencephalopathy. The search did not reveal any cases.

In addition, a search was performed of any post-marketing cases of Progressive multifocal leukoencephalopathy received on the Safety Database through November 15, 2016. This search also did not identify any cases.

Summary and Conclusion:

There is currently no evidence that treatment with palbociclib predisposes to the development of PML.

Evaluator comment:

The sponsor's response is accepted.

12.6.7 Safety clinical question 7

QUESTION 7

There needs to be a heading and discussion of the rates of infection and febrile neutropenia

(0.6% of patients receiving palbociclib and fulvestrant reported at 5 December 2014 cut-off – but what is it now with the later dataset?) An updated infection rate/febrile neutropenic rate has not been presented in this safety update for Study 1023 and this is needed, to ensure the figure quoted in the PI is accurate (Clinical Questions and PI comments).

Sponsor Response

Please refer to Safety Question 5.

Evaluator comment:

The sponsor's response is accepted.

12.6.8 Safety clinical question 8

QUESTION 8

Table 5 of the draft PI presents out of date data for Adverse Drug Reactions which is in the SOC format which needs to be updated with the 90-day safety update. Where there are clinical laboratory findings (eg for biochemical and haematological events), these should be included in any data presented as these are more accurate than TEAEs. It must be shown clearly how the figures used in the ADR table were reached and why any treatment-related events were discounted. This is required in the response (clearly indicating how these figures were reached) and to be inserted in the PI.

Sponsor Response

…the scope of the Day-90 SU was primarily to provide the US FDA with updated safety information on Study A5481023 which was the pivotal study of the Supplementary NDA under assessment. Thus, a comprehensive safety update was conducted only for the pivotal Study A5481023. The Adverse Drug Reactions (ADRs) table for Study A5481023 reported in the PI has been updated accordingly.

With regards to the ADRs table for the combination of palbociclib with letrozole, based on data from Study A5481003 and Study A5481008, the most recent cutoff have been used (please refer to PI Question 21 for further details) [not included in this document].

In general, adverse drug reactions were determined by the sponsor based on whether an AE could be reasonably associated with palbociclib treatment. The sponsor evaluated this potential association by examining the frequencies of all-causality AEs reported in the palbociclib plus letrozole combination in comparison with the placebo plus letrozole arm (Studies A5481003 and A5481008) and the palbociclib plus fulvestrant combination in comparison with the placebo plus fulvestrant arm (Study A5481023). Further, the sponsor considered the mechanism of action of palbociclib, the available nonclinical toxicity data, and the overall assessment of AEs by the investigators in considering whether reported AEs were reasonably associated with palbociclib treatment. In cases of uncertainty or for confirmation, the AE experience from palbociclib monotherapy studies was also considered.

This is consistent with the ICH guidance E6 definition of Adverse drug reactions 'In the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, that is, the relationship cannot be ruled out.'

…. the sponsor proposes to include Laboratory abnormality tables for Study A5481008 and Study A5481023 under the Adverse Effects section of the PI, which is the appropriate

location for this information and is aligned with the USPI.

The sponsor has already addressed the apparent discrepancy noted between the frequency of laboratory test abnormalities and the frequency of corresponding treatment emergent adverse events (TEAEs) in Safety Question 10, Safety Question 31 ….

References

ICH GUIDELINE FOR GOOD CLINICAL PRACTICE E6 (R1) Current Step 4 version dated 10 June 1996
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_ R1_Guideline.pdf

Evaluator comment:

The sponsor's response is accepted.

12.6.9 Safety clinical question 9

QUESTION 9

Study A5481023: Without a table providing side-by-side comparison of the adverse events of lower frequency, presented with similar terms collapsed to provide a single figure (as in the SOC presentation with like MedDRA terms collated, it is very difficult to determine whether there have been additional clinically significant adverse events occurring more commonly in the experimental arm. Given the importance of understanding these for both clinicians and patients, the sponsor is requested to present all the adverse events, (including all grades frequency, as well as Grade 3 and Grade 4) that occurred more often in the palbociclib and fulvestrant arm than the placebo and fulvestrant arm (Clinical Questions). These adverse events' preferred terms should be clustered to capture the same event being classified by a range of different terms.

Sponsor Response

The sponsor created a table with a side-by-side comparison of any Grade adverse events and Grade 3/4 adverse events experienced by subjects enrolled in the palbociclib plus fulvestrant arm (N=345) and the placebo plus fulvestrant arm (N=172) of Study A5481023.

Adverse events of lower frequency occurring more commonly in the experimental arm were examined for clinical significance. Note that the adverse event frequencies were not adjusted for the significantly longer median treatment duration in the palbociclib arm compared to the placebo arm (330 days vs. 137 days, respectively).

Twice as many subjects were randomised to the palbociclib plus fulvestrant arm than to the placebo plus fulvestrant arm and the median treatment duration was 2.4 times as long on the palbociclib arm. It is therefore not surprising that a variety of adverse events were reported on the palbociclib arm at low frequencies, which either were reported at lower frequencies or were not reported at all on the placebo arm, both for any Grade and for Grade 3 or 4 events.

A careful review of these events did not suggest that the creation of additional adverse event clusters would result in grouping adverse events that are truly medically related and/or that might constitute heretofore unidentified adverse drug reactions of palbociclib.

Evaluator comment:

Tables 1023.684.1 and 1023.684.2 have been provided by the sponsor and summarise the data side-by-side as requested, both for all AEs and for Grade 3 or 4 events, but have not been reproduced herein due to their length.

The sponsor's response is accepted.

12.6.10 Safety clinical question 10

QUESTION 10

For Study A5481023: It is difficult to determine whether the difference between the rates of thrombocytopenia from laboratory findings compared with the TEAEs of thrombocytopenia indicates a level of under-reporting of the events for the population as a whole for lower grade AEs of thrombocytopenia as it would be unusual for such a high percentage of patients who have received endocrine therapy as their last treatment to be thrombocytopenic (even Grade 1 or 2) at baseline; however, the reporting of TEAEs appears to match the total number with Grade 3 or 4 TEAEs although the distribution is different (one patient more is reported to be Grade 4 not Grade 3). The sponsor is requested to provide an explanation.

Sponsor Response

> *The sponsor agrees that some differences exist between the frequency of laboratory test abnormalities (for example, decrease in platelets) and the frequency of corresponding TEAE. During the data review/cleaning process queries had been generated for laboratory abnormalities that were not reported as a TEAE. This process mainly concerned the laboratory abnormalities with Grade 3 and 4 severity which may lead to a change in study drug dosing. Of note, the Study protocol (Section 8.4) includes guidelines for investigators to determine whether a laboratory test abnormality should be reported as an AE. In summary, an abnormality is to be reported as an AE or SAE if associated with accompanying symptoms, requiring additional diagnostic testing or medical intervention, leading to a change in study drug dosing or discontinuation from the study, or if necessitating additional concomitant therapy, or if considered to be an AE by the investigator or sponsor.*
>
> *It is the responsibility of investigators to decide when a laboratory test abnormality is to be considered a TEAE. This decision may be based on the clinical conditions of the patient or on the investigator's perspective as to whether an observed laboratory abnormality is clinically relevant. In many instances, the investigators may not have considered laboratory abnormalities with a Grade ≤2 severity as medically relevant and thus may not have reported these abnormalities as an AE.*
>
> *As for thrombocytopenia at baseline, only 1 patient in the palbociclib plus fulvestrant arm had a Grade 1 thrombocytopenia at baseline while 2 patients in the placebo plus fulvestrant arm had thrombocytopenia at baseline, one of Grade 1 and the other of Grade 2 in severity (Table 14.3.4.1.5.4 [Shift Summary Results of Labs by Maximum CTC Grade - Hematology, All Cycles]).*
>
> *In conclusion, consistent with the study protocol, not all laboratory test abnormalities are reported as AEs. The differences between the frequency of observed laboratory test abnormalities and the frequency of corresponding reported TEAEs are likely due to the investigator's clinical decision of what laboratory test abnormalities were reported as a TEAE rather than a level of under-reporting of events.*

Evaluator comment:

The sponsor's response explains the differences between adverse event counts and laboratory abnormalities.

It is recognised that the methodology, definitions and criteria for adverse event reporting used by the sponsor may result in some laboratory events not being reported as adverse events. However, this is in keeping with the ICH guidelines, which are generally accepted by the TGA.

The converse of the 'underreporting' of adverse event terms is that this system prevents the inclusion of reports that were not considered to be clinically relevant according to the investigator, thus increasing the significance of the events that are reported, and reducing signal noise.

The issue with this modus operandi is that prescribers reading the PI are not experts in MedDRA, adverse event reporting or CTCAE definitions, and are not likely to differentiate between 'adverse event' and 'laboratory abnormality'. This particularly true with something like thrombocytopenia, where by definition the adverse event IS a laboratory abnormality. In these cases, clinical assessment of the grade would be related to whether symptoms were associated with the abnormal reading and the extent of intervention – for example, if neutropenia extended a hospital stay as the count was so low the clinical decision was that isolation was required preventatively to avoid infection/febrile neutropenia. The inclusion of the laboratory abnormality tables in the PI in addition to the existing adverse event tables assists in addressing this issue, as both sets of data are then available for the prescriber.

The sponsor's response is accepted.

12.6.11 Safety clinical question 11

QUESTION 11

Study A5481023: The rates of epistaxis and thrombocytopenia are both noted to be increased in Study 1008 for the palbociclib arm and sponsor is requested for Study 1023, to state the rates for bleeding events by:

a. broadening the search criteria beyond 'Haemorrhage' and to use all MedDRA terms that are designed to cover the event of bruising, bleeding in any organ (including petechiae)

b. how many of these were associated with the events of thrombocytopenia in Study 1023?

Sponsor Response

As noted in Table 33 A5481023 90 Day Safety Update neither Grade 3 nor Grade 4 THROMBOCYTOPENIA (cluster term comprising the PT of Thrombocytopenia and Platelet count decreased) events were associated with bleeding episodes (based on Haemorrhage terms, excluding laboratory terms, within Standardized MedDRA Queries [Narrow]). Note: this SMQ contains the Preferred Terms of Contusion (bruising), and Petechiae.

Further information regarding the concurrence of bleeding events and thrombocytopenia can be found in the response to Efficacy Question 21.

Evaluator comment:

The sponsor's response is accepted.

12.6.12 Safety clinical question 12

QUESTION 12

Study A5481003: the sponsor is requested to provide the platelet count for the patient at the time of requiring a dose reduction for petechiae.

Sponsor Response

The platelet count was 83 x 10^9/L (reference range: 150-400 x 10^9/L) on 24 Jul 2012 (Cycle 17 Day 1) for the patient (Patient [information redacted]) who had palbociclib dose reduced from 100 mg to 75 mg due to Grade 3 Petechiae (previously dose reduced from

125 mg to 100 mg due to Grade 3 Fatigue at Cycle 16) ….

Evaluator comment:

The sponsor's response is accepted.

12.6.13 Safety clinical question 13

QUESTION 13

Study A5481008: table 6, (Summary of all-causality treatment-related adverse events) states that 6.1% and 5.0% of patients permanently discontinued letrozole due to an AE in the experimental and comparator arms, respectively. This figure exceeds that for those permanently discontinuing the study due to an AE for those arms (2.5% and 1.8%, respectively). The sponsor is requested to provide explicit details regarding how these patients were treated and followed up from this point of discontinuation.

a. Was palbociclib or placebo continued as monotherapy in any patients? If so, how many in each arm?

b. If both letrozole and the placebo or palbociclib were discontinued, what is the difference between the group who permanently discontinuing the study and those labelled as permanently discontinuing letrozole?

Sponsor Response

Study A5481008 includes two distinct post-randomisation periods: (1) the active treatment phase which is the period from randomisation until the last dose of study treatment and (2) the overall survival follow up phase which is the period from last dose of study treatment until patient's death, withdrawal of consent, or loss to follow-up. A patient is considered to have permanently discontinued study when they are no longer receiving study treatment and are no longer being followed-up for overall survival.

Question a):

Palbociclib or placebo was not continued as monotherapy in any patients who either 'permanently discontinued study due to AE' or 'permanently discontinued letrozole due to AE'. Per protocol, patients discontinuing letrozole treatment due to a treatment-related toxicity could not continue on blinded therapy alone and were to be permanently discontinued from the active treatment phase of the study at which point they would enter the overall survival follow-up phase of the study unless the patient withdrew consent. As a result none of the patients who permanently discontinued letrozole continued with palbociclib or placebo as monotherapy.

Question b):

In Table 6, 'permanently discontinued study due AE' and 'permanently discontinued letrozole due to AE' represent 2 distinct scenarios.

'Permanently discontinued study due to AE' represent the number of patients who not only permanently discontinued study drug due to an adverse event but also withdrew study consent as a result of the adverse event. No additional data could be collected from these patients once they withdrew consent. This included information on anticancer treatment administered beyond study discontinuation.

'Permanently discontinued letrozole due to AE' represent the number of patients who permanently discontinued letrozole treatment as a result of an adverse event regardless of whether patients continue to be followed-up on study in the overall survival follow-up phase or withdrew consent as a result of the AE.

The number of patients reported under 'permanently discontinued study due to AE' is a

subset of the patients reported under 'permanently discontinued letrozole due to AE'.

During the follow-up period the following information were collected every 6 months: post study survival status, patient reported outcome questionnaires, and details of any new anticancer therapies. The choice of follow-up anticancer therapy was left at the investigator's discretion. Follow-up systemic treatments are summarised in Section 10.4 A5481008 Clinical Study Report.

Evaluator comment:

The sponsor's response is accepted.

12.6.14 Safety clinical question 14

QUESTION 14

Study A5481008: Events rates for TEAEs of thrombocytopenia were not reported as occurring below 10% in Study 1008. This is an artefact of the high cut-off threshold of ≥ 10% in either arm and use of separate MedDRA terms for TEAE reporting; the combination of treatment-related thrombocytopenia/platelet count decreased was 14.9% in the experimental arm and 1.4% in the comparator that is, a 10-fold increase in risk, with the lower cut-off of 5% reporting the treatment-related AEs. Furthermore with the lower threshold in the treatment-related events table, the adverse event of epistaxis also emerges which could be linked to the low platelets (any correlation of these 2 adverse events should be addressed in the clinical overview and safety section when providing the CSR for Study 1008). When submitting the CSR for Study 1008, the sponsor is requested to include a table of TEAEs with a cut-off of 1% in either arm, treatment-related AEs with a cut-off of 1% in either arm to be consistent with the Grade 3/4/5 TEAE reporting provided. This will assist in identification of events that may require inclusion in the PI to inform clinicians and patients. The assessment of attribution of AEs considered treatment-related cannot be made without knowing the baseline percentage listed as treatment-emergent.

Sponsor Response

A5481008 Clinical Study Report Tables 14.3.1.1.3.1 and 14.3.1.2.4.1 provide the Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term (including Clusters of Preferred Terms) and Maximum CTCAE Grade in Descending Frequency Order (All causalities - All cycles and Treatment Related – All Cycles, respectively) without a frequency cut-off for the As Treated population. The following summary tables provide similar information but with a 1% cut-off as per the TGA's request.

- Table 1008.4083.1: Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term (including Clusters of Preferred Terms) and Maximum CTCAE Grade in Descending Frequency Order (All Causalities - All Cycles) reported in ≥ 1% of Patients.
- Table 1008.4083.2: Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term (including Clusters of Preferred Terms) and Maximum CTCAE Grade in Descending Frequency Order (Treatment Related - All Cycles) reported in ≥ 1% of Patients.

An evaluation of whether bleeding episodes (based on Standardized MedDRA Query of Hemorrhage terms, excluding laboratory terms) were associated with Thrombocytopenia events is discussed in the A5481008 Summary of Clinical Safety and Clinical Overview. A summary of the findings is provided below.

Thrombocytopenia experienced by patients in Study A5481008 as of 26 February 2016 is summarised below based on the cluster term THROMBOCYTOPENIA comprising the MedDRA Preferred Terms (PTs) of Thrombocytopenia and Platelet count decreased. All

causality THROMBOCYTOPENIA was reported in each treatment arm, with the frequency being higher in the palbociclib plus letrozole arm (15.5%) than in the placebo plus letrozole arm (1.4%) (A5481008 CSR Table 14.3.1.1.3.1).

Most AEs of THROMBOCYTOPENIA reported for patients in the palbociclib plus letrozole arm were of Grade 1 or Grade 2 severity (A5481008 CSR Table 14.3.1.1.3.1). THROMBOCYTOPENIA (14.6%) were considered to be related to treatment in most patients who had these events (A5481008 CSR Table 14.3.1.2.4.1). No events of THROMBOCYTOPENIA were assessed as serious (A5481008 CSR Table 14.3.1.4.1). There were no permanent discontinuations associated with THROMBOCYTOPENIA in either treatment arm (A5481008 CSR Table 14.3.1.5.1). Neither Grade 3 (1.4% of patients) nor Grade 4 (0.2%) THROMBOCYTOPENIA was associated with bleeding episodes (based on the Standardized MedDRA Query of Hemorrhage terms, excluding laboratory terms) in the palbociclib plus letrozole arm (Table 1) [Table 44 below].

Table 44: Summary of thrombocytopenia of Grade 3 or Grade 4 maximum severity (all cycles) reported in the palbociclib plus letrozole arm of Study A5481008 as of 26 February 2016 All treated patients.

Patient Category	Number (%) of Patients Palbociclib + Letrozole (N=444)
Patients with maximum Grade 3 THROMBOCYTOPENIA	**6 (1.4)**
With bleeding episodes[a]	0 (0)
With dose reduced/interrupted/cycle delayed due to Grade 3 or lower grade THROMBOCYTOPENIA	4 (66.7)
With permanent discontinuation due to Grade 3 or lower grade THROMBOCYTOPENIA	0 (0)
Patients with maximum Grade 4 THROMBOCYTOPENIA	**1 (0.2)**
With bleeding episodes[a]	0 (0)
With dose reduced/interrupted/cycle delayed due to Grade 4 or lower grade THROMBOCYTOPENIA	1 (100.0)
With permanent discontinuation due to Grade 4 or lower grade THROMBOCYTOPENIA	0 (0)

Data source: A5481008 SCS Table 1008.403.2.
MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PTs=preferred terms; SCS=Summary of Clinical Safety.
Notes: 1) Includes data from the start of treatment up to and including 28 days after the last dose of any study drug.
2) Each patient is counted once based on the maximum severity grade reported for the event.
3) THROMBOCYTOPENIA=PTs Thrombocytopenia and Platelet count decreased.
a. Based on the Standardized MedDRA Query of Hemorrhage terms, excluding laboratory terms.

Overall, the review of THROMBOCYTOPENIA in Study A5481008 is consistent with the known safety profile of palbociclib.

Evaluator comment:

Thrombocytopenia is included in the draft PI in adverse event tables and is described under 'myelosuppression' as an identified risk in the RMP.

The sponsor's response is accepted.

12.6.15 Safety clinical question 15

QUESTION 15

Study A5481008: Table 10, top-line summary provide frequencies for treatment-related adverse events by frequency of at least 5% in either arm. Given, rare events will be missed by presentation this way, the sponsor is requested to provide a table where the cut-off is 1% in either arm when submitting the CSR for Study 1008. The same threshold should be used for the TEAEs – it would be acceptable to add in a table to capture this rate of events. It is

recommended that these issues be addressed when submitting the Study 1008 to facilitate any evaluation.

Sponsor Response

Please refer to Safety Question 14

Evaluator comment:

It is presumed the sponsor meant to refer to 'Safety Question 14', not 'Efficacy Question 14'.

The sponsor's response is accepted.

12.6.16 Safety clinical question 16

QUESTION 16

Investigator-initiated research death on study: The narrative could not be located for evaluation of the case of ischaemic colitis on palbociclib monotherapy, and the sponsor is requested to provide a copy of it in the s31 response.

Sponsor Response

> *The Clinical Evaluation Report presents commentary under Section 8.4.5.4 on page 160 and page 161 and Section 8.8 page 174 regarding an Investigator-initiated research (IIR) death on-study from ischaemic colitis. A search was conducted for cases of ischaemic colitis (PT = Colitis ischaemic) reported to the Pfizer Safety database through November 10, 2016. There were two cases of ischaemic colitis reported from IIR studies and one case of ischaemic colitis reported in the Pfizer-sponsored Study A5481003. None of these cases had a fatal outcome. The sponsor accordingly notes these statements in the clinical evaluation as errors of fact. Key information on these cases is summarised in Table 1. Palbociclib was administered for 3 weeks followed by a scheduled 1 week off therapy (Schedule 3/1) in all of the 3 cases described below. The CIOMS reports of these cases are appended below.*

Evaluator comment:

The first round Clinical Evaluator raised concerns around differential incidence of thromboembolic adverse events in clinical studies (ischaemic colitis and DVT/PE), including:

Study 1001 (Grade 4 PE)

Study 1003 (2 DVT's and 7 PE's, 6 of which were Grade 4, and 1 case of ischaemic colitis, in the active arm of n=95 versus zero cases in the letrozole alone arm)

Study 1004 (in myeloma patients: 1 case of DVT)

Study 1023 (9 events including 1 death, compared to 1 Grade 2 event in the placebo + fulvestrant arm))

Investigator-initiated research (2 cases of ischaemic colitis, both non-fatal, as identified by the sponsor in their response)

The evaluator also notes treatment-emergent cases in Study 1023 that were not considered as they'd been allocated treatment-emergent status, and that this was likely due to investigators ascribing the events to the known elevated pro-thrombotic risk in cancer patients.

The sponsor has not addressed these concerns of the evaluator in their response to Question 16, however this issue is addressed in full detail [not included in this document].

The sponsor's response is accepted.

12.6.17 Safety clinical question 17

QUESTION 17

Study A5481023: The CTCAE grading system does not provide a numeric value for Grade 4 events of anaemia but defines this as 'Life-threatening consequences; urgent intervention indicated'. The sponsor is requested to provide the number of patients for whom transfusions were required in these circumstances and clinical details for such patients (Clinical Question).

Sponsor Response

As per CTCAE Version 4.0, Grade 3 anemia is defined as a condition in which either transfusion is indicated, or blood haemoglobin is <8g/dL (or both), while Grade 4 anemia is defined as a condition of reduced haemoglobin associated with either life-threatening consequences, or in which urgent intervention is indicated (or both). Thus, if a transfusion was given, the event anemia should generally be reported with severity of Grade 3 or Grade 4. However, oncologists may give a transfusion even if it is not strictly medically indicated, for example when haemoglobin levels are consistent with Grade 2 anemia in the absence of significant or clearly attributable symptomatology, or they may decide to transfuse a patient in anticipation of a further drop in haemoglobin. Further, whether a transfusion is considered indicated or not, is to some degree a subjective determination and there may not be agreement in every case among oncologists on the decision to transfuse a patient.

As of 31 July 2015, data cutoff date for the Study A5481023 90 Day Safety Update, Grade 3 ANEMIA (cluster term including the Preferred Terms of Anaemia, Haematocrit decreased, and Haemoglobin decreased) was reported in 12 patients (3.5%) on the palbociclib plus fulvestrant arm and 3 patients (1.7%) on the placebo plus fulvestrant arm. No Grade 4 ANEMIA was reported in either treatment arm (Table 1). Transfusions were administered to a total of 13 (3.8%) patients in the palbociclib plus fulvestrant arm and 5 patients (2.9%) in the placebo plus fulvestrant arm. Note that median treatment duration was longer for palbociclib (330 days; range: 1-596) than for fulvestrant in the control arm (137 days; range: 14-611).

As reported in Table 1, 5 of the 12 patients treated with palbociclib plus fulvestrant, for whom Grade 3 ANEMIA was reported, received at least one blood transfusion. Another 7 patients received a transfusion for Grade 2 Anaemia, while in 1 case a patient was transfused for Grade 1 Anaemia. Among patients treated with placebo plus fulvestrant, no patient for whom Grade 3 ANEMIA was reported, received a transfusion. Five patients received a transfusion for Grade 2 Anaemia. Of note, none of the cases for whom oncologists considered indicated a transfusion was reported as an SAE.

As reported in Table 1, in patients treated with palbociclib plus fulvestrant, Grade 3 Anaemia was the reason for palbociclib dose reduction in 1 patient (Patient ID [information redacted]; from 100 mg/day to 75 mg/day; Table 2), and Grade 2 Anaemia was the reason for palbociclib dosing interruption in 3 patients. In 1 patient Grade 2 Anaemia reported concurrently with Grade 2 Thrombocytopenia was associated with permanent discontinuation of study treatment (Patient ID [information redacted]; Table 2).

Clinical details and updated clinical outcomes (as of 31 October 2016) for the 13 patients in the palbociclib plus fulvestrant arm and 5 in the placebo plus fulvestrant arm who received blood transfusions are provided in Table 2.

Evaluator comment:

The sponsor's response is accepted.

12.6.18 Safety clinical question 18

QUESTION 18

Study A5481023: Study 1023 the CIOMS indicates that for the patient with 'drug-induced liver injury' (Subject No. [information redacted]) there was a substantial improvement in the liver function tests after discontinuing the study drugs, even though there is a background of progressive disease from which she died subsequently just over 2 months after the last dose of palbociclib. The evaluator agrees with the investigator and disagrees entirely with the conclusion of the sponsor who cite a 'progressive marked deterioration of hepatic function after discontinuation after study drugs' discontinuation' as a reason for this not being study related, when quite clearly, there was an improvement in liver function that would not be anticipated if this were solely progressive disease. The sponsor is requested to comment upon the quite dramatic improvement in liver function tests, the imaging results that suggest a new appearance to the liver contour, as these appear to have been overlooked in the causality assessment.

Sponsor Response

It appears the evaluator may have conflated the details of 2 cases with a reported PT of Hepatic Failure.

Case 1

The evaluator refers to Subject [information redacted] in the above question and in the Clinical Evaluation Report (CER) pages 132-133. The CIOMS narrative for patient [information redacted] is attached, from which it can be seen that patient 1 [information redacted] experienced a liver failure and disease progression and not drug-induced liver injury as reported by the evaluator. This serious adverse event (SAE) was consistently considered as not study drug related by both the Investigator and the sponsor.

A summary of Case [information redacted], Subject [information redacted], PT=Hepatic failure, is provided below:

This patient is a 36 year old female with metastatic breast cancer and a history of progressive metastatic liver disease who was treated with palbociclib and fulvestrant for 35 days while enrolled in Study A5481023. She was diagnosed with disease progression 34 days following initiation of treatment. It was planned to perform paracentesis and start chemotherapy, however, 9 days following the diagnosis of disease progression, total bilirubin was found to be 5.9mg/dL (reference range: 0.3-1.0 mg/dL) and liver failure was diagnosed (Preferred Term [PT] = Hepatic failure; Additional reported PTs were: Disease progression and Breast cancer metastatic, all reported events had a fatal outcome). Despite supportive therapy, the patient died 1 week later. An autopsy was not performed.

The investigator did not consider the reported hepatic failure to be related to blinded study drug (palbociclib), fulvestrant, goserelin, concomitant drugs or clinical trial procedure.

Discussion and Conclusion (Case 1)

As is evident from reviewing this case, the reported events are Hepatic failure, Disease progression, and Breast cancer metastatic, not Drug-induced liver injury. Further, there is no disagreement between the investigator and the sponsor in their causality assessment. Both agree that the hepatic failure was related to the underlying pre-existing hepatic disease, which became exacerbated when this patient experienced disease progression. Further, the statement made by the evaluator 'progressive marked deterioration of hepatic function after discontinuation after study drugs' discontinuation' does not seem to pertain to the case in question.

Case 2

A summary of the second case with the reported PT of Hepatic failure in Study A5481023 Case [information redacted], Subject [information redacted], is provided below and the CIOMS narrative attached:

A 56 year old female ([information redacted]) with breast cancer metastatic to the liver concomitantly treated with ergocalciferol and ascorbic acid was treated with palbociclib and fulvestrant while enrolled in Study A5481023 when liver dysfunction was noted on Day 35. There was no history of alcohol abuse, occupational exposure, or blood transfusion. Her baseline transaminases were abnormal (ALT=77 U/L; [reference range: 5-60] and AST=58 U/L [5-55]), while total bilirubin was normal (8µmol/L; [0-21]). The tumor marker Carbohydrate antigen 15-3 was elevated at 365 [0-25 U/L] at baseline while hepatic imaging at baseline showed 2 target lesions of 28 mm (segment V) and 26 mm (segment VII) in size. Her hepatic laboratory parameters on Day 15, 35, 50, 71, 77, and 98 on study were as follows: ALT [5-60 U/L]: 79, 186, 172, 249, 821, and 92 U/L; AST [5-55 U/L]: 68, 206, 392, 581, 2837, and 115 U/L; alkaline phosphatase [30-130 U/L]: 104, 238, 237, 883, U/L, and unavailable; total bilirubin [0-21µmol/L]: 4, 9, 9, 29, 45, and 22 µmol/L. Enlargement of hepatic target lesion in segment V from 28 to 30mm, and of hepatic target lesion in segment VII from 26 to 31mm was observed on Study Day 56. Study drugs were permanently discontinued on Day 57. The lesions had a decrease in density suggestive of necrosis and liver contour irregularities, as well as ascites were noted. On Day 77, tumor marker Ca15-3 increased to >3000 [0-25] from 365 at baseline. Testing for hepatitis A, B, and C was not performed. On Day 83, 4.2 liters of ascites were removed by paracentesis. She was considered recovered from the hepatic failure and was discharged the following day. On Day 98, her transaminases decreased to 1.53xULN (ALT) and 2.09xULN (AST), while GGT, which is indicative to biliary tract disease (not shown in table), was still elevated at 666 (no units or reference range provided).

A CT scan on Day 115 showed an increase in the number of hepatic metastases now occupying the majority of the liver, while there was no definitive biliary tree obstruction. The patient died on Day 121 from progression of breast cancer. An autopsy was not performed. While some progression of disease (not meeting RECIST criteria for progression) was noted, drug-induced hepatitis could not be ruled out and the observed hepatic contour irregularities were not present at baseline. The investigator considered that there was a reasonable possibility that the event was related to fulvestrant and blinded therapy (palbociclib), but not related to a concomitant drug or a clinical trial procedure. Although a significant rise in Carbohydrate antigen 15-3 was noted, drug induced hepatitis could not be totally excluded per the investigator.

The sponsor's assessment was as follows: 'The Company considers the event hepatic failure unrelated to blinded therapy (palbociclib or placebo) and fulvestrant and to any clinical trial procedure. The progressive marked deterioration of hepatic function after study drugs' discontinuation would argue against drug-induced toxicity. The documented increased hepatic metastases likely played a major role towards the event. It should be noted that the subject presented slight elevation of alanine aminotransferase and aspartate aminotransferase at baseline.'

Per FDA's Guidance for Industry on Drug-Induced Liver Injury (DILI; http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf), cases of drug-induced hepatocellular injury that are sufficiently severe to cause hyperbilirubinemia are defined as 'Hy's Law cases' and are characterized by elevations of transaminases (ALT being more specific than AST) by at least 3xULN and elevation of serum TBL[32] to >2xULN in the absence of initial findings of cholestasis (serum alkaline phosphatase <2xULN). However, concurrent elevations of transaminases and alkaline phosphatase may occur as

[32] TBL = total bilirubin

well and could signal a cholestatic type of liver injury or a biliary obstruction by a space occupying lesions, such as a tumor. As outlined in the FDA DILI Guidance, cholestatic liver injuries are generally considered to have a lesser likelihood of a fatal outcome. Of note, the above mentioned definition of a Hy's Law case does not necessarily fully apply to patients with abnormal liver laboratory parameters at baseline, nor was the Guidance developed considering the special circumstances of patients with hepatic metastases, as is acknowledged in the Guidance itself.

Table 3 examines the laboratory values again, additionally looking at the ULN over time.

Discussion (Case 2)

This patient's course is characterized by a rise in ALT and AST from an abnormal baseline to about 3xULN on Day 35 of treatment. The patient was diagnosed with hepatic failure, even though her bilirubin remained normal at this time and there was no evidence of coagulopathy or hepatic encephalopathy. Palbociclib was held. Over the next 42 days, her labs progressively worsened despite no longer being treated with study drugs. Bilirubin became marginally elevated (1.38xULN) only 36 days after last study drug administration, and reached 2.14xULN another 6 days later. At this point her prothrombin time became abnormal (17.4s) and concurrently, the tumor marker Ca 15-3 became elevated by a factor of at least 8.2 of her baseline and by a factor of at least 120 of normal. The R-value, which is used to distinguish hepatocellular, from mixed type, and cholestatic injury was initially 1.69 (Day 35) and later 1.58 (Day 50) and 0.61 (Day 71), thus categorizing the injury as a cholestatic one in this case.[33] Five days later, a large amount (4.2 liters) of ascites was removed and the patient was considered to have recovered from hepatic failure. The most significant rise in transaminases was observed not with the more liver specific enzyme ALT, but with AST, which reached 51.58xULN, while ALT reached 13.68xULN. While liver injury is almost always associated with a rise in both ALT and AST, the preponderance of AST elevation by a factor of almost 4 compared with the observed ALT increase could indicate an extrahepatic cause, which may have contributed to the observed laboratory findings and may have been in addition to any hepatic injury. In fact the relative imbalance between AST and ALT elevation (favouring AST over ALT) is may be atypical for cases of drug-induced liver injury, and the added value of AST may be limited to narrow the differential diagnosis (for example, differentiating muscle-related from liver related ALT elevations, etc.)[1]. Thus it is possible that at least a proportion of the rise of those enzymes may be accounted for by an extrahepatic cause (muscle injury or cell lysis, for example), while the progression of the hepatic metastases as evidenced by the rise in tumor marker and the CT scan findings could be the main factor responsible for the rise in bilirubin. Alternatively, a preponderance of AST over ALT may be indicative of ischemic injury[2] (see Giannini et al, Table 2[34]) which is also supported by the time course of transaminase elevations and bilirubin observed with ischemic injury (see Giannini et al, Figure 3).

As pointed out by the evaluator, hepatic contour abnormalities were observed at some point subsequent to Cycle 2 in this case. The extent and precise nature of these abnormalities are not clear, however, the medical literature indicates that abnormalities of the hepatic contour are not infrequently (75%) observed in breast cancer patients with hepatic metastases undergoing chemotherapy[3,4]. Hepatic contour abnormalities can be the one of the first abnormalities noted in breast cancer patients with hepatic metastases that develop pseudocirrhosis while undergoing treatment. As defined by Jeong[3], 'Pseudocirrhosis is a radiologic term that describes the serial development of diffuse

[33] An R value less than 2 indicates cholestatic injury per the NIH: https://livertox.nih.gov/glossary.html#jumpr

[34] Giannini EG, Testa R, Savarino V. Liver enzyme alterations: a guide for clinicians. CMAJ, 2005 Feb 1; 172(3): 367-379

hepatic nodularity caused by chemotherapy for hepatic metastasis, especially from breast cancer. It is characterized by morphologic changes mimicking liver cirrhosis following chronic liver disease, such as multifocal capsular retraction and enlargement of the caudate lobe, and is a potential cause of portal hypertension and hepatic failure.' Interestingly, almost all case reports[5-7] of hepatic pseudocirrhosis presented in below referenced literature articles indicate that elevation of AST was greater than that of ALT, which is consistent with this reported case of hepatic failure. Thus, there is a possibility that the hepatic failure observed in this patient could have been the result of the development of hepatic pseudocirrhosis. Hepatic failure in the context of pseudocirrhosis has been recently reported in 2 palbociclib treated patients. Vuppalanchi et al[8] seem at least partly to rely on the DILIN and RUCAM severity scores when concluding that palbociclib may likely be the cause of the observed pseudocirrhosis in these 2 patient, however, it appears that the specific and very complex clinical scenarios that are typically encountered in patients with advanced, as well as pre-treated metastatic breast cancer hardly lend themselves to the simple application of what might otherwise be a useful screening tool for drug-induced hepatotoxicity (see also: http://www.livertox.nih.gov/rucam.html). Overall, the information provided in this literature case report of 2 patients treated with palbociclib and letrozole for metastatic breast cancer does not provide sufficient evidence to establish a causal role of palbociclib, particularly since hepatic pseudocirrhosis is a well described, yet poorly understood phenomenon, which appears to be closely related to the diagnosis of metastatic breast cancer itself, and has never been linked to any specific chemotherapeutic or other compound. Pseudocirrhosis is a poorly defined predominantly radiographic term used to describe imaging findings not uncommonly encountered in patients with hepatic metastases from breast cancer independent of administered treatment.

Whether pseudocirrhosis is the result of a response to treatment or the result of drug toxicity, or both, has not been unequivocally established and the answer to this question may differ from patient to patient.

Conclusion (Case 2)

There are multiple valid and reasonable perspectives in interpreting this patient's laboratory findings and clinical course. While the progressive laboratory abnormalities are somewhat delayed and hepatic failure (as evidence by rise in bilirubin and elevation of prothrombin time) does not develop until several weeks after study drug discontinuation, this time course does not exclude drug-induced causality and the ultimate near-normalization of transaminases could be interpreted as the delayed consequence of stopping the potentially offending agent. The much more significant rise in AST (compared to ALT) could point to an ischemic event. Alternatively, this case could be interpreted as a case of possible hepatic pseudocirrhosis, since there are similarities to other such cases described in breast cancer patients with hepatic metastases. The greater rise of AST over ALT, the cholestatic component (AP, GGT), the noted hepatic imaging abnormalities (abnormal contour), and the ultimate outcome are in favor of this interpretation. Even though this entity is relatively well described, no agent has ever been causally associated with hepatic pseudocirrhosis. Based on the available evidence, it appears that hepatic pseudocirrhosis is in fact linked much more strongly to the underlying disease itself than to any specific treatment related toxicity. As such, it does appear reasonable to consider the hepatic failure experienced by this patient as a disease related process and not a drug related toxicity. The near-normalization of transaminases shortly before the patient's demise could be explained by the fact that based on the rise of Carbohydrate antigen 15-3, the findings on CT scan (increase in the number of hepatic metastases now occupying the majority of the liver), and the patients decreased synthetic hepatic function (prolongation of PT and decrease in serum albumin), this patient's remaining functional liver tissue was likely to be marginal, thus only small amounts of hepatic cells remained available to

release any further ALT or AST into serum.

References

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4. *Young ST, Paulson EK, Washington K, Gulliver DJ, Vredenburgh JJ, Baker ME. CT of the Liver in Patients with Metastatic Breast Carcinoma Treated by Chemotherapy: Findings Simulating Cirrhosis. American Journal of Roentgenology 1994;163: 1385-1388.*
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7. *Adike A, Karlin N, Menias C, Carey EJ. Pseudocirrhosis: A Case Series and Literature Review. Case Rep Gastroenterol 2016;10:381-391*
8. *Vuppalanchi R, Saxena R, Storniolo AMV, Chalasani N. Pseudocirrhosis and Liver Failure in Patients with Metastatic Breast Cancer after Treatment With Palbociclib. Hepatology [doi: 10.1002/hep.28720]*

Evaluator comment:

Pseudocirrhosis, as noted in the sponsor's response, is a 'radiologic term that describes the serial development of diffuse hepatic nodularity caused by chemotherapy for hepatic metastasis, especially from breast cancer.' The pathophysiology appears to be variable and may overlap, that is, hepatic sinusoidal obstructive syndrome may be caused by a combination of direct effects of tumour cells, in addition to the effect of necrosis of tumour cells, caused by treatment.

With regard to palbociclib causality:

- AST and ALT elevation are known adverse effects of palbociclib, as demonstrated by the rates in active versus placebo arms of clinical trials PALOMA-1 and PALOMA-2.
- In the second case above (Study 1023 case [information redacted]/Subject [information redacted]), supported by the two cases reported by Vuppalanchi et al[35], it is possible that palbociclib treatment contributed to the development of pseudocirrhosis and hepatic failure. However, in all of these cases, metastatic disease in the liver confounds causality assessment.

There is limited data available on this possible adverse effect at this time, insufficient to warrant addition of pseudocirrhosis to the PI. However, close monitoring of hepatic adverse events is

[35] Vuppalanchi R, Saxena R, Storniolo AMV, Chalasani N. Pseudocirrhosis and Liver Failure in Patients with Metastatic Breast Cancer after Treatment With Palbociclib. Hepatology [doi: 10.1002/hep.28720]

warranted, and Product Safety Update Reports should include a signal analysis for hepatotoxicity. This has been addressed already by the sponsor: per the Australian Specific Annex to the European RMP: 'Pfizer has complied with the TGA request to add *Hepatic failure and drug-induced liver injury* as an Important Potential Risk, and *Male patients, including use in male breast cancer*[36], as Missing Information in the ASA only. These are agreed safety concerns for Australia that are additional to those included in the EU RMP.'

The sponsor's response is accepted.

12.6.19 Safety clinical question 19

QUESTION *19*

Study A5481023: no information is provided about the case of Grade 4 increase in bilirubin – please provide the clinical details for this patient surrounding this event, including details of all the liver function tests that were performed, any diagnostic imaging, whether the study drug dose was reduced, delayed or discontinued and comment on these.

Sponsor Response

> *The questions refers to Patient [information redacted], a 53-year old woman enrolled in Study A5481023 who had metastatic breast cancer (bone only disease). She had an ECOG performance status (PS) of 1 at study entry and a medical history negative for gastrointestinal diseases. There was no known history of alcohol abuse, occupational exposure or any pre-existing or concomitant liver disease or infection. Her hepatic laboratory parameters at start of palbociclib plus fulvestrant treatment were as follows: ALT 13 IU/L (normal range: 14-54 IU/L), AST 22 IU/L (normal range: 15-41 IU/L), alkaline phosphatase 86 IU/L (normal range: 32-92 IU/L), total bilirubin 0.5 mg/dL (normal range: 0.4-2 mg/dL).*
>
> *Concomitant drugs at study entry were: hydrocodone for pain, zoledronic acid for bone metastasis and supportive therapy.*
>
> *This patient received 19 cycles of palbociclib plus fulvestrant treatment and permanently discontinued treatment in July 2015, due to her refusal to continue participation for personal reasons (long distance to get to the hospital), not related to any adverse event occurrence. She remained on survival follow-up at the time of data cutoff.*
>
> *On Cycle 4 Day 15 (16 March 2014), palbociclib dose was reduced from 125 mg QD to 100 mg QD due to the occurrence of a Grade 3 neutropenia.*
>
> *On Cycle 18 Day 1 (8 May 2015) total bilirubin level was recorded as 55 mg/dL (Grade 4), while other hepatic laboratory parameters were within normal limits (ALT 17 IU/L, AST 24 IU/L , alkaline phosphatase 55 IU/L).At the end of Cycle 18, total bilirubin was reported within normal limits (0.9 mg/dL; 4 June 2015). Of note, palbociclib had been temporarily stopped from 23 April 2015 due to another episode of Grade 3 neutropenia and re-started on 9 May 2015. Thus, the patient had been off palbociclib treatment slightly longer than 2 weeks when the Grade 4 total bilirubin increase was recorded in her CRF.*
>
> *Transaminases never increased above the normal range during the study treatment period. Similarly, total bilirubin was always within normal limits, with the exception of the increase noted at the beginning of Cycle 18. ECOG PS did not worsen during the course of study treatment. The palbociclib dose (100 mg QD) was not further reduced as a consequence of the recorded abnormal total bilirubin laboratory test result at the*

[36] The EU RMP includes *Male patients* as Missing Information, but does not specify the additional wording 'including use in male breast cancer'.

beginning of Cycle 18, which was indicative of hyperbilirubinemia. A tumor assessment performed on Cycle 18 Day 1 (8 May 2015) indicated stable disease for the recorded single skeleton lesion and a spiral CT scan did not reveal any new lesions. The investigator considered this transient Grade 4 total bilirubin value as not serious and it was not reported as an adverse event on the CRF.

In order to further explain the apparent discrepancy of the high total bilirubin level (55mg/dL), which appeared not to be consistent with the patient's clinical conditions, medical history and liver assessment, the sponsor recently verified this patient's laboratory values with the site and the Investigator. Of note, a query in this regards had been previously generated during the Study A5481023 data cleaning, but at that time the Investigator mistakenly confirmed the incorrect total bilirubin value. This result was then re-queried and the sponsor ultimately received confirmation that the total bilirubin value of 55 mg/dL was erroneously recorded in this patient's CRF. The study database has now been appropriately updated, by recording the correct total bilirubin value, 1.0 mg/dL, at Cycle 18 Day 1.

Evaluator comment:

The sponsor's response is accepted.

12.6.20 Safety clinical question 20

QUESTION 20

Study 1003: the remaining CIOMS for the SAEs (acute renal failure) and 2 Grade 3 events (nephropathy[37] and nephrolithiasis) of renal and urinary disorders could not be located and should be provided by the sponsor.

Sponsor Response

In Study A5481003 there was one case each reported for Acute kidney injury (Grade 3), Nephrolithiasis (Grade 3) and Nephropathy (Grade 1). The sponsor would like to clarify there were no Grade 3 events of nephropathy in Study A5481003. There was one Grade 1 case reported (Subject [information redacted]) as noted on page 163 of the CER, however this was not an SAE and therefore a CIOMS narrative is not available.

One case of Grade 3 Acute kidney injury (Preferred Term) was reported (Subject ID [information redacted], Case No. [information redacted]) and the CIOMS narrative for this patient was provided in Module 5.3.5.1, Study A5481003 Narratives-SAE-Other-90D-SU on page 100.

One case of Grade 3 Nephrolithiasis was reported (Subject ID [information redacted], Case No. [information redacted]) and the CIOMS narrative for this patient was provided in Module 5.3.5.1, Study A5481003 Clinical Study Report on page 1388.

Evaluator comment:

The CIOMS have been reviewed.

Case No. [information redacted] was acute renal failure secondary to bilateral ureteric involvement of metastatic disease in the sacrum. Alternatively could have been caused by radiological contrast from a CT performed 6 days prior to onset (this seems unlikely though).

Case [information redacted] occurred in a subject with an approximately 20 month history of chronic pancreatitis and pyelonephritis, who developed renal calculus with right ureteric obstruction. It had resolved by 9 days after onset, and palbociclib was recommenced.

[37]Nephropathy was Grade 1

The sponsor's response is accepted.

12.6.21 Safety clinical question 21

QUESTION 21

Study 1023: the Study protocol states that CTCAE v 4.0 was used. A review of this reveals no such classification of Grade 1 for ventricular tachycardia (as this necessarily requires medical attention). Similarly, there are no CTCAE terms for 'bradycardia', 'tachycardia' or 'ventricular extrasystoles.' The sponsor is requested to comment and provide updated details and classifications regarding these adverse events, and to provide clinical details surrounding the event of ventricular tachycardia.

Sponsor Response

For clarity the sponsor has addressed the query in 3 different parts.

1. *'A review of this reveals no such classification of Grade 1 for ventricular tachycardia…'*

The sponsor concurs that there is not a CTCAE grading of Grade 1 for the event 'ventricular tachycardia'. The site was queried and the database has been appropriately updated. This will also be corrected in the next CSR. Please see #3 below for the narrative with the clinical details of this case.

2. *'Similarly, there are no CTCAE terms for 'bradycardia', 'tachycardia' or 'ventricular extrasystoles.'*

For the grading of the adverse events (CTCAE, version 4.0) of 'bradycardia', 'tachycardia' or 'ventricular extrasystole' the existing classifications of 'sinus bradycardia', 'sinus tachycardia' and 'ventricular arrhythmia' can be used respectively.

3. *Please see below the clinical detailed narrative for the 1 report of ventricular tachycardia:*

Patient [information redacted]: Ventricular Tachycardia

This is a 63-year-old Russian female with a past medical history of hypertension since February 2012, ischemic heart disease since February 2012, obesity Grade 3 (126 kg) and chronic pancreatitis since December 2011. The patient did not receive any concomitant medications prior to start of study treatment (11 July 2014), and was only treated with a paracetamol preparation for the flu in October 2014. The patient was initially diagnosed with stage IIA ductal carcinoma of the left breast unknown grade on 14 February 2012. She underwent radical resection of the left breast in February 2012, adjuvant radiation to the left breast and left regional lymph nodes in April 2012 and adjuvant anastrozole therapy from November 2013 until documented progression in May 2014. The patient had visceral disease at the time of study entry, which included a liver lesion on segment VI as well a non-target lesion in the lung. Electrolyte laboratory test results on Cycle 1 Day 1 (11 July 2014) included: calcium, 2.7 mmol/L (2.20-2.65mmol/L); magnesium, 0.8 mmol/L (0.73-1.03 mmol/L); potassium was not done. The results of her screening ECGs (triplicate) are shown in Table 1.

The patient was treated for six cycles until disease progression in lung and skin, documented on 29 December 2014. The last dose of palbociclib was given on 01 Jan 2015 and she was discontinued from treatment on 02 Jan 2015 due to disease progression. The end of treatment (EOT) visit occurred on 12 January 2015. The patient subsequently started paclitaxel chemotherapy on 2 March 2015 and the patient was alive and remained on long term follow up at the time of the data cutoff date of 31 July 2015.

At the time of the EOT visit (12 days after the last dose of palbociclib was taken) electrolyte laboratory test results on that day included: calcium, 2.35 mmol/L (2.20-2.65mmol/L);

magnesium, 0.85 mmol/L (0.73-1.03 mmol/L); and potassium, 4.2 mmol/L (3.5-5.1 mmol/L). Additionally, study mandated ECGs (triplicate) were performed, and results are shown below in Table 2. Grade 1 AEs of Atrial fibrillation and Ventricular tachycardia (VT) were documented on that date. The investigator assessed these events as possibly related to palbociclib and fulvestrant. No treatment was given for the AE of atrial fibrillation and the AE was still ongoing at the time of data cutoff. However, upon query, the site indicated that this patient was asymptomatic and that the adverse event of VT was entered in error. The CRF was updated accordingly.

Evaluator comment:

The sponsor's response is accepted.

12.6.22 Safety clinical question 22

QUESTION 22

Given the proposed usage is in postmenopausal women and the frequency in older women, the sponsor is requested to provide a breakdown for the events reported in Table 45, 90-day safety update for those > 75 years of age and include this in the PI.

Sponsor Response

As requested, the sponsor is providing the updated Table 45 reported in the 90-Day Safety Update, with the age subgroups defined as <65 years, ≥ 65 to ≤75 years and >75 years (Table 1 in this document). The subgroup of patients >75 years is smaller than the other 2 subgroups of patients in both treatment arms and in particular in the placebo plus fulvestrant arm (N=5) (Table 1). Overall, the summary of AEs was generally comparable among the 3 age subgroups in the palbociclib plus fulvestrant arm. Some frequency differences were present in the subgroup of patients >75 years who were treated with placebo plus fulvestrant compared to the other 2 age subgroups. These differences were very likely due to the low number of patients included in this subgroup. The sponsor does not believe any update to the PI is warranted.

Evaluator comment:

The sponsor's response is accepted.

12.6.23 Safety clinical question 23

QUESTION 23

Study 1003: The sponsor is requested to explain the unusual dose levels in the range accompanying the median daily dose included in the Phase II part of Study 1003 (stated range: 79.6 mg to 266.7 mg).

Sponsor Response

The average daily dose administrated for palbociclib in Study 1003 was calculated using the following formula:

Average Daily Dose Administered (mg) = (Total dose administered)/(Total days on drug)

As shown in Table 1 [Table 45 below], the range of average daily dose administered of palbociclib was 79.6 mg to 266.7 mg.

The minimum value of the range of the average daily dose administered of palbociclib (79.6 mg) was attributed by Patient 11433007. She was treated with palbociclib 125 mg on Schedule 3/1 (3 weeks of treatment followed by 1 week off treatment) in Cycle 1, 100 mg on Schedule 3/1 in Cycles 2 and 3, and 75 mg on Schedule 3/1 from Cycle 4 to Cycle 22.

The maximum value of the range of the average daily dose administered of palbociclib (266.7 mg) was attributed by Patient 10793003. She took 250 mg of palbociclib daily from Day 1 to Day 16 of Cycle 1, and 400 mg daily from Day 17 to Day 18 due to dispensing error by the site.

Table 45: Average daily dose of palbociclib + letrozole

Table 1: Average Daily Dose of Palbociclib + Letrozole

	Palbociclib + Letrozole (N=83)
Average Daily Dose Administered (mg)	
Mean (STD)	119.5 (19.86)
Median	125.0
(Min, Max)	(79.6, 266.7)

Source: Table 14.4.1.3.1.2.b
Abbreviations: Min= minmum; Max= maximum; STD=Standard deviation.

Evaluator comment:

The sponsor's response is accepted.

12.6.24 Safety clinical question 24

QUESTION 24

Thrombocytopenia/platelet count decreased was more common (19.3%) with palbociclib and letrozole compared with letrozole alone (1.3%), including Grade 3 events. There was an increased rate of epistaxis (6% versus 1.3%; all Grade 1 events in both arms) in the palbociclib and letrozole arm. Whether these were associated with thrombocytopenia is not discussed and the sponsor is requested to state: a. the platelet count at the time of each event of epistaxis for these patients b. provide a breakdown of the events by MedDRA PT of any haemorrhage or bleeding in any organ, by treatment arm with the platelet count at that time for each patient experiencing an event.

Sponsor Response

Response a)

As of the A5481003 CSR data cut-off (29-Nov-2013), there were 9 patients (10.8%) who experienced Grade 1 Epistaxis on the palbociclib plus letrozole arm vs. 1 patient (1.3%) on the letrozole arm (A5481003 CSR Table 14.3.1.1.2.b). As of the updated data cut-off of 02-Jan-2015, the numbers remained the same: 10.8% vs. 1.3% (Table 14.3.1.1.2.b). The platelet count at the time of each event of epistaxis for the 9 patients from the palbociclib plus letrozole arm and 1 patient from the letrozole arm are listed below:

Response b)

Based on the search of database (as of the data cut-off of 02-Jan-2015) using the Standardized MedDRA Queries (SMQ) Haemorrhage terms in the following patients with the corresponding adverse event, and each patient's platelet count at the time of the event are listed below:

Summary:

Twelve episodes of epistaxis were experienced by 9 patients treated with palbociclib plus letrozole in Study A5481003. In only 2 of those 12 episodes, were platelet counts below the lower limit of normal. The lowest abnormal platelet count was 52 x 10^9/L, while the other abnormal platelet counts were 88, 83, and 139 x 10^9/L. Four patients treated with palbociclib plus letrozole experienced bleeding events other than epistaxis, one of which (Patient [information redacted]) additionally experienced epistaxis. These events were

Gingival bleeding, Haematoma (x2), and Petechiae. Abnormal platelet counts were observed in the patient with Petechiae (72 x 10^9/L) and in one of the patients with Haematoma (78 x 10^9/L).

Conclusions:

While epistaxis occurred more frequently on the palbociclib plus letrozole arm of the study than in the letrozole alone arm, other bleeding events were distributed evenly between treatment arms. Most bleeding events (particularly those of epistaxis) were not associated with thrombocytopenia.

Evaluator comment:

Two cases of significant bleeding issues in context of thrombocytopenia are identified in Study 1003.

The sponsor's response is accepted.

12.6.25 Safety clinical question 25

QUESTION 25

Study 1003: The sponsor states: 'Both patients (2.4%) with Grade 3 Thrombocytopenia in the palbociclib plus letrozole arm had their dose reduced, interrupted or their cycle delayed (due to Grade 3 or lower Thrombocytopenia). No patients in either treatment arm were permanently discontinued due to a TEAE of Grade 3 Thrombocytopenia. No patients in either treatment arm had a TEAE of Grade 4 Thrombocytopenia. None of the events of Thrombocytopenia were serious or led to death' Study 1003 CSR. The sponsor is requested to provide the same information regarding any adverse events or dose level and schedule adjustments for the 2 cases with Grade 3 platelet count decreased adverse events (Clinical Questions).

Sponsor Response

In Study 1003, there were no cases of Grade 3 Platelet count decreased. The sponsor believes the query refers to the 2 patients with Grade 3 Thrombocytopenia, Patients 11053004 and 11403001. The adverse events experienced by each patient along with dose reduction or interruption data are provided below. Note: the protocol defined cycle length is 28 days on Schedule 3/1 (3 weeks on treatment followed by 1 week off treatment).

Patient [information redacted] had her dose reduced from 125 mg QD to 100 mg QD at the start of Cycle 2 due to Grade 3 Leukopenia and dose interrupted during Cycle 3 due to Grade 4 Bone pain and Grade 3 Thrombocytopenia. Other adverse events experienced by the patient are listed below:

Patient [information redacted] had her dose reduced from 125 mg QD to 100 mg QD at the start of Cycle 2 due to Grade 3 Neutropenia and further reduced to 75 mg QD at the start of Cycle 23 due to Grade 3 Neutropenia and Grade 3 Thrombocytopenia. The patient had delay in starting Cycles 2, 14, and 16-22 due to Grade 3 Neutropenia. Other adverse events experienced by the patient are listed below:

Evaluator comment:

The sponsor's response is accepted.

12.6.26 Safety clinical question 26

QUESTION 26

Study 1003: No update of Table 68 from the CSR Overview of treatment-emergent adverse

events Phase II As treated set, Study A5481003 CSR, cut-off date November 29 2013 was provided, nor text to update this information – the sponsor is requested to provide an updated table containing the latest data.

Sponsor Response

The update of Table 68 from the CSR for Study A5481003 is provided below with the data cut-off of 02 January 2015 (Table 1).

Evaluator comments:

The updated table is not very different from that using the previous cut-off date (reproduced in this CER), despite the extra approximately 1 year of follow up time.

The sponsor's response is accepted.

12.6.27 Safety clinical question 27

QUESTION 27

Investigator-initiated research: the safety update report states that detailed narratives are available in Appendix 2 for all 4 patients where the events were considered treatment-related. The evaluator could not locate them in Appendix 2 and the sponsor is requested to provide these in the section 31 response for the two patients: a. the patient (Case Number [information redacted]) with dyspnoea and pneumonia who was discontinued from palbociclib on day 232 (why?) and then developed dyspnoea and a nosocomial infection on day 257. Pneumonitis or interstitial lung disease need to be considered.

Sponsor Response

The sponsor believes the query refers to page 146 of the sNDA Study A5481023 90 Day Safety Update which discusses four patients from Investigator-initiated research (IIR) studies: [information redacted]. The sponsor notes this query initially refers to narratives for four patients from IIR studies in the 90 Day Safety Update although the four patients are not specified. The query subsequently requests narratives for two patients although only specify the Case Number for one patient: [information redacted].

The sponsor is therefore not clear which narratives for which patients the assessor wishes to view and as such has provided the narratives for all four cases.

Investigator-initiated research studies are conducted separately to and independently of the sponsor. Reports of serious adverse events only are received from IIR studies into the Pfizer Safety database, therefore any information available on adverse events reported from IIR studies is contingent on the detail supplied. As is evident from the narrative of case [information redacted], the patient in question was extensively evaluated for her respiratory symptoms and a diagnosis of nosocomial pneumonia was made as a result. The CIOMS case narratives for cases [information redacted] are attached below.

Evaluator comments:

The CIOMS forms for all of these 4 patients have been reviewed and do not raise new safety concerns.

In the case specified by the first round evaluator ([information redacted]), hospital-acquired pneumonia was diagnosed after the subject had been in hospital for 3 weeks due to sepsis. Chest angio-CT showed pleural effusion, no PE, and right posterobasal parenchymal consolidation. The palbociclib and exemestane had been withdrawn at the time of admission for sepsis. Both sepsis and pneumonia resolved on May 11 after broad spectrum antibiotics, suggesting an infectious diagnosis.

The sponsor's response is accepted.

12.6.28 Safety clinical question 28

QUESTION 28 Investigator-initiated research palbociclib monotherapy for non-breast cancer patients: The 90-day report cites Table 5.8.1.2 as including 2 patients with fatal SAEs considered treatment-related (IIR SU Table 5.8.1.2) but the clinical evaluator notes 3 cases are listed here – no detailed narratives could be located for any of these 3 patients are the sponsor is requested to provide these.

Sponsor Response

> *This query seeks narratives from Investigator-initiated research (IIR) studies of palbociclib monotherapy for non-breast cancer for three patients with fatal SAEs considered treatment related in the sNDA Study A5481023 90 Day Safety Update. Investigator-initiated research studies are conducted separately to and independently of the sponsor. Reports of Serious adverse events (SAEs) are received from the IIR study into the Pfizer Safety database therefore information available for IIR adverse events is contingent on the level of detail supplied.*
>
> *The sponsor notes the query refers to '3 cases' however would like to clarify one case did not occur on study since death occurred >28 days after the last dose of palbociclib and therefore no narrative is available. For this patient the last dose of palbociclib treatment was recorded on Day 203 and death occurred on Day 256 (Table 5.8.1.5 Individual Listing of Deaths (Events with a Fatal Clinical Outcome) - Treatment Related).*
>
> *The sponsor believes the remaining two cases refer to Case No. [information redacted] and Case No. [information redacted] discussed in the 90 Day Safety Update. These two cases were male patients who received palbociclib monotherapy for gastrointestinal stromal tumour (GIST) and glioblastoma multiforme (GBM) respectively. The CIOMs narratives are provided herein.*
>
> *The sponsor is not clear on the relevance of the additional information requested for these two IIR cases of male patients with underlying tumour other than breast cancer, considering the clinical assessor opted not to evaluate the data set for Study A5481004 submitted in the initial registration application. Pages 26 and 109 of the Clinical Evaluation Report (CER) discuss that Study 1004, a Phase I/II Open-Label Study of the Safety and Efficacy of PD- 0332991 in combination with bortezomib and dexamethasone in patients with refractory multiple myeloma was not evaluated as the use and different disease does not provide supportive evidence for registration and does not contribute to the understanding of safety for the proposed usage.*

Evaluator comment:

The paragraph in the 90 day safety report (page 148) refers to two treatment-related cases amongst 16 SAEs that were fatal *on-study* in subjects receiving palbociclib monotherapy for non-breast malignant solid tumours.

The third case was not included in the paragraph as it occurred 53 days after study finish – this was a report of 'Death NOS' (not otherwise specified). The reporter causality was 'unrelated' and company causality was related. The reason for this causality assessment by the company is not clear but may be related to guidelines that are designed to avoid relevant reports being missed by regulators and may mean that some irrelevant reports/noise are included in reports to regulators. This case does not add meaningfully to safety knowledge around palbociclib.

The other two cases are described in brief in the safety update text on page 148 and the full CIOMS for both have been provided.

One ([information redacted]) was of sudden death in a 66 year old male patient with metastatic GIST, with narrative suggesting a cardiac sudden death as he was found sitting upright at home, and had a history of HT on beta-blockade, hypercholesterolaemia, coronary stenosis requiring

stenting and LVH. Renal insufficiency was reported as an additional term based on bloods taken in the community earlier the day of death, which showed creatinine of 224 µmol/ml and GFR 27.1.

The other ([information redacted]) is a fatal case of pneumonia in a 78 year old male subject with recurrent GBM. Three days after finishing his first cycle of palbociclib, he presented with acute abdominal pain, Grade 3 oral mucositis and blood results suggestive of bone marrow suppression (decreased WBC, ANC, lymphocytes and platelets). A CXR on day of admission showed consolidation and per the narrative, the patient died three days later 'due to lung infection (pneumonia) secondary to neutropenia.

The first case does not add to any particular safety signal, whilst the second is in keeping with the adverse event profile and precautions in the PI.

The sponsor's response is accepted.

12.6.29 Safety clinical question 29

QUESTION 29

Study 1023: Was a single patient able to be recorded as having both neutrophil count decreased and neutropenia by MedDRA PT (that is, 2 terms for the same clinical event)? If so, the sponsor is requested to provide the number of patients with an event of NEUTROPENIA (cluster term) without such double reporting (that is, individual patients should be presented as having only one event recorded).

Sponsor Response

The sponsor confirms that it is possible that for a patient with multiple episodes of low neutrophil counts, an investigator may report these findings using one verbatim term for some episodes and another one for others. Thus, during the AE coding process, these verbatim terms will have been coded as either Neutropenia (MedDRA Preferred Term) or Neutrophil count decreased (MedDRA Preferred Term) depending on the investigator terminology.

In Table 1, reported adverse events related to the observed decreased neutrophil counts are captured using the cluster term of NEUTROPENIA, which comprises the two MedDRA Preferred Terms (PTs) of Neutropenia and Neutrophil count decreased, thus avoiding any potential duplication of reporting decreased neutrophil counts in individual patients.

Table 46: Number of patients with treatment-emergent neutropenia listed by cluster term and by preferred term.

Table 1. Number of Patients with Treatment-emergent Neutropenia Listed by Cluster Term and by Preferred Terms

	Palbociclib/ Fulvestrant N=345 n (%)
	All Grades
Patients with NEUTROPENIA (cluster term)*	287 (83.2)
Patients with Neutropenia (PT) only	208 (60.3)
Patients with Neutrophil count decreased (PT) only	59 (17.1)
Patients with reports of Neutropenia (PT) and Neutrophil count decreased (PT)	20 (5.8)

Source: Tables 14.3.1.1.3.1 and 1023.686.1
*= NEUTROPENIA (cluster term) as reported in Table 14.3.1.1.3.1 from 90-Day Safety Update.
Abbreviations: n=number of patients with event.

Evaluator comment:

Although a single patient could have multiple terms recorded, a single episode would only be recorded as one or the other. The high rate of neutropenia is described in the PI under adverse effects.

The sponsor's response is accepted.

12.6.30 Safety clinical question 30

QUESTION 30

Study 1023: following on from the question immediately before this one, the figures do not appear to tally between Tables 7 and 21 compared with Table 22 for the number of patients reported to have Grade 3/4 events as defined by the cluster term NEUTROPENIA (Table 21 and subsequent text). 287 patients were reported to have NEUTROPENIA events of any severity (based on figures from Table 7) with the text following Table 21 stating 240 of these patients had Grade 3/4 severity (citing Table 7). However, Table 22 demonstrates that the number with maximum Grade of 3 was 191 patients and the number with a maximum of Grade 4 was 37 which equal 228 patients. The sponsor is requested to state which are the correct figures and explain why these differences occurred.

Sponsor Response

As requested, the sponsor is clarifying the differences in reporting adverse events (AEs) in Table 7, Table 21 and Table 22 reported in the Study A5481023 90 Day Safety Update (data cutoff date: 31 July 2015). The differences in the reported figures in the 3 tables are due to different ways of presenting these data and not due to data inconsistencies, as shown below.

Table 7 (Summary of All-Causality, Treatment-Emergent Adverse Events [All Cycles] Experienced by at Least 10% of Patients in Either Treatment Arm of Study A5481023 as of 31 July 2015 by MedDRA PT and Maximum Severity Grade Sorted by Decreasing Frequency [All Severity Grades] for Patients Receiving Palbociclib Plus Fulvestrant – All Treated Patients).

\This table includes all patients with AEs reported using MedDRA preferred terms (PTs) and each patient is counted once based on the highest severity grade reported for a specific event. In this table, patients with a reported event of Neutropenia and patients with a reported event of Neutrophil count decreased are shown separately. Thus, as an example, there were 152 patients in the palbociclib plus fulvestrant arm with Grade 3 Neutropenia, and for these 152 patients, the highest severity grade reported for Neutropenia was Grade 3.

Table 21 (Summary of Patients Who Experienced NEUTROPENIA [All Cycles] in Study A5481023 as of 31 July 2015 – All Treated Patients).

In this table, the decrease of neutrophil count is presented using the cluster term NEUTROPENIA, which comprises the MedDRA PTs of Neutropenia and Neutrophil count decreased. The purpose of using the cluster term is to show the number of patients who had at least one episode of decreased neutrophil count independent of the reported adverse event term. In cases of multiple episodes of decreased neutrophil count in the same patient investigators may have reported in the CRF only the PT Neutropenia, only the PT Neutrophil count decreased, or they may have reported both PTs for different episodes. In Table 7, the highest severity grade of Neutropenia and/or Neutrophil count decreased was reported for each patient. For this reason the total number of patients with NEUTROPENIA (n=287) in the palbociclib plus fulvestrant arm is lower than the total number of patients with Neutropenia (n=228) plus the total number of patients with Neutrophil count

decreased (n=79) in the palbociclib plus fulvestrant arm reported in Table 7.

Table 22 (Summary of Patients Who Experienced NEUTROPENIA of Grade 3 or Grade 4 Maximum Severity [All Cycles] in Study A5481023 as of 31 July 2015 – All Treated Patients).

The table includes patients with maximum Grade 3 NEUTROPENIA (cluster term) and those with maximum Grade 4 NEUTROPENIA (cluster term). As per the definition of the cluster term, patients with Grade 3 NEUTROPENIA are those patients who may have had their neutrophil count decrease reported using the PT Neutropenia or the PT Neutrophil count decreased, or both PTs for different episodes and the episode of decreased neutrophil count was of maximum Grade 3 severity in each at least once. The same applies for patients with Grade 4 NEUTROPENIA. Also, the highest severity grade was reported for each patient in this table. For the reasons described above, the total number of patients with maximum Grade 3 NEUTROPENIA (n=191 in investigational arm) is lower than the total number of patients with Grade 3 Neutropenia (n=152 in investigational arm, Table 7) plus the total number of patients with Grade 3 Neutrophil count decreased (n=50 in investigational arm, Table 7).

For these reasons, the sponsor considers the data in the above mentioned tables to be accurate.

Evaluator comment:

The sponsor's response is accepted.

12.6.31 Safety clinical question 31

QUESTION 31

Study 1023: The TEAEs should be a subset of the clinical laboratory abnormalities, as this AE grading is based on a blood test. The sponsor is requested to explain how there are discrepancies between the clinical laboratory abnormalities and the MedDRA PT reported AEs including:

a. More patients are reported to have Grade 3/4 neutropenia or neutrophil count decreased by MedDRA PT compared with those determined by clinical laboratory abnormalities (228 or 240 versus 225);

b. 2 patients in the comparator arm had Grade 4 events on blood tests which were not recorded as TEAEs. In a blinded study, any Grade 4 events of neutropenia should be reported as AEs but the 2 events in the placebo and fulvestrant arm were not recorded as AEs.

Sponsor Response

As previously discussed in the response to Safety Question 10, the sponsor reiterates that some differences may exist between the frequency of laboratory test abnormalities (for example, decrease in neutrophil counts) and the frequency of corresponding treatment emergent adverse events (TEAEs). Please refer to the response to Safety Question 10 for a more detailed explanation.

In order to clarify the figures reported in point a), the sponsor would like to refer the evaluator to Table 1 below [Table 47], which is derived from Table 14.3.1.1.3.1 (Summary of TEAEs by MedDRA Preferred Term [including Clusters of Preferred Term] and Maximum CTCAE Grade in Descending Frequency Order [All Causalities and All Cycles]- As Treated), which lists the frequencies of Neutropenia, Neutrophil count decreased and NEUTROPENIA (cluster term including the Preferred Terms of Neutropenia and Neutrophil count decreased)of Grade 3 and Grade 4 events. In addition, the laboratory data of absolute

neutrophil counts corresponding to Grade 3 and Grade 4 have been reported based on Table 14.3.4.1.5.1 (Summary Results of Labs by Maximum CTC Grade [Hematology, All Cycles] - As Treated).

Both Tables 14.3.1.1.3.1 and 14.3.4.1.5.1 are included in the 90-Day Safety Update (cutoff 31 July 2015).

Table 47: Summary of TEAEs of neutropenia, neutrophil count decreased and neutropenia and laboratory data of absolute neutrophil counts of Grade 3 and Grade 4

Table 1. Summary of TEAEs Neutropenia, Neutrophil count decreased and NEUTROPENIA, and Laboratory Data of Absolute neutrophil counts of Grade 3 and Grade 4.

		Palbociclib/Fulvestrant (N=345)		
		Grade 3	Grade 4	Grade 3+Grade 4
Patients with Adverse Event				
A	Neutropenia	152	26	178
B	Neutrophil count decreased	50	12	62
	Total	*202*	*38*	*240*
C	NEUTROPENIA (cluster term)	191	37	**228**
Patients with Laboratory Abnormality				
D	Absolute Neutrophil Count	189	36	**225**

Source: Tables 14.3.1.1.3.1 and 14.3.4.1.5.1.

Abbreviations: N=total number of patients; TEAE=Treatment-emergent adverse event

As discussed in the response to Safety Question 29, it is possible that in a patient with multiple episodes of low neutrophil counts, an investigator may report these findings using one verbatim term for some episodes and another one for others.

Similarly, during the AE coding process, reported verbatim terms or Lower Level Terms (LLTs) may have been coded as either Neutropenia (MedDRA Preferred Term) or Neutrophil count decreased (MedDRA Preferred Term).

For such patients with reports of both PTs (Neutropenia and Neutrophil count decreased), each Preferred Term is counted once as per maximum severity. As an example, the TEAE Grade 4 Neutropenia would be reflected in row A of Table 1, while the TEAE of Grade 4 Neutrophil count decreased would additionally be reflected in row B (Table 1). Therefore, both events are counted (once in row A and once in row B), even though only one patient is affected.

When using the NEUTROPENIA cluster term, only the maximum Grade of either reported PT (Neutropenia or Neutrophil count decreased) is counted in any one patient (see row C in Table 1).

Laboratory data that corroborate the low neutrophils reported as TEAE are reported in row D (Table 1).

In conclusion, the number of patients with maximum Grade 3 and Grade 4 NEUTROPENIA (228 patients) is not substantially different from the number of patients with Grade 3 and 4 neutropenia based on laboratory tests (225 patients). There are only 3 cases of Grade 3 and 4 NEUTROPENIA without a corresponding laboratory abnormality. This difference may be accounted for by additional hematologic testing performed by investigators which may not have been reported in the database.

As for point b), the sponsor acknowledges that the 2 cases of Grade 4 neutropenia based on laboratory tests should have been reported as TEAE.

Evaluator comment:

The sponsor's response is accepted.

12.6.32 Safety clinical question 32

QUESTION 32

The sponsor is requested to provide details of clinical laboratory findings for glucose for the 2 patients with cataracts and any elevated HbA1c results as this is more likely to capture events of hyperglycaemia than isolated terms used to identify TEAEs.

Sponsor Response

Clinical laboratory findings for glucose or HbA1c in Study 1003 are not available as such testing was not required per protocol.

Evaluator comment:

The sponsor's response is accepted.

12.6.33 Safety clinical question 33

QUESTION 33

The sponsor is requested to characterise further the nature of the conditions leading to reports of visual impairment and provide a discussion about the increased rate of events affecting vision/visual acuity which would compromise vision in those receiving palbociclib, as seen in Study 103 in the palbociclib and fulvestrant arm. Were there any preclinical data which identified visual impairment besides cataract development? The CIOMS and narrative for the patient with 'blindness' attributed to cerebral metastases is requested. This would require a significant metastasis or haemorrhage into such a lesion in the occipital region for such blindness to occur and be attributable to metastases.

Sponsor Response

The sponsor has separated the response into 3 separate parts.

Response Part 1:

Please see below the clinical details of the patients in Study A5481023 with a reported PT of Visual impairment. If during the data review additional ocular AEs were identified in any of these patients, these AEs were also included. Seven patients with pertinent adverse events (AEs) associated with visual impairment were identified and their narratives are presented in the following.

Patients included in the palbociclib and fulvestrant arm:

Patient [information redacted]: *This is a 48 year old white (72 kg) patient, with a past medical history of tibial and fibular fractures, and thalassemia minor. Concomitant medications include: magaldrate, paracetamol and ibandronate for bone metastatic disease. The patient was initially diagnosed with breast cancer in 2003, underwent surgical resection of the right breast and axillary dissection, followed by adjuvant doxorubicin and cyclophosphamide chemotherapy, adjuvant radiation to the right breast and adjuvant tamoxifen and LHRH agonist from 2004 until 2009, presented with metastatic disease in 2013. The patient was randomised into Study 1023 on 07 August 2014 with bone only disease. The patient did not have eye examinations performed during the study. During Cycle 8 (Day 22) a Grade 1 AE of 'visual disturbance' (code to PT= Visual impairment) was reported. The event was considered unrelated to study medication, but related to other illness of myopia, the AE was still present at the time of data cutoff. There*

was no associated SAE and no action was taken with study medication. Haemoglobin A1c was 6.2% (reference range: 4.0-6.0%) on Cycle 10. The patient remained on study treatment at the time of data cutoff.

Patient [information redacted]: *This is a 62 year old Asian (64.9 kg) patient, with a past medical history of hyperlipidaemia, wheezing, depression, cataracts and cervical polyp. Concomitant medications include: antimalarials, certizine, hydrochlorothiazide, fluoxetine, naproxen, paracetamol, systane lubricant and zolendronic acid. The patient was diagnosed with stage III locally advanced breast cancer in 2009, underwent surgical resection and axillary dissection of the left breast, followed by fluorouracil, epirubicin, cyclophosphamide, docetaxel chemotherapy, radiation to the breast and bone, followed by letrozole and exemestane. The patient was randomised into Study 1023 on July 2014, with bone only disease. The patient did not have eye examinations performed during the study. During Cycle 4 (Day 13), a Grade 1 AE of 'right eye visual problems' (code to PT= Visual impairment) was reported, the event was considered possibly related to palbociclib but not to fulvestrant, resolved after cataract removal. There was not associated SAE, and no action was taken with study medication. On Cycle 6 Day 13, a Grade 2 SAE of 'worsening cataracts' (coded to PT= Cataract) was reported (the event was considered medically significant by the investigator) the cataract was removed on 15 Feb 2016, the event was considered possibly related to palbociclib but not to fulvestrant. Two additional AEs of Grade 1 'dry eye' (coded to PT=Dry eye) were reported, the first occurring during Cycle 4 (Day 23) resolved and the second event began during Cycle 13 (Day 1) and was still present at the time of data cutoff, both events were considered possibly related to palbociclib and not to fulvestrant and no action was taken with study medication. Haemoglobin A1c was 33 mmol/mol (reference range: 0-42 mmol/mol) on Cycle 13 (Day 1). The patient remained on study treatment at the time of data cutoff.*

Patient [information redacted]: *This is a 57 year old white (66 kg) patient, with a past medical history of constipation, insomnia, obesity, osteopenia, intermittent vaginal infections. Concomitant medication include: alprazolam, calcium, ergocalciferol, eye drops and zolendronic acid. The patient was initially diagnosed with breast cancer in 1997, had a lumpectomy in 1997 and mastectomy in 2010, followed by adjuvant docetaxel and cyclophosphamide chemotherapy, adjuvant anastrozole, presented with metastatic disease in 2014. The patient was randomised into Study 1023 on 17 March 2014, with bone only disease. The patient did not have eye examinations performed during the study. During Cycle 3 (Day 1), an AE of Grade 1 of 'eye floaters' (coded to PT=Vitreous floaters) was reported, was not considered to be related to study medication, but to another unknown condition. There was no associated SAE and no action was taken with study medication. During Cycle 5 (Day 1), a Grade 2 'eye irritation' (coded to PT=Eye irritation) and a Grade 2 'vision change' (code to PT= Visual impairment) were reported, both were considered possibly related to palbociclib and not to fulvestrant. Both AEs resolved and no action was taken with study medication. Haemoglobin A1c was not collected. The patient remained on study treatment at the time of data cutoff.*

Patient [information redacted]: *This is a 51 year old white (111 kg) patient, with a past medical history of back pain, hiatal hernia, hot flashes, acid reflux and allergies. Concomitant medications include: Emergent-C, tums, fermented papaya, green tea, garlic capsules, ibuprofen, fiber, regenemax, selenium, lysine, compazine, loratidine, passiflora, omega-3 fatty acids, cetirizine and herbal preparations. The patient was initially diagnosed with breast cancer in 2009, underwent partial mastectomy in 2009 and total mastectomy with lymph node dissection in 2012, followed by adjuvant docetaxel and cyclophosphamide chemotherapy, adjuvant radiation therapy to the right breast and adjuvant therapy with tamoxifen, anastrozole and exemestane. The patient presented with metastatic disease in November 2013, the patient was randomised into Study 1023 on December 2013, with disease in the right chest wall and lymph nodes. The patient did not*

have eye examinations performed during the study. During Cycle 3 (Day 26) a Grade 1 AE of 'visual disturbance' (code to PT= Visual impairment) was reported, the AE resolved in 1 day was considered unrelated to study medication but related to an intercurrent illness. There was no associated SAE and no action was taken with study medication. Haemoglobin A1c was not collected. The patient was alive and remained on treatment up to Cycle 21 at the time of data cut-off.

Patient [information redacted]: *This is a 66 year old black (59.2 kg) patient, with a past medical history of arthritis, back pain, hypersensitivity, hypertension and skin hemorrhage (skin lesion upper back). Concomitant medications include: calcium, vitamins C and D, clodronic acid, zopiclone, mometasone furoate, cetirizine, naproxen, paracetamol and herbal preparations. The patient presented with stage IV at the time of the initial diagnosis in 2009, received treatment with letrozole from 2010-2012 and exemestane from 2012-2014. The patient was randomised into Study 1023 on 21 March 2014 with extensive disease sites including the breast, lung, liver, bone, lymph nodes, skin and thyroid. The patient had an eye examination during Cycle 8 (15 Oct 2014) visual acuity was 20/30 on the right eye and 20/40 on the left eye. On Cycle 7 Day 26 (29 Sept 2014), a Grade 1 AE of 'visual disturbance' (code to PT= Visual impairment) was reported, was considered unrelated to study medication but related to other unknown. There was no associated SAE and no action was taken with study medication. The AE was still present at the time of permanent treatment discontinuation during Cycle 14 during which the tumor assessment revealed stable disease; however the patient permanently discontinued treatment due to global health deterioration on 28 May 2015. Haemoglobin A1c was not collected. The patient was started on Tamoxifen and remained on long term follow up at the time of data cut-off.*

Patient [information redacted]: *This is a 49 year old white (61.1 kg) patient, with a past medical history of bone pain, constipation, insomnia and nausea. Concomitant medications include: calcium, Vitamins C and D, docusate, denosumab, trazodone, naproxen, hydromorphone and ranitidine. The patient was initially diagnosed with breast cancer in 2010, had a left modified radical mastectomy and axillary lymph node dissection in 2010, followed by adjuvant docetaxel, doxorubicin, cyclophosphamide chemotherapy and adjuvant tamoxifen, presented with metastatic disease in 2012 received letrozole, anastrozole and exemestane. The patient was randomised into Study 1023 on 25 July 2014, with bone and liver disease. During Cycle 2 (Day 7) (28 Aug 2014) a Grade 2 AE of 'visual distortion left eye' (code to PT= Visual impairment) was reported, the AE resolved in 1 day, the event was considered unrelated to study treatment but to other condition unknown. There was no associated SAE and no action was taken with study medication. The patient had protocol required eye examination on Cycle 2 (Day 17) (08 Sep 2014); visual acuity was 20/20 in both eyes, however the investigator reported an AE of 'right eye corneal spoke' (coded to PT= Corneal disorder) and an AE of 'left eye small clump of drusen along the interior arcade' (coded to PT= Eye disorder) both Grade 1 in severity based on the results of the eye examination. These AEs were still present at the time of data cutoff and were considered unrelated to study medication but to other condition unknown. There were no associated SAEs and no action was taken with study medication. Haemoglobin A1c was not collected. The patient permanently discontinued from the study because of disease progression on 15 Sep 2014, after which the patient was started on capecitabine. The patient remained on long term follow up at the time of data cut-off.*

Patients included in the placebo and fulvestrant arm:

Patient [information redacted]: *This is 65 year old white patient (63.9 kg), with a past medical history of reactive airway disease, gout, carotid endarterectomy and esophageal stricture. Concomitant medications include: amlodipine, docusate, dimenhydrinate, hydromorphone, lisinopril, lorazepam, pamidronate, paracetamol, pregabalin,*

prochlorperazine, ranitidine and sennosides. The patient was initially diagnosed with breast cancer in 2010, had a lumpectomy in 2010, followed by adjuvant tamoxifen, presented with metastatic disease in 2013 and received fluorouracil, doxorubicin, cyclophosphamide chemotherapy and letrozole for advanced disease. The patient was randomised into Study 1023 on 25 July 2014, with bone, liver lung and pleural disease. The patient did not have eye examination performed during the study. During Cycle 4 (Day 3), a Grade 1 AE of 'vision changes' (code to PT= Visual impairment) was reported, considered unrelated to study medication but to other condition unknown. This AE resolved in 1 day. There was no associated SAE and no action was taken with study medication. Haemoglobin A1c was not collected during the study. The patient permanently discontinued treatment because of disease progression on 03 Mar 2015, after which the patient was started on paclitaxel and reolysin, followed by exemestane/everolimus. The patient remained on long term follow up at the time data cutoff.

Discussion

As noted, the above patients had a variety of ocular adverse events, most of them were of Grade 1 in severity, and only 2 Grade 2 events of Visual impairment were reported. Most of the reported events were of short duration and most of the AE's were not considered related to the study medication. Furthermore, 6/7 patients had taken bone modifying drugs as concomitant medication, mostly bisphosphonates. Although ocular AEs of bisphosphonates are rare, they have been reported and include a spectrum of AEs from abnormal to blurred vision, ocular pain, photophobia, conjunctivitis, anterior uveitis, episcleritis, and scleritis.[1]

Response Part 2: *Where there any pre-clinical which identified visual impermanent besides cataracts?*

There were no preclinical findings with the potential to cause visual impairment other than cataracts and the microscopic correlate of lens degeneration (associated with alterations in glucose metabolism). The lens degeneration was seen in rats treated with the lowest dose (50 mg/kg in the female) and (10 mg/kg in the male). This exposure was comparable to clinical exposure.

Response Part 3: *The CIOMS/ narrative of the patient with 'blindness' is requested. The patient with reported 'blindness' is from Study 1003 and not Study 1023. The narrative report for this patient is appended to this response and a brief narrative is provided below:*

Patient [information redacted] (Study 1003): This is a 52-year-old White patient who was enrolled in Phase II Part 2 of the 1003 study, and was randomised to receive palbociclib and letrozole. The patient received study treatment from 02 Mar 2012 to 25 Sep 2013 for a (18 cycles). The patient was diagnosed with lobular breast cancer on 2009 and with metastatic disease on 28 Oct 2011. The patient had undergone a lumpectomy, lymphadenectomy, hysterectomy and bilateral uterine adnexectomy surgery followed by docetaxel, doxorubicin cyclophosphamide adjuvant chemotherapy, and radiation therapy and adjuvant tamoxifen. An AE Grade 2 of 'vision loss' (code to PT=Blindness) was reported on 16 September 2013. Due to this event a brain CT scan was performed on 16 Sep 2013. Since the patient continued to present with vision loss, a brain MRI was performed on 23 Sep 2013 which showed a new lesion (leptomeningeal carcinomatosis with involvement of optic nerve and cranial nerves), and the patient was permanently discontinued from treatment on 26 Sep 2013 due to objective progression. The post-study treatment of this patient included capecitabine started on 04 Oct 2013 ongoing at the time of data cut-off.

References:

1. Fraunfelder, Frederick W. & Fraunfelder, Frederick T. Bisphosphonates and Ocular Inflammation New England Journal of Medicine. 2003, 348:12, 1187-1188.

Evaluator comment:

Regarding response part 2 – the TGA toxicology reviewer noted these changes, which were correlated with a diabetic state and likely secondary to this. The current RMP includes hyperglycaemia as an important potential risk on this basis (see page 86 of European RMP).

The sponsor's response is accepted.

13 Study 1008 findings relevant to the round 2 evaluation

The following is a list of findings from Study 1008, which were assumed to be accurate in reviewing the above clinical and PK/PD questions (including those related to the PI/CMI) or in reviewing the second round product documentation.

i. A sensitivity analysis was performed to evaluate whether there was a difference when using CRF data for Disease Site as the stratification factor, compared to Impala data (sensitivity analysis #4 in Study A5481008 CSR). The results showed a HR of 0.572 with 95% CI (0.459, 0.713) similar to the primary PFS analysis which showed a HR of 0.576 with 95% CI (0.463, 0.718).

   Relevant to Efficacy question 7

ii. Pre-specified efficacy subgroup analyses were in the SAP, which specified the effect of age, ethnic origin, ECOG performance status, geographical region, selected biomarkers, and stratification factors on the primary PFS, OS, and OR endpoints may be evaluated. In addition, to assess the impact of the concomitant use of proton pump inhibitors and the impact of palbociclib administered under fasting conditions, PFS was also evaluated in the population excluding patients who took proton-pump inhibitors and/or any other antacid medications concomitantly with study drug under fasting conditions during the active treatment phase.'

   Relevant to Efficacy question 8

iii. As of the data cutoff date 26 February 2016 a total of 257 patients were still on study drug: 199 patients in the palbociclib + letrozole arm and 58 in the placebo + letrozole arm.

   Relevant to Efficacy question 9

iv. In describing some of the subjects who were censored in Study 1008 in the primary efficacy (PFS) analysis, the phrase/category 'in follow up for progression' is presumed to refer to subjects in whom progression has not yet occurred, and they are being followed up 'for progression' in that they are being followed up to see when progression will occur. The first round evaluator had thought this category potentially included subjects in whom progression had occurred, who remained on treatment and were being followed up due to diagnosis of progression not yet having been radiologically established. The sponsor's response indicates that all subjects in that category remained on treatment at the time of analysis, suggesting the former definition is correct.

   Relevant to Efficacy question 9

v. The sponsor indicates that CIOMS narratives for all cases in which a patient died without evidence of disease progression have been included in the CSR document in Section 143.3.1 of the CSR, whilst details and causality are summarised in Tables 50 and 51 of that document. There were more such cases in the active arm (7: 1.6%) than the control arm (2: 0.9%).

   Relevant to Efficacy question 10.

vi. The HR for the subgroup of patients with metastatic disease at diagnosis (de novo) for the active versus placebo arm falls just inside nominal statistical significance (0.674 [95% CI: 0.457, 0.993]) and was above 1 prior to data cleaning. However, given the natural history of de novo metastatic disease (no prior treatment, thus generally better response to initial treatment), it is possible that PFS in this group is a less mature dataset than other subgroups. Given that the data cut-off date for Study 1008 was ten months ago, is it possible to request an updated efficacy analysis in the de novo subgroup with a later cut-off date? Alternatively, the submission of further data to this point when available could be made a condition of registration, as this subgroup analysis should not be considered an absolute barrier to registration.

Relevant to Efficacy question 11.

vii. The sponsor in response to an s31 question provided efficacy data for all ER-/PR-positive subjects in Study 1023. There were 16 such subjects in total. Only one had an objective response, which lasted 3.71 months. This subject was in the placebo arm. There is no evidence for efficacy in this subgroup from this trial*. Restriction of the indication to 'ER-positive' rather than 'HR+' disease may be appropriate if there is no evidence of efficacy in ER-/PR-positive disease seen Study 1008.*

Relevant to Efficacy question 19.

viii. An imbalance in psychiatric disorders was seen between the palbociclib and placebo arm in trial 1023. The absolute number of cases was small enough that it is statistically not significant. However, if this trend was also seen in Study 1008 this would raise concerns for a safety signal.

Relevant to Safety question 2 and Safety question 4

ix. Is there evidence of an increased risk of bleeding in Study 1008?

Relevant to Safety question 14 and the case of subarachnoid haemorrhage noted in study 1010

x. Does Study 1008 support the proposed indication in the PI?

Relevant to PI text.

xi. Does the ECG sub-study of Study 1008 provide adequate evidence that QT prolongation is not a clinical concern, and support the proposed PI text?

Relevant to PI text**Error! Reference source not found.**

xii. PI text has been proposed that describes Study 1008 and its findings.

14 Second round benefit-risk assessment

14.1 Second round assessment of benefits

The second round evaluator is not able to make a full assessment of the treatment benefits due to the necessarily limited nature of the second round evaluation. However, the following has been noted in review of the sponsor's responses:

- Efficacy in ER-/PR-positive disease has not been separately established, but this is not considered a clinically relevant subgroup for the purposes of hormone-receptor based treatment.
- Evidence for efficacy in de novo disease only reaches statistical significance after data cleaning activities were carried out, with a HR of 0.674 [95% CI: 0.457, 0.993]. However,

the results are concordant with those for patients with other durations of remission prior to diagnosis of metastatic recurrence, and data maturity may improve with more time. The Delegate may wish to consider requiring submission of more mature data to this point as a condition of registration.

14.2 Second round assessment of risks

The second round evaluator is not able to make a full assessment of the treatment risks due to the necessarily limited nature of the second round evaluation. However, the following has been noted in review of the sponsor's responses:

- Consistent with palbociclib's mechanism of action, myelosuppression is the predominant adverse effect seen throughout clinical trials.
- Secondary susceptibility to infections also features, and it is worth considering that other events downstream of haematological insufficiencies should be monitored for in safety updates – particularly bleeding. The isolated case of a fatal sub-arachnoid haemorrhage in a Japanese subject in one of the supporting trials (Study 1010) appears to have been reported newly since the initial dossier was received, and is the principal reason for concern around monitoring for bleeding safety events. It is perfectly plausible that in subjects with other risk factors, palbociclib might elevate the risk of such events occurring.
- Other adverse effects are described adequately in the PI and include stomatitis, gastrointestinal symptomatology, mild vision disturbances, and skin-related symptoms.

14.3 Second round assessment of benefit-risk balance

The second round evaluator is not able to make a full assessment of the benefit-risk balance of this treatment due to process-related resource limitations.

15 Second round recommendation regarding authorisation

The second round evaluator is not able to make a recommendation regarding authorisation due to process-related resource limitations.

16 Clinical Evaluation Report for Study A5481008 (PALOMA-2)

16.1 Background

This supplementary clinical evaluation focuses on evaluation of the PALOMA-2 study (A5481008). This study is pivotal in support of one the two indications proposed by the sponsor for this product, namely:

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 or metastatic breast cancer:

- with letrozole as initial endocrine-based therapy in postmenopausal women

Top-line results from PALOMA-2 were included in the initial dossier, with the following documents included:

- The top-line summary document extended to 38 pages, plus Tables.

There are two first round clinical evaluation reports for this submission:

- palbociclib (Ibrance) - Pfizer - Submission PM-2016-01317-1-4 - Clinical Evaluation Report (CER) - Efficacy and safety
- palbociclib (Ibrance) - Pfizer - Submission PM-2016-01317-1-4 - Clinical Evaluation Report (CER) - Pharmacology

The first round evaluation of efficacy and safety ('CER-ES') did consider the top-line data noted above. In the sponsor's response to questions asked in that first round report, the full Clinical Study Report (CSR) for PALOMA-2 was supplied.

A single second round report has been written (by a different evaluator), addressing the sponsor's response to questions asked in both first round reports. The second round evaluator has not been asked to evaluate the full CSR for PALOMA-2; instead, it is being evaluated separately, by the Delegate, in this document.

This supplementary CER should be read in conjunction with the first round and second round reports mentioned above.

16.1.1 Contents of the clinical dossier

Only the full CSR for PALOMA-2 will be evaluated in this report. Other components of the sponsor's response are being evaluated in a second round report as noted earlier.

A supplemental Clinical Overview (date: 'Approved On: 14-Oct-2016') and summaries of efficacy and safety were also submitted in the later dossier version. These have been consulted only with regard to specific issues in PALOMA-2.

16.2 Pharmacokinetics

16.2.1 Background

The following information within the CSR for PALOMA-2 is considered relevant from a PK perspective:

Study 1008 used palbociclib free base capsules that were intended for commercialisation and have subsequently been approved for the use by multiple regulatory bodies including the United States (US) Food and Drug Administration (FDA). Initially, the administration instructions for the free base capsules in Study 1008 were consistent with the instructions provided for the isethionate capsules used in Study 1003, namely that patients were to be fasting from at least 1 hour before to at least 2 hours after administration of palbociclib / placebo capsules, referred to as 'minimally fasted conditions,' and there were no restrictions in the Study 1008 protocol with regard to the use of agents that suppress gastric acid production.

During study conduct, the results across several clinical pharmacology studies showed that approximately 13% of all PK profiles observed after palbociclib free base capsule formulations were administered in healthy subjects under an overnight fasted condition (single dose) were associated with substantially lower palbociclib exposure, compared with that seen with PK profiles from the rest of subjects. These profiles with substantially lower exposure, referred to as 'low-liers', were not observed when palbociclib free base capsules were administered with high-fat and low-fat meals or in between meals (that is, moderate-fat meal 1 hour before and 2 hours after dosing) in the food effect study (Study 1021). The administration of palbociclib with or in between meals eliminates the occurrence of low liers and significantly reduced the intersubject variability of AUC_{inf} and C_{max}, from 39% for AUC_{inf} and 73% for C_{max} under overnight fasted conditions to 23% to 27% for AUC_{inf} and 21% to 24% for C_{max} under fed conditions,

irrespective of the timing or the fat and calorie content of the food. Additionally, the supplemental analysis excluding low-liers from the overnight fasted treatment showed bioequivalence between palbociclib given under each of the fed conditions and palbociclib given under overnight fasted condition, indicating that food intake did not change the exposure of subjects who were not low-liers. In addition, the results from Study 1018 showed that palbociclib exposure was substantially decreased when palbociclib free base capsules were administered under fasted conditions concomitantly with PPIs. Therefore, protocol Amendment 2 of Study 1008 revised the study drug administration instructions from administration in a minimally fasted state to administration with food and also to prohibit the concomitant use of PPIs.

Taking into account the results from Studies 1018 and 1021, it was assumed that drug exposures in Study 1008 would be different in patients who took palbociclib in a minimally fasted state or in patients who took palbociclib under fasted conditions concomitantly with antacids (including local antacids and H2RAs in addition to PPIs, under the assumption that these agents would have a similar effect as PPIs when given concomitantly with palbociclib under fasted conditions) relative to those patients who did not. This assumed difference in drug exposure could potentially affect the efficacy outcome in these patients and thus the ability to estimate the treatment effect of palbociclib in the ITT population under the original study design. After the discussion with the US FDA, protocol Amendment 3 of Study 1008 was distributed to the study sites prior to the planned interim analysis to increase the sample size from 450 patients to 650 patients to preserve the desired statistical power and an alternative analysis population for the primary endpoint was included in the Statistical Analysis Plan (SAP) to assess the efficacy of palbociclib in the sub-population of patients who were administered palbociclib under fed conditions (that is, patients randomised after Amendment 2 of Study 1008 protocol was distributed to the study sites).

16.2.2 PK assessment in PALOMA-2

There was a PK assessment component to PALOMA-2. Palbociclib concentrations were measured to assess the following:

Table 48: Pharmacokinetic parameters assessed

Parameter	Definition	Method of Determination
	Group 1 [a] (Cycle 1 Day 14)	
C_{max}	Maximum observed plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
AUC_{24} [b]	Area under the plasma concentration-time curve from time 0 to 24 hours	Linear/Log trapezoidal method
CL/F	Apparent oral clearance at steadystate	Dose / AUC_{24}
	PK Analysis Set [c] (Day 14 of Cycles 1 and 2)	
C_{trough}	Pre-dose concentration s that met dose-compliant acceptance criteria	Observed directly from data

(Group 1 refers to the QTc monitoring subset, where ECGs were time-matched to serial PK draws.)

Given the evidence of a food effect, and also of PPIs in the fasted state, PK datasets were sub-grouped into Group A (fasting with antacid use), Group B (fasting without antacid use), Group C (fed regardless of antacid use) and Group D (Groups B + C), based on an assumption that patients were taking palbociclib fasted (as instructed) until 21 January 2014 (when directives were issued about food / PPI effects).

16.2.3 PK outcomes in PALOMA-2

In the 'fasted' dose-compliant group, steady-state PK outcomes were as follows:

Table 49: Pharmacokinetic outcomes in the fasted group

Parameter [Units]	Palbociclib PK Parameter Summary Statistics[a] by Administration Group		
	Palbociclib plus Letrozole Administration Group A [†]	Palbociclib plus Letrozole Administration Group B [†]	Palbociclib plus Letrozole All Group 1 Patients
N, n[b]	9,9	34,32	43,41
AUC_{24} [ng·hr/mL][c]	1721 (39)	2076 (33)	1992(35)
C_{max} [ng/mL]	100.7 (40)	113.1 (34)	110.4 (35)
T_{max} [hr]	4.58 (1.87-8.00)	5.90 (1.90-8.18)	5.83 (1.87-8.18)
CL/F [L/hr]	72.61 (39)	60.17 (33)	62.71 (35)

Trough levels were also measured, across a larger number of patients. Trough levels did not vary drastically according to 'group' as defined above, with Ctrough of 64.9 ng/mL across n=243 subjects (based on cycle 1 day 14 and cycle 2 day 14 data), although Ctrough was higher in fed than fasted patients (67.4 versus 58.1-58.6 ng/mL).

The CSR notes in this regard (emphasis added):

The differences in reported palbociclib PK parameters observed in this study between administration conditions were directionally consistent with those reported in prior clinical pharmacology studies dedicated to assessing the impact of these conditions on palbociclib PK but the differences observed in this study were less pronounced. This is presumably due to the PK data being collected in a less controlled and less extreme setting in this study than in the prior dedicated clinical pharmacology studies (eg, minimal fasting administration instructions in this study in place of the overnight fasting conditions used in clinical pharmacology studies, using a real-world selection of antacids of varying potency without controls on relative dosing times that maximize potential effects when palbociclib was still instructed to be administered under minimal fasting conditions).

16.2.4 Pharmacodynamics

In PALOMA-2, blood was also taken pre-dose at the cycle 1 day 1 visit 'to be retained for potential pharmacogenomics analyses related to drug response or adverse drug reactions' and possibly other research.

Tissue sample from 568 of the 666 randomised patients had biomarker results. ER, Rb, CCND1, p16 and Ki67 expression was assessed; see below.

16.2.5 Dosage selection for the pivotal studies

The CSR for PALOMA-2 states that dose escalation Study 1001 (n=74 patients with advanced cancer) examined two dosing schedules: 3/1 (daily dosing with 3 weeks on, 1 week off) and 2/1 (daily dosing with 2 weeks on, 1 week off):

Based on the relatively improved safety profile of Schedule 3/1, and the efficacy results from this study, Schedule 3/1 was selected for further clinical development and the recommended Phase II dose (RP2D) for this schedule was determined to be 125 mg QD.

The 125 mg QD 3/1 schedule was further tested in the Phase 1I/II Study 1003.

16.3 Clinical efficacy

16.3.1 Pivotal or main efficacy studies

A5481008 'PALOMA-2'

Study design, objectives, locations and dates

Design

PALOMA-2 is a multicentre, randomised, double-blind, placebo-controlled, Phase III study of palbociclib + letrozole versus placebo + letrozole in postmenopausal women with ER-positive / HER2-negative advanced breast cancer, previously untreated with systemic anti-cancer therapy for locoregionally recurrent or metastatic disease.

Objectives

The CSR for PALOMA-2 states (Study Rationale):

The Phase III double-blind study, Study 1008, was initiated to confirm the favourable benefit / risk profile observed with the combination of palbociclib with letrozole in the open label Phase 1/2 Study 1003 in a similar patient population. This Phase III study was designed to demonstrate that palbociclib in combination with letrozole provides superior clinical benefit compared to letrozole in combination with placebo in postmenopausal women with ER-positive/HER2-negative locoregionally recurrent or metastatic BC who have not received any prior systemic anti-cancer therapies for their advanced disease.

The formal primary objective of the study was:

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.

Locations

666 women enrolled at 186 sites in 17 countries, mainly in Europe and North America. The largest study site in any country had 34 enrolees; this was Russian site 1056.

Region / Country	Number	Patients (number in	Patients (number in
North America		168 (37.8%)	99 (44.6%)
USA	48	126 (28.4%)	71 (32.0%)
Canada	14	42 (9.5%)	28 (12.6%)
Europe		212 (47.7%)	95 (42.8%)
Russian Federation	10	38 (8.6%)	22 (9.9%)
Spain	21	38 (8.6%)	19 (8.6%)
Ukraine	7	27 (6.1%)	12 (5.4%)

Region / Country	Number of sites	Patients (number in palbociclib arm; percent of n=444 total)	Patients (number in placebo arm; percent of n=222 total)
France	10	19 (4.3%)	14 (6.3%)
Belgium	8	22 (5.0%)	6 (2.7%)
Germany	11	20 (4.5%)	7 (3.2%)
Ireland	7	15 (3.4%)	7 (3.2%)
UK	6	14 (3.2%)	4 (1.8%)
Italy	6	9 (2.0%)	2 (0.9%)
Hungary	3	5 (1.1%)	2 (0.9%)
Poland	2	5 (1.1%)	0
Asia/Pacific		64 (14.4%)	28 (12.6%)
Japan	15	32 (7.2%)	14 (6.3%)
Korea	6	15 (3.4%)	9 (4.1%)
Australia	10	15 (3.4%)	5 (2.3%)
Taiwan	2	2 (0.5%)	0

Dates

The 666 women were randomised between 28 February 2013 and 29 July 2014.

Interim analysis of efficacy and safety was performed by the External Data Monitoring Committee (E-DMC) on 12 September 2015 (data cutoff 1 May 2015), with 236 PFS events. The recommendation was for the study to continue as planned.

The CSR evaluated here presents the final progression-free survival (PFS) analysis. The CSR states:

A data cutoff date (26 February 2016) was applied for this final analysis. Data reported in this CSR occurred on or before 26 February 2016, with the snapshot of the active clinical database for the purpose of final analysis made on 08 April 2016.

(The Topline Summary presented earlier to the TGA also used the 26 February 2016 cutoff date.)

The CSR was dated 4 October 2016. The study is ongoing (subjects are being followed up for the purpose of a final overall survival [OS] analysis).

16.3.2 Questions 1-2 for sponsor

1. *It is noted in the EMA's Second Joint Rapporteur's Assessment Report (JRAR) that:*

   The sponsor also commits to submit the final OS results from Study 1008 when they

become available. Based on current projections, the readout is estimated to occur in May 2020 and the final report would be submitted by November 2020, as a type 2 variation.

Please provide an update about when the final OS outcomes are anticipated, and when the CSR reporting final OS outcomes will be available.

2. *Beyond the OS analyses conducted at the time of the initial and final PFS analysis, are any OS analyses to be conducted (by the E-DMC, sponsor, or any other party) prior to the final OS analysis?*

Inclusion and exclusion criteria

Inclusion

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 was not clinically indicated;
2. Documentation of histologically or cytologically confirmed diagnosis of ER-positive BC based on local laboratory results;
3. Previously untreated with any systemic anti-cancer therapy for their locoregionally recurrent or metastatic ER-positive disease;
4. Postmenopausal women defined as women with:
   - Prior bilateral surgical oophorectomy, or
   - Medically confirmed postmenopausal 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). Tumor lesions previously irradiated or subjected to other locoregional therapy were only deemed measurable if disease progression at the treated site after completion of therapy was clearly documented;
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2;
7. Adequate organ and marrow function defined as follows:
   - Absolute neutrophil count (ANC) ≥ 1,500/mm^3 (1.5 x 109/L),
   - Platelets ≥ 100,000/mm^3 (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 (≤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 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 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 had to agree to provide tumor tissues for centralized retrospective confirmation of estrogen receptor (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 tumor samples had to be provided whenever possible. If such a biopsy was not feasible or could not be safely performed, then an archived tumor sample could be accepted. In either case a formalin fixed, paraffin embedded (FFPE) block or 12 unstained FFPE slides were required for patient participation;
11. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) was informed of all pertinent aspects of the study before any study-specific activity was performed.

Exclusion

1. HER2-positive tumor as defined by documentation of erbB-2 gene amplification by Fluorescent In Situ hybridization (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 immunohistochemistry (IHC) (defined as IHC3+ or IHC2+ with FISH or CISH confirmation) based on local laboratory results utilizing one of the Sponsor-approved assays (Appendix 2 of the protocol, provided in Section 16.1.1). If HER2 status is unavailable or was determined using a test other than a Sponsor-approved assay, then testing had to have been performed/repeated using one of these assays prior to randomization. If tissue sample from both primary and recurrent/metastatic tumors were available, HER2 assessment from the most recent sample (ie, recurrent/metastatic sample) should be used to define eligibility whenever feasible;
2. Patients with advanced, symptomatic, visceral spread, who 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 CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression were eligible if they had been definitively treated with local therapy (eg, radiotherapy, stereotactic surgery) and were clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization;
4. Prior neoadjuvant or adjuvant treatment with a nonsteroidal 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 known to be CYP3A4 inhibitors (ie, 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 known to be CYP3A4 inducers (ie, carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort),
   - Drugs 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 were not eligible independent of when it was received;

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;
10. Uncontrolled electrolyte disorders that could compound the effects of a QTc-prolonging drug (eg, hypocalcaemia, hypokalaemia, hypomagnesaemia);
11. Any of the following within 6 months of randomization: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE v 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 diarrhea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection;
13. Known hypersensitivity to letrozole, or any of its excipients, or to any palbociclib / placebo excipients;
14. Known human immunodeficiency virus infection;
15. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with study participation or study drug administration or could interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into the study;
16. Patients who were investigational site staff members or relatives of those site staff members or patients who were Pfizer employees directly involved in the conduct of the study;
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 study;
18. Recent or active suicidal ideation or behaviour.

Study treatments

The CSR for PALOMA-2 states:

Patients randomised to Arm A (experimental arm) received:

- Palbociclib, 125 mg, 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).

Patients randomized to Arm B (control arm) received:

- 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).

Palbociclib was supplied as capsules containing 75 mg, 100 mg (each for use in the case of dose

reductions) or 125 mg equivalents of palbociclib free base. Patients were instructed to swallow palbociclib / placebo capsules whole and not to chew them prior to swallowing. The CSR also states:

Patients were to continue receiving assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. However, patients could continue treatment as assigned at randomization beyond the time of RECIST-defined PD at the discretion of the investigator if that was considered to be in the best interest of the patient and as long as no new anti-cancer treatment was initiated.

16.3.3 Question 3 for sponsor

3. How many patients continued to receive palbociclib beyond RECIST-defined PD? Provide a summary of the benefits (if any) observed in PALOMA-2 with such treatment, e.g. median duration of treatment post-progression; PFS relative to others with PD who did not receive palbociclib post-PD; evidence of any tumour response after progression.

Crossover between treatment arms was not allowed in the study.

Dosing interruption was required by protocol in the following circumstances:

- Uncomplicated Grade 3 neutropenia (ANC<1000/mm^3);
- Grade 3 neutropenia (ANC<1000/mm^3) associated with a documented infection or fever ≥ 38.5°C;
- Grade 4 neutropenia (ANC<500/mm^3);
- Grade 4 thrombocytopenia (platelet count <25,000/mm^3);
- Grade ≥ 3 non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment);
- Grade 3 QTc prolongation (QTc ≥ 501 msec on at least 2 separate ECGs).

Retreatment following treatment interruption for treatment-related toxicity or at the start of any new cycle required platelet count ≥ 50 000/mm^3, ANC ≥ 1000/mm^3 and no fever, recovery of severe AEs to grades 0-1 (or grade 2 if not a 'safety risk') and QTc <501 msec with reversible causes corrected. If these parameters were not met after 2 weeks of treatment interruption, permanent discontinuation was to be considered, but this was at the investigator's discretion.

Dose reduction criteria were specified, with re-escalation not allowed. Reductions were for treatment-related toxicities requiring treatment interruption / delay or persisting despite optimal medical treatment:

Table 50: Dose reduction criteria

Toxicity	Restart Palbociclib/Placebo Treatment at:
Uncomplicated Grade 3 neutropenia *(ANC<1000/mm^3)*	Same dose level
Grade 3 neutropenia *(ANC<1000/mm^3)* associated with a documented infection or fever ≥38.5°C	↓1 dose level
Grade 4 neutropenia *(ANC<500/mm^3)*	↓1 dose level
Grade 4 thrombocytopenia *(Platelet count <25,000/mm^3)*	↓1 dose level
Grade ≥3 non-hematologic toxicity *(including nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment)*	↓1 dose level

There were specific criteria for relating to QT prolongation:

Efficacy variables and assessments

Disease assessment was performed every 12 weeks; patients with baseline bone lesions were to have repeat bone scans every 24 weeks. The CSR states:

Efficacy analyses were to be performed using the local radiologist's/investigator's tumor assessments as primary data source. However, a blinded independent third-party core imaging laboratory completed a retrospective review of all radiographic images and clinical information collected on-study to verify the protocol-defined endpoints of tumor response and disease progression as assessed by the investigator.

Tumour assessments involved CT or MRI, radionuclide bone scan and correlative bone imaging, and photographs of superficial lesions (CSR page 80). Baseline brain scans were only required if signs and symptoms suggested metastatic brain disease. Detailed special rules applied to interpretation of response for bone-only disease.

RECIST v1.1 was used to determine objective response to treatment.

Patient-reported outcomes were assessed with FACT-B and EuroQol-5D questionnaires, completed pre-dose on day 1 of selected cycles. The CSR states:

The FACT-B consists of the Functional Assessment of Cancer Therapy-General (FACT-G) (27-items) and a breast-specific module: a 10-item instrument designed to assess patient concerns relating to BC. The FACT-G is a 27-item compilation of general questions divided into 4 domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. Patients were asked to respond to a Likert scale where 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much.

The EQ-5D is a 6-item instrument designed to assess health status in terms of a single index value or utility score. It contains 5 descriptors of current health state (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with each dimension having 3 levels of function (1=no problem, 2=some problem, and 3=extreme problem). The scores on the 5 descriptors are summarized to create a single summary score. The EQ-5D also includes a visual analog scale (EQ-VAS), in which the patients self-rate their overall health status on a scale from 0 (worst imaginable) to 100 (best imaginable).

After the active treatment phase, patients were followed up with FACT-B questionnaire, survival and new anti-cancer therapy information.

In addition to the above, the study was to include:

- QTc monitoring to evaluate the effect of palbociclib on QT interval via triplicate ECGs time-matched with select serial PK draws (subset study in at least 60 patients enrolled at selected sites, Group 1);
- Quantification of trough palbociclib plasma concentration;
- A molecular profiling component aimed at assessing the relationship between breast tumour sensitivity and resistance to palbociclib and the alteration of cell cycle pathway-related genes and proteins in tumour tissues.

Randomisation and blinding methods

The CSR for PALOMA-2 states:

At least 650 eligible patients were to be randomized 2:1 to receive either palbociclib plus letrozole (Arm A: at least 433 patients) or placebo plus letrozole (Arm B: at least 217 patients).

Patients were to be stratified by site of disease (visceral, non-visceral), by disease-free interval since completion of prior (neo) adjuvant therapy (de novo metastatic, ≤12 months, >12 months), and by the nature of prior (neo) adjuvant anti-cancer treatment received (prior hormonal therapy, no prior hormonal therapy).

Of note, 'visceral' referred to any lung (including pleura) and/or liver involvement and 'non-visceral' referred to absence of lung (including pleura) and/or liver involvement.

The study was double-blind, and placebo capsules matched palbociclib ones.

Tumour assessments were performed by investigators, but there was also a blinded independent central review (BICR) by a third-party imaging laboratory, with these data used for supportive analyses. ECG data were sent to a core laboratory for blinded manual measurement. The CSR also states:

The Sponsor study team was blinded from study treatments for each patient. All data review and data cleaning activities were performed in a blinded fashion until the database was released after the database snapshot (08 April 2016).

Analysis populations

All efficacy analyses were conducted on the ITT population. Numbers in key populations are described below:

Table 51: Analysis populations

Number (%) of patients	Palbociclib plus Letrozole	Placebo plus Letrozole	Total
Analyzed for efficacy			
ITT	444	222	666
mITT1	338 (76.1)	166 (74.8)	504 (75.7)
mITT2	294 (66.2)	143 (64.4)	437 (65.6)
Analyzed for safety			
Adverse events	444 (100)	222 (100)	666 (100)
Laboratory data	444 (100)	221 (99.5)	665 (99.8)
Analyzed for QTc	77 (17.3)	48 (21.6)	125 (18.8)
Analyzed for biomarkers	379 (85.4)	189 (85.1)	568 (85.3)
Analyzed for PRO			
EQ-5D	437 (98.4)	218 (98.2)	655 (98.3)
FACT-B	439 (98.9)	218 (98.2)	657 (98.6)

Source: Section 14.1, Table 14.1.1.1
Abbreviations: EQ-5D=EuroQoL 5D; FACT-B=Functional Assessment of Cancer Therapy-Breast; QTc=QT interval corrected for heart rate; ITT=intent-to-treat population; mITT1=modified intent-to-treat-1 population; mITT2=modified intent-to-treatment-2 population; PRO=patient reported outcome.
The percentages were calculated based on the number of patients randomized to treatment arms.

Sample size

Sample size of ~650 patients assumed median PFS for letrozole of 9 months, and risk reduction of 31% (HR 0.69) with addition of palbociclib, or improvement to 13 months for median PFS, along with various other assumptions.

This sample size would also allow assessment of differences in OS; no crossover was permitted to palbociclib. The CSR states:

The OS outcome of a reported Phase III clinical study with a similar patient population was 34 months for the arm receiving letrozole. Using this value as an assumption with a hypothesized 26% reduction risk (a HR of 0.74) of 35% improvement in median OS (from 34 months to 46 months) in patients randomized to receive palbociclib plus letrozole and follow-up period of approximately 68 months, evaluation of 390 events using a 1-sided, unstratified log-rank test was required for a significance level of 0.025 and power of 80% to detect the difference.

Protocol amendment 3 (21 March 2014) increased sample size from 450 to 650 due to a concern that drug exposure prior to amendment 2 (stipulating that palbociclib should be taken with food and without PPI use) might be different. This increase in sample size reflected a shift in assumed PFS HR from 0.64 to 0.69, resulting in an increase of PFS events required for the final analysis by 108 events (from 239 to 347 events).

Statistical methods

Statistical Analysis Plan (SAP) version 3.0 (updated for study Protocol Amendment 7, and titled in Docubridge 'Statistical Methods Interim Analysis Plan') was provided in the s31 response.

Primary efficacy evaluation

The primary endpoint was PFS based on investigator assessment. In this regard the CSR also explains:

The primary and secondary analyses of endpoints dependent on disease assessments (PFS, objective response [OR], duration of response [DOR], and disease control/clinical benefit response [DC/CBR]) were based on the target lesion measurements, non-target lesion assessments, and new lesion records provided by the investigator, independent of the overall response category provided by the investigator, and hereafter are referred to as the investigator assessments of tumor response and progression.

16.3.4 Questions 4-5 for sponsor

4. Please confirm that for the 'investigator' assessment of PFS, assignment of the overall response category was not made by the investigator, but was 'independent of the overall response category provided by the investigator'. Who – sponsor, DMC or other agent – assigned the overall response category for the purpose of investigator-assessed PFS and related investigator-assessed outcomes?

5. Please describe the level of concordance between the investigator's overall response category and the overall response category designated by the sponsor / DMC / other agent based on lesion measurements / assessments provided by the investigator. For example, how many patients per arm had discordance between an objective response and stable disease, or between stable disease and progressive disease?

For final analysis of PFS, there were two assessments: one in the ITT population, and one in the subgroup of patients given palbociclib with food ('mITT2'), i.e. those patients randomised after 21 January 2014 when guidance about administration of palbociclib with food and prohibition of PPIs had been communicated to study sites – elsewhere in the CSR described as a subpopulation characterised by optimal exposure to palbociclib.

Requirements for a positive study

The CSR states:

This study was considered a positive study if the 1-sided, stratified log-rank test for PFS based on randomization stratification factors is significant at the significance level of 0.000013 at the interim analysis or 0.025 at the final analysis in favor of palbociclib plus letrozole combination.

Also of note:

OS was to be hierarchically tested for significance at the time of PFS analyses, provided the primary endpoint, PFS, was statistically significant at the interim and/or final PFS analyses. If OS did not yield a statistically significant result at the interim analysis, OS will be statistically evaluated at the final OS analysis. However, if PFS was not significant at the interim and/or final PFS analyses, OS would not be statistically evaluated.

Regarding OS, 1-, 2- and 3-year survival probabilities were also to be calculated.

Interim analyses

The study was designed to have an interim analysis after ~226 PFS events and a final analysis at 347 PFS events. An interim analysis of OS was also pre-specified, and to be performed at the time of the interim analysis of PFS and of the final PFS analysis. A reasonable time for the OS interim analysis was estimated to be at 131 deaths, at the estimated time for the planned PFS

final analysis. If OS was not significant at the time of the final PFS analysis, a final OS analysis was to be performed after 390 deaths.

Participant flow

666 women were randomised: 444 to palbociclib + letrozole; 222 to placebo + letrozole. All randomised patients were treated.

Disposition at end of treatment is shown below:

Table 52: Disposition at the end of treatment

Number (%) of Patients	Palbociclib plus Letrozole (N=444) n (%)	Placebo plus Letrozole (N=222) n (%)	Total (N=666) n (%)
Ongoing	205 (46.2)	61 (27.5)	266 (39.9)
Discontinued	239 (53.8)	161 (72.5)	400 (60.1)
Reason for discontinuation			
Objective progression or relapse	172 (38.7)	125 (56.3)	297 (44.6)
Adverse event	20 (4.5)	9 (4.1)	29 (4.4)
Global deterioration of health status	16 (3.6)	9 (4.1)	25 (3.8)
Subject refused continued treatment for reason other than AE	12 (2.7)	9 (4.1)	21 (3.2)
Other	6 (1.4)	4 (1.8)	10 (1.5)
Subject died	6 (1.4)	2 (<1.0)	8 (1.2)
Protocol violation	5 (1.1)	3 (1.4)	8 (1.2)
Lost to follow-up	1 (<1.0)	0	1 (<1.0)
Study terminated by Sponsor	1 (<1.0)	0	1 (<1.0)
Medication error without associated AE	0	0	0

Comment: There was a large imbalance in the percentage of patients who discontinued due to objective progression or relapse: 38.7% (palbociclib-containing arm) versus 56.3% (placebo-containing arm).

Disposition at end of study is shown below:

Table 53: Disposition at the end of study

	Palbociclib (PD-0332991) + Letrozole (N=444)		Placebo + Letrozole (N=222)		Total (N=666)	
Number(%) of Subjects	n	(%)	n	(%)	n	(%)
Ongoing	324	(73.0)	164	(73.9)	488	(73.3)
Discontinued	120	(27.0)	58	(26.1)	178	(26.7)
Reason for Discontinuation						
Subject Died	94	(21.2)	38	(17.1)	132	(19.8)
Subject Refused Further Follow-Up	19	(4.3)	14	(6.3)	33	(5.0)
Lost to Follow-Up	4	(<1.0)	6	(2.7)	10	(1.5)
Other	2	(<1.0)	0		2	(<1.0)
Study Terminated by Sponsor	1	(<1.0)	0		1	(<1.0)
Medication error Without Associated Adverse Event	0		0		0	

Comment: This reflects that many patients died after the 'end of treatment', i.e. after 28 days after the last dose was received, so deaths were not considered 'on treatment'.

The numbers of deaths reported here for 'end of study' (n=94 deaths in the palbociclib arm, n=38 in the placebo arm) correspond imperfectly with the OS outcome data for PALOMA-2, where n=95 and n=38 respectively died (from start of treatment onwards).

Major protocol violations/deviations

Frequency of major protocol deviations was high. For example, 21.2% of palbociclib + letrozole arm patients were given prohibited concomitant medications during active treatment, versus 12.2% of placebo + letrozole arm patients. 58-59% of patients per arm had some form of deviation from informed consent.

16.3.5 Question 6 for sponsor

6. Please point to a tabulation in the CSR (or create a tabulation) of the use of commoner prohibited concomitant medications (capturing type of medication, typical reason/s for use and extent of use), allowing comparison across arms.

Baseline data

Demographic characteristics were balanced across arms. Median age was 62.0 years, and 40.8% (palbociclib arm) versus 36.5% (placebo arm) were ≥ 65 yrs of age. 77.5% across arms were of White race, and 14.3% were of Asian race.

Baseline disease characteristics were reasonably balanced. A prominent imbalance was in ECOG performance status: 58% had ECOG PS = 0 in the palbociclib-containing arm, versus 46% in the placebo-containing arm. Median duration since breast cancer diagnosis was 4.5 yrs (palbociclib-containing arm) versus 4.0 yrs (placebo-containing arm).

Measurable disease was present at baseline in 76.1% and 77% respectively. Based on sensitivity analysis 11.3, it appears 103/444 (23.2%) versus 48/222 (21.6%) had bone-only disease at baseline – these figures may account for the extent of non-measurable disease noted above. However, bone disease was present in 73% of patients.

Almost all patients had metastatic disease; and about a third of patients had de novo metastatic disease.

About half of patients had visceral disease. 1-2 patients per arm had brain disease.

Comment: Initial presentation of breast cancer with metastatic disease (i.e. de novo metastatic disease) may be less common in the community than was the case in PALOMA-2, where a third of patients had de novo metastatic disease. This might be due in part to exclusion criteria such as the exclusion of patients with recurrence inside 12 months of neoadjuvant / adjuvant NSAI therapy.

Arms were balanced for prior systemic therapies used to treat breast cancer. Also:

- 167/444 (37.6%; palbociclib + letrozole) versus 81/222 (36.5%; placebo + letrozole) had no prior systemic therapy (median age 64 yrs). Presumably, this group would overlap considerably with patients with 'de novo metastatic disease' but it seems likely there remains a group of patients without de novo metastatic disease who had not received prior systemic therapy; see below.
- 99/444 (22.3%) versus 48/222 (21.6%) had a disease-free interval of ≤12 months after last systemic therapy (these patients tended to be younger; median age 53 yrs)
- 178/444 (40.1%) versus 93/222 (41.2%) had a disease-free interval of >12 months (median age 62 yrs)

A further breakdown is provided in the EMA Second JRAR, Table 2, that notes:

Table 54: From EMA Second JRAR (Table 2)

	Palbociclib plus Letrozole (N=444) n (%)			Placebo plus Letrozole (N=222) n (%)		
Disease Free Interval*	De Novo	≤12 months	>12 months	De Novo	≤12 months	>12 months
Recurrence Type						
Locoregional Recurrence	0	1 (1.0)	1 (<1.0)	0	0	2 (2.2)
Local Recurrence	2 (1.2)	1 (1.0)	3 (1.7)	0	1 (2.1)	2 (2.2)
Regional Recurrence	0	0	3 (1.7)	0	0	1 (1.1)
Distant Recurrence	26 (15.6)	97 (98.0)	171 (96.1)	10 (12.3)	47 (97.9)	88 (94.6)
Newly Diagnosed	139 (83.2)	0	0	71 (87.7)	0	0

This indicates that 28/167 palbociclib-arm patients described as 'de novo' actually had a

recurrence, implying existence of an earlier diagnosis of breast cancer so not truly 'de novo' advanced disease.

16.3.6 Question 7 for sponsor

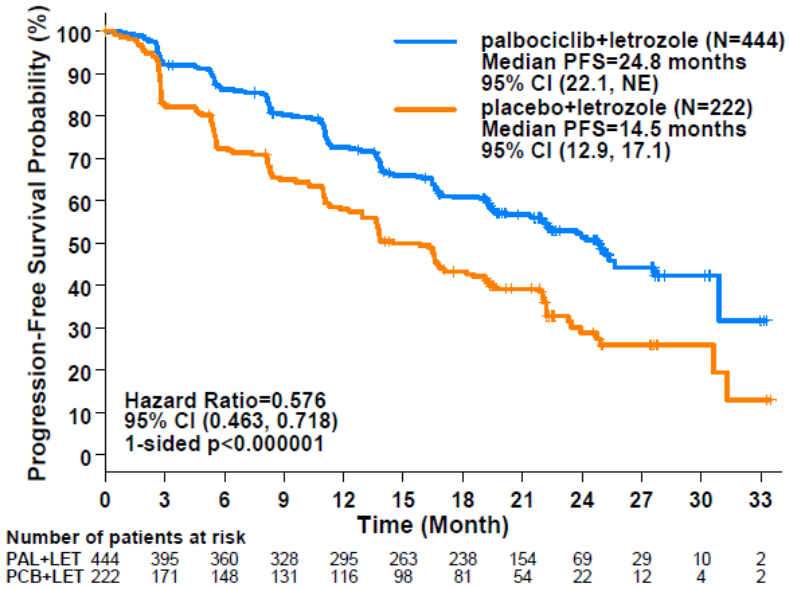
7. In CSR Table 19 using CRF data, the study population is divided by disease free interval ('since completion of prior (neo) adjuvant therapy') into: De Novo (n=167 versus 81); ≤12 months (n=99 versus 48); and >12 months (n=178 versus 93). Could the sponsor confirm that by 'de novo' in this classification, what is meant is 'no prior systemic therapy' presumably equating to no prior neoadjuvant or adjuvant systemic therapy (rather than 'de novo metastatic disease')? Reference is also made to CSR Table 15, where n=167 versus 81 had no prior systemic therapies (either chemotherapy or hormonal)[38], and to CSR Table 18, where n=139 versus 71 had 'newly diagnosed' recurrence type (other categories involving 'recurrence' whether locoregional or distant imply earlier diagnosis of breast cancer).

How many patients per arm had no prior systemic therapy for advanced disease despite not having 'de novo metastatic disease' on enrolment into the study? Why had these patients not received endocrine or at least systemic therapy at initial diagnosis of 'advanced' breast cancer? What was this group's median length of time since diagnosis? Provide PFS and ORR outcomes per arm for this subgroup. Also provide PFS and ORR outcomes per arm for the subgroup described in CSR Table 18 as 'newly diagnosed' (taken by this evaluator to be truly 'de novo' advanced disease), based on investigator and BICR assessments (and according to both IMPALA and CRF analyses).

Results for the primary efficacy outcome

The primary efficacy outcome was PFS, as assessed by the investigator, at the final (PFS) analysis in the ITT population. PFS outcomes are summarised in Table 6 on page 54; the median PFS was 24.8 months in the palbociclib + letrozole arm, and 14.5 months in the placebo + letrozole arm, with a PFS hazard ratio (HR) of 0.58 (95% CI 0.46-0.72). The Kaplan Meier (KM) curve is shown below:

Figure 14: Kaplan-Meier plot PFS versus time



[38] From this table it can be calculated that n=28 had prior chemotherapy only, n=64 had prior hormonal therapy only, and n=185 had prior chemotherapy and hormonal therapy, as neo(adjuvant) therapy, in the palbociclib + letrozole arm

Results were similar in the mITT2 population.

Subgroup analyses presented a consistent picture of investigator-assessed PFS benefit, as did 13 sensitivity analyses (including 4 addressing bone-only disease). While the degree of PFS benefit might have varied by subgroup, no particular subgroup analysed by the sponsor showed any dramatic loss of efficacy. For example, for patients in the sponsor-defined 'de novo metastases' subgroup, PFS HR was 0.674: 'less impressive' than for recurrent subgroups (HR 0.501-0.516) but still delivering PFS benefit. There were two sources of information used to define subgroups: IMPALA and CRF[39]. The sponsor concluded that CRF was more accurate. Subgroup analyses are based on CRF information; but for subgroup analysis of investigator-assessed PFS, there were no large discrepancies between IMPALA and CRF –based analyses.

BICR outcomes

The PALOMA-2 CSR explained that primary efficacy assessment of PFS would be based on investigator assessment.

The clinical evaluator of the initial Dossier considered that a deficiency of the top-line summary was the absence of BICR outcomes. The full CSR included BICR outcomes. Overall results based on the BICR were broadly similar to those based on investigator assessment, with a PFS HR of 0.653 (95% CI 0.505-0.844), although median PFSBICR was 30.5 months versus 19.3 months.

Subgroup analysis of BICR-assessed PFS was also presented.

According to IMPALA analysis, those with de novo metastatic disease did not benefit from addition of palbociclib (HR 1.05, 95% CI 0.64-1.74; mPFS not reached (palbociclib-containing arm) versus 33.1 months (placebo-containing arm); according to CRF analysis – considered more accurate – the PFSBICR HR was 0.876.

Comment: In Study 1003, there was no indication from subgroup analysis of investigator-assessed PFS that patients with de novo advanced disease did not benefit in terms of PFS from the addition of palbociclib.

While PFS benefit was maintained in subjects with 'no visceral metastases' by hazard ratio (HRBICR IMPALA 0.724, 95% CI 0.479-1.093), median PFS was similar across arms, at ~30.5 months (regardless of source of data, IMPALA or CRF), quite different than with investigator-assessed PFS.

Investigator versus BICR outcomes

A comparison was made between PFS assessed by the investigator versus BICR; there were discordant PFS event assessments in 19.4% (palbociclib arm) versus 27.5% (placebo arm), with most of this imbalance due to a higher number of events declared by the investigator but not by the BICR (64/444 palbociclib; 51/222 placebo).

Comment: Although this suggests the possibility of investigator bias, overall outcomes were similarly favourable for palbociclib + letrozole for PFS when based on BICR assessment.

PFS by biomarker status

By way of background, the Clinical Overview provided in Dossier version [0004] notes:

…preclinical cell line studies have observed that cell lines with high levels of CCND1, low levels

[39] IMPALA was the name of the study interactive randomization technology; CRF = case report form; randomization in IMPALA occurred prior to the data being verified by the Sponsor, so there were "minor discrepancies" in the distribution of patients by the stratification factors following data cleaning activities based on the CRF data. "For this reason, the CRF source document verified data were considered more accurate…" [s31 response]

of the CDK inhibitor 2A (CDKN2A; also known as 'p16INK4A'), and the presence of the Rb 1 gene were more sensitive to palbociclib treatment. Sensitive cell lines represented mostly the luminal ER-positive subtype.

Discussion in the EMA Second JRAR (Question 9, about the Rb biomarker) is noted, including the statement:

Further biomarker analyses are planned or ongoing with the specimens collected on Study 1008: Cyclin D1 amplification and p16 deletion by FISH test; CDK4, CDK6, CDK2, Cyclin E1, Cyclin E2, p16, and Rb mRNA expression. A standalone biomarker analysis report will be provided by the end of 2017.

The EMA Second JRAR assessment of this issue also concluded that the SmPC should include information pertaining to uncertainty about significance of Rb-status.

There were no robust differences according to biomarker-defined subgroups, although various biomarkers conferred prognostic advantage / disadvantage. There were very few CCND1-negative patients, but in these patients, the PFS HR was 0.997 (the CSR authors considered that sample size precluded valid comparison for CCND1 negative subjects). There were very few 'p16 high' patients, but here the PFS HR was 0.255.

Comment: In Study 1003, enrolment was focused on patients with CCND1 gene amplification and / or loss of CDKN2A (since preclinical data suggested that such tumours were particularly sensitive to palbociclib). However, interim data found no influence of these biomarkers. It is interesting that in the very few CCND1-negative subjects in PALOMA-2, palbociclib did not confer obvious benefit.

Results for other efficacy outcomes

Objective response

Investigator-assessed confirmed responses were reported in 42.1% (palbociclib) versus 34.7% (placebo), as indicated below:

Figure 15: Confirmed complete response or partial response

	Palbociclib plus Letrozole (N=444) n (%)	Placebo plus Letrozole (N=222) n (%)
Confirmed complete response or partial response		
Complete response	9 (2.0)	5 (2.3)
Partial response	178 (40.1)	72 (32.4)
Stable/no response	210 (47.3)	96 (43.2)
Objective progression	34 (7.7)	37 (16.7)
Indeterminate	13 (2.9)	12 (5.4)
Objective response, CR + PR (ORR)	187 (42.1)	77 (34.7)
95% exact CI for ORR [a]	[37.5, 46.9]	[28.4, 41.3]
Stratified analysis [d]		
Odds ratio [b]	1.400	
95% exact CI	[0.984, 2.008]	
p-value [c]	0.0310	

Confirmed ORRs were lower using BICR assessments (34.7% palbociclib + letrozole versus 23.9% placebo + letrozole).

The above ORRs include patients with no measurable disease at baseline.

Median duration of response (based on investigator-assessed, confirmed ORs) was 22.5 months (palbociclib + letrozole) versus 16.8 months (placebo + letrozole).

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

A more detailed discussion of OS outcomes is included in the Delegate's Overview (see Overall Risk-Benefit analysis in AusPAR), but some basic considerations are set out below.

The CSR states (page 175):

The planned interim OS analysis was performed at the time of the final PFS analyses based on 133 deaths (Table 14.3.3.1) from 666 patients (34% of expected 390 total deaths for the final OS analysis) since the primary analysis for PFS was statistically significant. However, the prespecified level of significance for the interim analysis was not met. The patients continue to be followed for survival and the final OS analysis will be performed when 390 deaths have been reported. Of note, at the time of the data cutoff, the median follow-up time in the palbociclib plus letrozole arm was 23.0 months (95% CI: 22.6, 23.4) and in the placebo plus letrozole arm was 22.3 months (95% CI: 21.9, 22.9) (Table 14.4.1.5).

For deaths within 28 days of the last dose, the following comments help explain those deaths categorised as having an 'other' cause (CSR):

Cause of death was reported as 'unknown' for 1 patient in the placebo letrozole arm only. 'Other' was reported for 7 patients in the palbociclib plus letrozole arm and for 1 patient in the placebo plus letrozole arm. 'Other' was further specified as follows for the 7 patients in the palbociclib plus letrozole arm: 1 death during the injection of an unknown medicine to relieve shoulder pain in another study site, 1 death possibly related to acute respiratory viral infection, 1 death due to pneumonia/respiratory failure, 1 death due to cardiogenic shock of unknown origin, 1 death due to cardiopulmonary failure, 1 death due to thrombosis of pulmonary arteries with unknown thrombus, and 1 death due to acute transmural myocardial infarction of left ventricle posterior wall. 'Oher' for the 1 patient in the placebo plus letrozole arm was chest infection (see Errata).

The EMA's Second JRAR Clinical report goes into the issue of OS. The relevant section is attached in Section 17 on page 61. The sponsor explained to the EMA that the applicant is blinded to the interim OS analysis.

In this regard, the TGA has adopted an EU guidance document on Data Monitoring Committees which does note that '*policies to avoid the dissemination of interim study result prior to unblinding have to be in place'*. The guidance further states that '*In case of a submission the working procedures of a DMC as well as all DMC reports (open and closed sessions) should form part of the submission*.' The EU guidance on statistical principles notes, in Section 4.6, that DMC procedures 'should also address the control of dissemination of interim trial results within the sponsor organisation' – which does not seem to preclude limited dissemination of key outcomes.

16.3.7 Questions 8-9 for sponsor

8. Provide the interim OS analysis that was performed at the time of the final PFS analysis, and any update. Provide 12- and 24-month OS rates per arm, estimated median OS per arm, an estimated OS hazard ratio, and estimated KM curves for OS.

9. Please comment in detail on the apparent discordance between mature PFS and immature OS outcomes.

The SAP version 3.0 states:

A supportive analysis will be performed by combining the OS data from this study and from the randomized phase 2 Study A5481003 with similar approaches described above. The Study as a stratification factor (A5481003 vs. A5481008) will also be included in the analysis. Since the median OS time for the studied patient population is relatively long and it is anticipated a small fraction of OS events would be available at the time of OS interim analysis, this analysis will certainly increase the power of detecting the OS difference between two treatment arms, given both randomized studies have similar patient populations and OS follow up processes.

This implies that the supportive analysis will be conducted prior to OS final analysis.

16.3.8 Question 10 for sponsor

10. Please provide this supportive analysis of OS outcomes across studies 1003 and 1008.

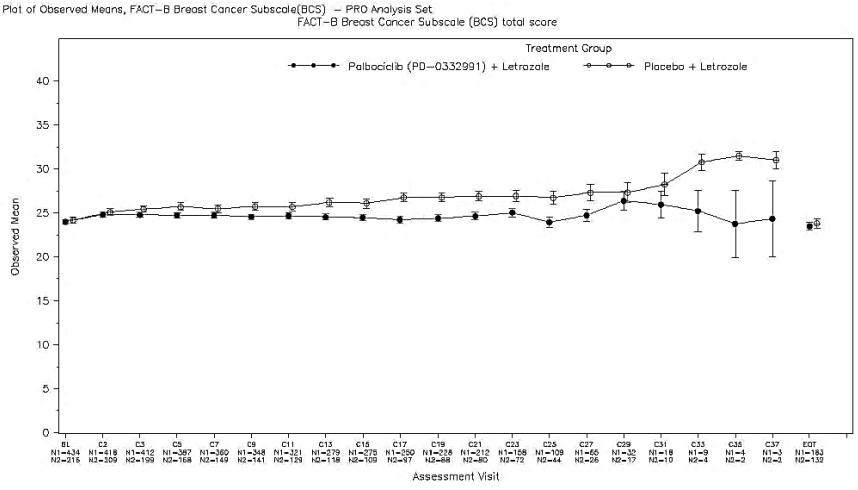
Comment: In Study 1003, after 61 deaths across 165 patients and median 28-30 months follow-up, estimated median OS in the palbociclib + letrozole arm was 37.5 months versus 33.3 months in the letrozole-only arm. Median follow-up time in Study 1003 (28-30 months) was not too dissimilar from median follow-up time in Study 1008 (22-23 months); however, the proportion of patients who had died was ~37% for Study 1003 versus ~20% for Study 1008. In both studies, OS outcomes are considered immature.

Patient-reported outcomes

FACT-B and FACT-G baseline scores were similar across arms. No statistically significant differences were observed between treatment arms in overall FACT-B or FACT-G scores, on treatment.

For the breast cancer subscale (BCS, range 0-36, higher score indicating better quality of life or better well-being), baseline scores were similar across arms; no statistically significant difference was observed overall on treatment, although from cycle 13 to cycle 25 a difference in means of 1.6-2.8 was seen, with higher scores in the placebo arm. However, there was no statistically significant difference in time to deterioration for BCS (i.e. time between baseline and first occurrence of a decrease of 2+ points).

Figure 16: Time to deterioration for BCS



No appreciable differences in EQ-5D were seen.

16.3.9 Questions 11-12 for sponsor

11. In PALOMA-3, there was a delay in time to deterioration for pain symptoms, in the palbociclib-containing arm. What outcomes were observed for pain symptoms in PALOMA-2?

12. The clinical evaluator for the main dossier writes that assessment of benefit in patients with bone-only disease relies on measures of quality of life such as improvement in pain, reduced skeletal event rates, etc. What patient-reported outcomes for pain symptoms were observed in patients with bone-only disease?

Follow-up use of systemic therapies

Follow-up systemic treatments for breast cancer were used in 42.1% (palbociclib + letrozole) versus 60.8% (placebo + letrozole), e.g. fulvestrant (13.5% versus 21.6%), capecitabine (12.6% versus 17.6%), exemestane (10.1% versus 18.5%), everolimus (7.4% versus 13.5%), paclitaxel (8.8% versus 14.4%) and letrozole (7.4% versus 10.4%).

Table 56: Follow up of systemic therapies

	Palbociclib (PD-0332991) + Letrozole (N=444) n (%)	Placebo + Letrozole (N=222) n (%)
Follow-up Systemic Therapy		
No	257 (57.9)	87 (39.2)
Yes	187 (42.1)	135 (60.8)
# of Regimens		
1	96 (21.6)	70 (31.5)
2	52 (11.7)	37 (16.7)
>=3	39 (8.8)	27 (12.2)
Not Reported	0	1 (0.5)

16.3.10 Analyses performed across trials: pooled and meta analyses

See question above about pooled analysis of OS across Study 1003 and Study 1008.

16.3.11 Evaluator's conclusions on clinical efficacy

In PALOMA-2 there was a large 10.3 month improvement in median progression-free survival (PFS) for patients receiving palbociclib + letrozole, relative to those receiving placebo + letrozole. There was a substantial improvement in objective response (CR + PR; 42.1% versus 34.7%) and in clinical benefit (defined as CR + PR + SD; 89.4% versus 77.9%).

Benefits were seen in both investigator and BICR -based analyses. The most prominent discordance between investigator and BICR –based analyses was for subjects with de novo metastatic disease; based on BICR assessment of tumour response, these patients had little if any PFS improvement with the addition of palbociclib.

Overall survival (OS) outcomes are immature; a relatively small proportion of subjects on study have died. More data are needed to understand the impact of palbociclib on OS outcomes.

There were no large or consistent differences across arms in patient-reported outcomes – but PROs can be difficult to assay with sensitivity.

Overall, addition of palbociclib to letrozole appears to have a major anti-tumour impact in this setting, but there is an important unresolved concern about impact on survival.

16.4 Clinical safety

16.4.1 Patient exposure in PALOMA-2

Median duration of treatment was ~50% longer in the palbociclib + letrozole arm, for each component (603 + 618 days respectively), than in the placebo + letrozole arm (413 + 420 days respectively).

Adverse event (AE) analyses were not adjusted for longer median duration of treatment in the

palbociclib + letrozole arm than the placebo + letrozole arm.

Relative dose intensity[40] was 93% for palbociclib, and ~100% for other components in both arms.

At least one dose reduction was reported for 36% (160/444) in the palbociclib arm; and in 63 of these patients, i.e. 63/444 (14.2%) of the whole cohort, a further reduction was required.

Dose interruption was required in the palbociclib + letrozole arm in 66.9% + 52.5% of patients respectively; and was required in the placebo + letrozole arm in 41.4% + 43.7% of patients respectively.

16.4.2 8.2. Adverse events

An overview of AEs is shown below, from CSR page 194:

Table 57: Overview of AEs

	Palbociclib plus Letrozole N (%)	Placebo plus Letrozole N (%)	Total N (%)
Number of patients			
Patients evaluable for AEs	444	222	666
Number of AEs	6081	2136	8217
Patients with AEs	439 (98.9)	212 (95.5)	651 (97.7)
Patients with SAEs	87 (19.6)	28 (12.6)	115 (17.3)
Patients with Grade 3 or 4 AEs	344 (77.5)	56 (25.2)	400 (60.1)
Patients with Grade 5 AEs	10 (2.3)	4 (1.8)	14 (2.1)
Patients permanently discontinued study associated with AEs	11 (2.5)	4 (1.8)	15 (2.3)
Patient permanently discontinued palbociclib or placebo associated with AEs	41 (9.2)	12 (5.4)	53 (8.0)
Patients permanently discontinued letrozole associated with AEs	27 (6.1)	11 (5.0)	38 (5.7)
Patients temporarily discontinued palbociclib/placebo associated with AEs	332 (74.8)	35 (15.8)	367 (55.1)
Patients temporarily discontinued letrozole associated with AEs	77 (17.3)	22 (9.9)	99 (14.9)
Patients with palbociclib or placebo dose reduction associated with AEs	160 (36.0)	3 (1.4)	163 (24.5)

Source: Section 14.1, Table 14.3.1.1.1
Abbreviations: AE=adverse event; N=number of patients; SAE=serious adverse event.
Includes data up to 28 days after last dose of study drug.
Except for the number of AE, patients are counted only once per treatment in each row.
SAE - according to the Investigator's assessment.

16.4.3 All adverse events (irrespective of relationship to study treatment)

Table 8 on page 57 shows all-causality AEs reported in ≥ 10% of patients in either arm. Most prominent[41] AEs for the palbociclib arm (relative to placebo) were:

- neutropenia (79.5%, versus 6.3% for the placebo arm), in the context of more:
  - laboratory abnormalities of 'neutrophils decreased' (95% versus 20%, including 67% versus 2% grade 3-4 findings[42], as per CSR Table 53)
  - infection (59.7% versus 42.3%), including grade 3-5 infection (6.5% versus 4.5%); and

[40] Actual dose intensity divided by intended dose intensity x 100%
[41] Crudely limited to those AEs in Table 8 with a >>50% frequency relative to placebo, to offset the imbalance in exposure
[42] From https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf:

	Grade				
Adverse Event	1	2	3	4	5
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-

Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.

  - febrile neutropenia (2.5% versus 0%; grade 3-4 in 1.8% versus 0%)[43][44]
- leucopenia (39% versus 2.3%);
- alopecia (32.9% versus 15.8%);
- stomatitis (30.4% versus 13.5%);
- anaemia (24.1% versus 9%), alongside:
  - laboratory abnormalities of 'anaemia'[45] in 78% versus 42% (including grade 3-4 findings in 6% versus 2%, as per CSR Table 53)
- thrombocytopaenia (15.5% versus 1.4%), noting also an increase in:
  - laboratory abnormalities of 'platelets decreased'[46] (63% versus 14%, including grade 3-4 findings in 2% versus 0%)
  - treatment-related epistaxis (6.3% versus 2.7% in the CSR, 9.2% versus 6.3% in the Clinical Overview for Dossier version [0004]; the sponsor states that no grade 3-4 thrombocytopenia AEs were associated with bleeding events, but in the sponsor's s31 response to CER-ES safety Q24, multiple low-grade AEs of epistaxis were temporally associated with thrombocytopenia)
- decreased appetite (14.9% versus 9.0%);
- dry skin (12.4% versus 5.9%);

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[43] CSR Table 14.3.1.3.2.1 reports 1.6% with febrile neutropenia in the palbociclib + letrozole arm, however Table 14.3.1.8.1.1 reports 1.8% with grade 3-4 febrile neutropenia (all causality), and on page 209 of the CSR it states that febrile neutropenia was experienced by 11 (2.5%) in that arm, sourced from Table 14.3.1.1.3 (TEAEs, all causality, all cycles, with a comment that "reported cases of grade 1-2 febrile neutropenia are currently under review since CTC AE criteria may not have been met for this event". The SCS further states that "reported cases of grade 1 or grade 2 febrile neutropenia (3 patients) did not meet CTCAE version 4.0 criteria for febrile neutropenia and were subsequently corrected (were considered not to be consistent with febrile neutropenia) in the clinical database after the database snapshot. It is not entirely clear whether the 3 patients have already been removed to arrive at 11 (2.5%) or whether, once removed, 8 patients remain (1.8%).

[44] From https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf:

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.

[45] From https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf:

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.

[46] From https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf:

Adverse Event	**1**	**2**	**3**	**4**	**5**
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-

Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.

- abdominal pain (11.3% versus 5.4%);
- peripheral oedema (11.3% versus 6.3%); and
- dysgeusia (10.1% versus 5.0%).

16.4.4 Questions 13-14 for sponsor

13. In relation to alopecia, please characterise this further. For affected patients in the palbociclib-containing arm, was there typically 'complete' hair loss as might be seen with some chemotherapies or 'thinning' as might be seen with, for example, letrozole? Was there scalp tenderness? Did hair re-grow normally on treatment discontinuation?

14. It was noted from the CSR that there were several cases of intracranial haemorrhage in the palbociclib-containing arm (patient IDs 13331001 and 10131001). Were there other cases of significant bleeding? Was any case associated with thrombocytopenia of any grade?

Also of note, regarding rarer AEs:

- cataracts were reported in 3.4% versus 0.5%; one case in the palbociclib arm was grade 3 and required bilateral cataract surgery (overall on treatment, 9 patients in the palbociclib-containing arm and 1 in the placebo-containing arm had cataract surgery). While these were not necessarily mediated by hyperglycaemia, there was a distinct imbalance across arms (beyond what can easily be explained by imbalance in treatment duration) suggesting a treatment effect.

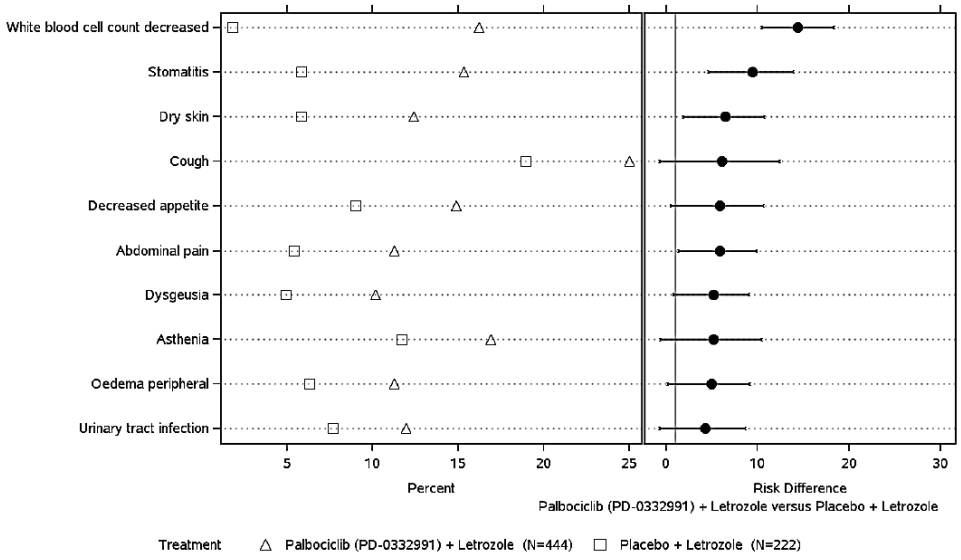
16.4.5 Question 15 for sponsor

15. Was sufficient information gathered to understand whether the imbalance in cataract surgery extended more than 28 days after the last dose?

- interstitial lung disease or pneumonitis was reported in 0.7% (3/444) versus 0.5% (1/222), although all three AEs in the palbociclib arm were considered related and the one AE in the placebo arm was not considered related

The following graph indicates AEs with wider risk differences:

Figure 17: AE with wider risk differences



There was a lower reporting frequency of headache (21.4% versus 26.1%; including grade 3-4 headache, 0.2% versus 1.8%) and hot flushes (20.9% versus 30.6%) in the palbociclib-

containing arm. There was also a lower reporting frequency of grade 3-4 hypertension (3.4% versus 5.9%).

Comment: Headache, hot flushes and hypertension are commonly reported with letrozole. The lower frequency of these AEs in the palbociclib + letrozole arm versus the placebo + letrozole arm, despite no PK interaction, raises the suspicion that there may be a PD interaction between the two drugs, which might lessen some activities of letrozole.

16.4.6 Question 16 for sponsor

16. Is there any indication that palbociclib and letrozole may have a pharmacodynamics interaction that could explain higher rates of headache, hot flushes and hypertension in the placebo-containing arm?

Additional AEs that were imbalanced, with >1 report, from consideration of all causality grade 3-4 AEs, include:

- AST increased (2.5% versus 0.9%), an imbalance consistent with:
  - the total number of treatment-related AST elevation AEs (6.8% versus 2.7%) and
  - the frequency of laboratory abnormalities for AST increased (52% versus 34%, including grade 3 findings in 3% versus 1%)
- ALT increased (2.2% versus 0%), an imbalance consistent with
  - the total number of treatment-related AST elevation AEs (6.8% versus 1.8%)
  - the frequency of laboratory abnormalities for ALT increased (43% versus 30%, including grade 3-4 findings in 2.5% versus 0%)
- Acute kidney injury (0.5% versus 0%)

16.4.7 Question 17 for sponsor

17. In the supplemental Clinical Overview with Dossier version [0004], Table 8 shows ADRs (which are usually equated with treatment-related AEs). The frequency of some ADRs in that Table differs from the frequency of treatment-related AEs in the CSR; the data cut-off date is the same. For example, in Clinical Overview Table 8, ALT increased is reported as occurring in 9.9% of patients in the palbociclib-containing arm. In CSR Table 40, ALT increased is reported as occurring in 6.8%. It is noted a slightly different MedDRA coding version is used. Please account for the differences observed.

It is also noteworthy in the EMA Second JRAR that:

2 cases of fatal hepatic toxicity (Vuppalanchi, R., Saxena, R., Storniolo, A. M. V. and Chalasani, N. (2016), Pseudocirrhosis and liver failure in patients with metastatic breast cancer after treatment with palbociclib. Hepatology. doi:10.1002/hep.28720) have been recently reported with palbociclib associated to letrozole.

These cases are noted in the response to Safety Question 18, with the assertion made that pseudocirrhosis is more closely related to underlying disease than treatment.

16.4.8 Treatment related adverse events (adverse drug reactions)

These were qualitatively similar to all-causality AEs described above.

Treatment-related infections were reported in 19.1% (palbociclib-containing arm) versus 8.1% (placebo-containing arm), and treatment-related rashes were reported in 10.8% versus 5.4% respectively.

16.4.9 Deaths and other serious adverse events

Deaths are reported above, under 'overall survival'. Most were due to disease progression. Narratives of deaths in CSR Section 14.3.3.1 amounted to CIOMS forms not consolidated narratives. For some reports it was difficult to discern whether the patient had received palbociclib or placebo.

16.4.10 Questions 18-20 for sponsor

18. Indicate the location within the CSR, or provide separately, consolidated narratives for patients who died on treatment (or within 28 days of last dose), including information about whether palbociclib or placebo was given. Draft CIOMS forms are not considered sufficient, especially when treatment allocation is not revealed.

19. Regarding subject ID [information redacted], the autopsy concluded cardiogenic shock of unknown origin. Had this patient had QTcS assessment during the study, e.g. baseline? Was there QTc prolongation? It is noted this patient was on venlafaxine amongst other agents.

20. Regarding subject ID [information redacted], the autopsy found acute cardiovascular insufficiency. Which arm was the patient randomised to? Had this patient had QTcS assessment during the study, e.g. baseline? Was there QTc prolongation?

Serious AEs including deaths were reported in 19.6% (palbociclib-containing arm) versus 12.6% (placebo-containing arm), including data up to 28 days after last dose of study drug. Infections, febrile neutropenia and pulmonary embolism were the most common serious AEs.

An 84 year old female on palbociclib had an AE of syncope which was explained by 'mild subarachnoid haemorrhage' and a term called 'bifrontal cortical confusion' on CT.

16.4.11 Question 21-22 for sponsor

21. In tabulation of AEs, was this event classified only as 'syncope', or also as 'subarachnoid hemorrhage' or some related term? It is noted that in Table 14.3.1.1.2, there are also events of cerebral haemorrhage (1 x grade 2) and cerebrovascular accident (1 x grade 3). How many distinct patients in the palbociclib versus placebo arms had any intracranial bleeding events on treatment? Is it known whether these bleeds were associated with intracranial metastases?

22. It is also noted in the SCS [Dossier version [0004]] that in Study 1010, SAEs included cerebral haemorrhage and subarachnoid haemorrhage (the latter, fatal). Please provide a signal analysis across randomised studies of palbociclib for 'serious bleeding' terms.

16.4.12 Discontinuations due to adverse events

The following table (from CSR) shows all-causality AEs leading to permanent discontinuation (for more than one patient):

Table 58: All causality AEs leading to permanent discontinuation

	Palbociclib Plus Letrozole N = 444 n (%)	Placebo Plus Letrozole N = 222 n (%)
Any AE[a]	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

Dose reduction in the palbociclib-containing arm was typically due to neutropenia / low neutrophils (in 131/444, 29.5%) and less commonly due to febrile neutropenia (1.4%), anaemia (1.6%), leukopenia (1.1%) and fatigue (1.1%).

16.4.13 Evaluation of issues with possible regulatory impact

16.4.13.1 Renal function and renal toxicity

Lab-based creatinine outcomes showed grade 3-4 elevations in 1.4% (palbociclib-containing arm) versus 0% (placebo-containing arm), consistent with the imbalance in the AE of acute kidney injury (0.5% versus 0%) reported earlier.

16.4.13.2 Other clinical chemistry

Clinical chemistry lab-based outcomes (CSR; OTR indicates a non-missing lab value outside the grading range, i.e. normal value) are shown below:

Table 59: Clinical chemistry outcomes

Parameter	Palbociclib plus Letrozole N=444				Placebo plus Letrozole N=221			
	OTR n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	OTR n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Alanine aminotransferase (ALT)	253 (57.0)	180 (40.5)	10 (2.3)	1 (0.2)	155 (70.1)	66 (29.9)	0	0
Alkaline phosphatase	279 (62.8)	159 (35.8)	6 (1.4)	0	129 (58.4)	92 (41.6)	0	0
Aspartate aminotransferase (AST)	215 (48.4)	214 (48.2)	15 (3.4)	0	145 (65.6)	74 (33.5)	2 (0.9)	0
Bilirubin (total)	417 (93.9)	24 (5.4)	3 (0.7)	0	209 (94.6)	12 (5.4)	0	0
Creatinine	19 (4.3)	419 (94.4)	5 (1.1)	1 (0.2)	21 (9.5)	200 (90.5)	0	0
Hypercalcemia	356 (80.2)	88 (19.8)	0	0	169 (76.5)	50 (22.6)	2 (0.9)	0
Hyperkalemia	346 (77.9)	94 (21.2)	4 (0.9)	0	181 (81.9)	39 (17.6)	1 (0.5)	0
Hypermagnesemia	382 (86.0)	57 (12.8)	4 (0.9)	1 (0.2)	192 (86.9)	25 (11.3)	4 (1.8)	0
Hypernatremia	363 (81.8)	75 (16.9)	6 (1.4)	0	188 (85.1)	32 (14.5)	1 (0.5)	0
Hypoalbuminemia	349 (78.6)	94 (21.2)	1 (0.2)		180 (81.4)	41 (18.6)	0	
Hypocalcemia	297 (66.9)	138 (31.1)	4 (0.9)	5 (1.1)	175 (79.2)	45 (20.4)	1 (0.5)	0
Hypokalemia	348 (78.4)	87 (19.6)	9 (2.0)	0	187 (84.6)	32 (14.5)	2 (0.9)	0
Hypomagnesemia	333 (75.0)	109 (24.5)	1 (0.2)	1 (0.2)	185 (83.7)	36 (16.3)	0	0
Hyponatremia	353 (79.5)	82 (18.5)	9 (2.0)	0	186 (84.2)	31 (14.0)	4 (1.8)	0

Given the difference in duration of treatment across arms, there were no dramatic imbalances, although grade 3-4 hypocalcaemia was more prominent in the palbociclib-containing arm (2.0% versus 0.5%).

While three patients in the palbociclib-containing arm met lab criteria for potential Hy's Law cases, none fully met Hy's Law criteria. One had a stricture in the common bile duct requiring a stent; one had hepatic metastases and chronic cholecystitis; one had hepatic steatosis. There were no reports of drug-induced liver injury or hepatic failure.

16.4.13.3 Haematology and haematological toxicity

The AE profile described in above clearly indicates that palbociclib has a major effect on haematology indices, confirmed by lab-based assessment (CSR; OTR indicates a non-missing lab value outside the grading range, i.e. normal value):

Table 60: Haematology outcomes

Parameter	Palbociclib plus Letrozole N=444				Placebo plus Letrozole N=221			
	OTR n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	OTR n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Anemia	98 (22.1)	320 (72.1)	26 (5.9)		129 (58.4)	87 (39.4)	5 (2.3)	
Hemoglobin increased	433 (97.5)	10 (2.3)	1 (0.2)		201 (91.0)	20 (9.0)	0	
Neutrophils (absolute)	21 (4.7)	125 (28.2)	247 (55.6)	51 (11.5)	176 (79.6)	41 (18.6)	3 (1.4)	1 (0.5)
Platelets	164 (36.9)	272 (61.3)	6 (1.4)	2 (0.5)	191 (86.4)	30 (13.6)	0	0
White blood cells	15 (3.4)	271 (61.0)	153 (34.5)	5 (1.1)	165 (74.7)	55 (24.9)	1 (0.5)	0

16.4.13.4 Electrocardiograph findings and cardiovascular safety

There were no dramatic imbalances in frequency of QT prolongation, although prolongation of QTc interval ≥ 60 msec was observed in 3/441 (0.7%) versus 0/220, using a study-specific correction factor reasonably deemed more suitable at compensating for heart rate than QTcF or QTcB.

In PALOMA-2, more intensive ECG subgroup analysis was conducted in 125 patients (77 in the palbociclib-containing arm, 48 in the placebo-containing arm). Cycle 1 day 14 outcomes (in msec) are shown below:

Table 61: Cycle 1 Day 14 outcomes in 125 patients

Planned Time Postdose	Palbociclib plus Letrozole			Placebo plus Letrozole		
	n	LS Mean (Standard Error) Change from Baseline	90% CI of LS Mean Change from Baseline	n	LS Mean (Standard Error) Change from Baseline	90% CI of LS Mean Change from Baseline
0 h	76	0.80 (1.495)	(-1.67, 3.26)	46	2.95 (1.906)	(-0.19, 6.10)
2 h	71	3.32 (1.535)	(0.79, 5.85)	47	1.65 (1.897)	(-1.48, 4.78)
4 h	71	2.76 (1.535)	(0.23, 5.30)	47	1.74 (1.897)	(-1.39, 4.87)
6 h	71	4.49 (1.535)	(1.96, 7.02)	47	0.72 (1.897)	(-2.41, 3.85)
8 h	70	0.94 (1.542)	(-1.60, 3.48)	47	3.14 (1.897)	(0.01, 6.27)

While there is no positive control in this substudy, the outcomes do not suggest a strong effect of palbociclib on QTc interval. The 6 hr time point where the widest difference between palbociclib and placebo arms lay coincides with T_{max} of 4-8 hrs. The threshold of regulatory concern described in the TGA-adopted EU guideline CHMP/ICH/2/04 is 5 ms (or upper bound of 95% CI 10 ms). Also, in this subgroup analysis, outlier analysis indicated no differences across arms.

16.4.14 Question 23 for sponsor

23. Ninety percent (90%) CIs are calculated in the above Table. Please provide 95% CIs around the

LS mean change from baseline for each time point and each arm.

16.4.14.1 Other safety parameters

Concomitant use of some drug classes was imbalanced by >10% (CSR):

Table 62: Concomitant use of other drugs

Class	Palbociclib + letrozole	Placebo + letrozole
Antibacterials for systemic use	47.5%	35.1%
Otologicals	35.4%	23.0%
Ophthalmologicals	65.1%	52.7%
Immunostimulants, e.g. filgrastim	12.2%	0%
Vasoprotectives, e.g. dexamethasone	29.7%	17.6%
Corticosteroids (skin)	29.5%	17.6%
Ophthalmological and otological	25.0%	14.0%
Antibiotics (skin)	26.8%	16.2%
Nasal preparations	36.3%	25.7%
Gynaecological antiinfectives and antiseptics	27.5%	17.1%

16.4.15 Evaluator's overall conclusions on clinical safety

Prominent AEs were myelosuppression, alopecia and stomatitis, the same as those seen with cytotoxic chemotherapy. Quantitatively there were differences between AEs seen with palbociclib and those seen with more traditional chemotherapy. Alopecia was not reported uniformly; and severe stomatitis was not common. The frequency of serious infection was not clearly increased in the palbociclib-containing arm (noting imbalances in duration of treatment across arms).

Given that in PALOMA-2, palbociclib was 'added on' to the letrozole standard of care, it is not surprising that AEs in the palbociclib + letrozole were significantly imbalanced versus comparator. The impact of additional toxicity must be seen in the light of palbociclib's anti-tumour efficacy.

16.5 First round benefit-risk assessment for PALOMA-2

16.5.1 First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Large PFS benefit	*Uncertainty: do benefits in PFS and ORR*

Indication	
Benefits	**Strengths and Uncertainties**
Moderate ORR benefit *Large benefit in preventing disease progression as best objective response*	*translate into OS benefit?* *Uncertainty: impact on OS* *Uncertainty: extent of impact on QoL is not clear (no major differences seen)*

16.5.2 First round assessment of risks

Risks	Strengths and Uncertainties
Myelosuppression (neutropenia, anaemia, thrombocytopenia) *Alopecia* *Stomatitis* *Cataracts* *Modest increase in LFT derangements*	*Uncertainty: extent to which neutropenia causes additional infection* *Uncertainty: extent to which thrombocytopenia causes additional bleeding* *Uncertainty: a few typically letrozole-related AEs were recorded at lower frequencies in the palbociclib + letrozole arm; it is unclear if this is a real effect*

16.5.3 First round assessment of benefit-risk balance

A detailed assessment of risk-balance is reserved for the Delegate's Overview.

16.5.4 First round recommendation regarding authorisation

Recommendations regarding authorisation are reserved for the Delegate's Overview.

16.6 Clinical questions

1. It is noted in the EMA's Second Joint Rapporteur's Assessment Report (JRAR) that:

The sponsor also commits to submit the final OS results from Study 1008 when they become available. Based on current projections, the readout is estimated to occur in May 2020 and the final report would be submitted by November 2020, as a type 2 variation.

Please provide an update about when the **final OS outcomes** are anticipated, and when the CSR reporting final OS outcomes will be available.

2. Beyond the OS analyses conducted at the time of the initial and final PFS analysis, are any OS analyses to be conducted (by the E-DMC, sponsor, or any other party) prior to the final OS analysis?

3. How many patients continued to receive palbociclib beyond RECIST-defined PD? Provide a summary of the benefits (if any) observed in PALOMA-2 with such treatment, e.g. median duration of treatment post-progression; PFS relative to others with PD who did not receive palbociclib post-PD; evidence of any tumour response after progression.

4. Please confirm that for the 'investigator' assessment of PFS, assignment of the overall response category was not made by the investigator, but was 'independent of the overall response category provided by the investigator'. Who – sponsor, DMC or other agent – assigned the overall response category for the purpose of investigator-assessed PFS and related

investigator-assessed outcomes?

5. Please describe the level of concordance between the investigator's overall response category and the overall response category designated by the sponsor / DMC / other agent based on lesion measurements / assessments provided by the investigator. For example, how many patients per arm had discordance between an objective response and stable disease, or between stable disease and progressive disease?

6. Please point to a tabulation in the CSR (or create a tabulation) of the use of commoner prohibited concomitant medications (capturing type of medication, typical reason/s for use and extent of use), allowing comparison across arms.

7. In CSR Table 19 *using CRF data*, the study population is divided by disease free interval ('since completion of prior (neo) adjuvant therapy') into: De Novo (n=167 versus 81); ≤12 months (n=99 versus 48); and >12 months (n=178 versus 93). Could the sponsor confirm that by 'de novo' in this classification, what is meant is *'no prior systemic therapy'* presumably equating to no prior neoadjuvant or adjuvant systemic therapy (rather than *'de novo metastatic disease'*)? Reference is also made to CSR Table 15, where n=167 versus 81 had no prior systemic therapies (either chemotherapy or hormonal), and to CSR Table 18, where n=139 versus 71 had 'newly diagnosed' recurrence type (other categories involving 'recurrence' whether locoregional or distant imply earlier diagnosis of breast cancer).

How many patients per arm had no prior systemic therapy for advanced disease despite not having 'de novo metastatic disease' on enrolment into the study? Why had these patients not received endocrine or at least systemic therapy at initial diagnosis of 'advanced' breast cancer? What was this group's median length of time since diagnosis? Provide PFS and ORR outcomes per arm for this subgroup. Also provide PFS and ORR outcomes per arm for the subgroup described in CSR Table 18 as 'newly diagnosed' (taken by this evaluator to be truly 'de novo' advanced disease), based on investigator and BICR assessments (and according to both IMPALA and CRF analyses).

8. Provide the interim OS analysis that was performed at the time of the final PFS analysis, and any update. Provide 12- and 24-month OS rates per arm, estimated median OS per arm, an estimated OS hazard ratio, and estimated KM curves for OS.

9. Please comment in detail on the apparent discordance between mature PFS and immature OS outcomes.

10. The SAP version 3.0 states:

A supportive analysis will be performed by combining the OS data from this study and from the randomized Phase II Study A5481003 with similar approaches described above. The Study as a stratification factor (A5481003 vs. A5481008) will also be included in the analysis. Since the median OS time for the studied patient population is relatively long and it is anticipated a small fraction of OS events would be available at the time of OS interim analysis, this analysis will certainly increase the power of detecting the OS difference between two treatment arms, given both randomized studies have similar patient populations and OS follow up processes.

This implies that the supportive analysis will be conducted prior to OS final analysis.

Please provide this supportive analysis of OS outcomes across studies 1003 and 1008.

11. In PALOMA-3, there was a delay in time to deterioration for pain symptoms, in the palbociclib-containing arm. What outcomes were observed for pain symptoms in PALOMA-2?

12. The Clinical Evaluator for the main Dossier writes that assessment of benefit in patients with bone-only disease relies on measures of quality of life such as improvement in pain, reduced skeletal event rates, etc. What patient-reported outcomes for pain symptoms were observed in patients with bone-only disease?

13. In relation to alopecia, please characterise this further. For affected patients in the palbociclib-containing arm, was there typically 'complete' hair loss as might be seen with some chemotherapies or 'thinning' as might be seen with, for example, letrozole? Was there scalp tenderness? Did hair re-grow normally on treatment discontinuation?

14. It was noted from the CSR that there were several cases of intracranial haemorrhage in the palbociclib-containing arm (patient IDs 13331001 and 10131001). Were there other cases of significant bleeding? Was any case associated with thrombocytopenia of any grade?

15. Was sufficient information gathered to understand whether the imbalance in cataract surgery extended more than 28 days after the last dose?

16. Is there any indication that palbociclib and letrozole may have a pharmacodynamics interaction that could explain higher rates of headache, hot flushes and hypertension in the placebo-containing arm?

17. In the supplemental Clinical Overview with Dossier version [0004], Table 8 shows ADRs (which are usually equated with treatment-related AEs). The frequency of some ADRs in that Table differs from the frequency of treatment-related AEs in the CSR; the data cut-off date is the same. For example, in Clinical Overview Table 8, ALT increased is reported as occurring in 9.9% of patients in the palbociclib-containing arm. In CSR Table 40, ALT increased is reported as occurring in 6.8%. It is noted a slightly different MedDRA coding version is used. Please account for the differences observed.

18. Indicate the location within the CSR, or provide separately, consolidated narratives for patients who died on treatment (or within 28 days of last dose), including information about whether palbociclib or placebo was given. Draft CIOMS forms are not considered sufficient, especially when treatment allocation is not revealed.

19. Regarding subject ID 11921004, the autopsy concluded cardiogenic shock of unknown origin. Had this patient had QTcS assessment during the study, e.g. baseline? Was there QTc prolongation? It is noted this patient was on venlafaxine amongst other agents.

20. Regarding subject ID 10551006, the autopsy found acute cardiovascular insufficiency. Which arm was the patient randomised to? Had this patient had QTcS assessment during the study, e.g. baseline? Was there QTc prolongation?

21. An 84 year old female on palbociclib had an AE of syncope which was explained by 'mild subarachnoid haemorrhage' and a term called 'bifrontal cortical confusion' on CT.

In tabulation of AEs, was this event classified only as 'syncope', or also as 'subarachnoid hemorrhage' or some related term? It is noted that in Table 14.3.1.1.2, there are also events of cerebral haemorrhage (1 x grade 2) and cerebrovascular accident (1 x grade 3). How many distinct patients in the palbociclib versus placebo arms had any intracranial bleeding events on treatment? Is it known whether these bleeds were associated with intracranial metastases?

22. It is also noted in the SCS [Dossier version [0004]] that in Study 1010, SAEs included cerebral haemorrhage and subarachnoid haemorrhage (the latter, fatal). Please provide a signal analysis across randomised studies of palbociclib for 'serious bleeding' terms.

23. Ninety percent (90%) CIs are calculated in the above Table [refer to Section 8.3.4 above]. Please provide 95% CIs around the LS mean change from baseline for each time point and each arm.

24. Could the sponsor clarify their best estimate of the frequency of febrile neutropenia in PALOMA-2 (refer also to the footnote #11 earlier in this CER).

The sponsor's answers to these questions were reviewed by the Delegate and taken into consideration during the decision process.

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