



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Palbociclib

Proprietary Product Name: Ibrance

Sponsor: Pfizer Australia Pty Ltd

April 2018

TGA Health Safety
Regulation

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
ABC	Advanced breast cancer
ADI	Average dose intensity
ADME	Absorption, distribution, metabolism and elimination
AE	Adverse Event
AIC	Akaike information criteria
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANOVA	Analysis Of Variance
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
ATC	Absolute Thrombocyte Count
AUC	Area Under The Plasma Concentration/Time Curve
AUC _{inf}	AUC from time zero extrapolated to infinite time
AUC _{inf} (dn)	Dose normalised auc _{inf}
AUC _{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C _{last})
BA	Bioavailability
BALB	Baseline albumin
BALK	Baseline Alkaline Phosphatase
BALT	Baseline Alanine Aminotransferase
BAST	Baseline Aspartate Aminotransferase
BBIL	Baseline Total Bilirubin
BCCL	Baseline Creatinine Clearance
BLYM	Baseline Lymphocytes
BMI	Body Mass Index

Abbreviation	Meaning
BP	Blood Pressure
BSCR	Baseline Serum Creatinine
C _{avg}	Average Drug Concentration
CDK	Cyclin-Dependent Kinase
cf.	Compared With
CI	Confidence Interval
CIRC ₀	Baseline Level Of Circulating Cells In The Blood Stream
CIRC _t	Circulating Cells In The Blood Stream At A Given Time T
CL	Clearance
CL/F	Apparent Clearance
CL _r	Renal Clearance
C _{max}	Maximum Observed Plasma Concentration
C _{min}	Trough (Pre-Dose) Concentrations
CR	Complete Response
CT	Computed tomography
CV	Coefficient of variation
CYP3A	Cytochrome P450, family 3, subfamily A
DDI	Drug-drug interaction
DLT	Dose-limiting toxicities
DR	Duration of response
EBE	Empirical Bayes estimate
EC ₅₀	Concentration corresponding to 50% of the maximum effect
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED	Drug Effect Or Stimulus
EM	Extensive Metabolisers

Abbreviation	Meaning
E _{max}	Maximum Observed Or Estimated PD Effect
EOT	End Of Treatment
ER-positive	Oestrogen Receptor Positive
FAS	Full Analysis Set
FB	Free Base
[¹⁸ F]-FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
[¹⁸ F]-FLT-PET	Fluoro-L-Thymidine-Positron Emission Tomography
GM	Geometric Mean
GMR	Geometric Mean Ratio
h	H/S
HEM	Heterozygous Extensive Metaboliser
HER2-negative	Human Epidermal Growth Factor Receptor 2 Negative
HFI	Hand-Filled Isethionate
HPLC-MS/MS	High-Performance Liquid Chromatography Tandem Mass Spectrometric
ICH	International Conference on Harmonization
IM	Intermediate metabolisers
IR	Immediate-release
IU	International unit
IV	Intravenous
K _a	Absorption rate constant
K _{circ}	Elimination rate constant from blood circulation compartment
K _{tr}	Inter-compartment transit rate constant
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
MCL	Mantle cell lymphoma

Abbreviation	Meaning
MedDRA	Medical Dictionary for Regulatory Activities
min	minute/s
MRAUC _{inf}	Metabolite to parent ratio auc _{inf}
MRAUC _{last}	Metabolite to parent ratio auc _{last}
MRC _{max}	Metabolite to parent ratio of C _{max}
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MTT	Mean transit time
NCI	National cancer institute
NHL	Non-Hodgkin's lymphoma
OFV	Objective function value
ORR	Objective response rate
PD	Pharmacodynamics
PET	Positron emission tomography
PFS	Progression-free survival
PF-05089326	Lactam metabolite of palbociclib
PK	Pharmacology
PM	Poor metaboliser
PMAP	Population modelling analysis plan
pop ⁿ	Populations
popPK	Population pharmacokinetics
PPI	Proton-pump inhibitor
PR	Partial response
p-Rb	Phosphorylated retinoblastoma
PrD	Progressive disease
PREDDP	Prediction population pharmacokinetics

Abbreviation	Meaning
QD	Once daily
Q/F	Apparent inter-compartmental clearance
QTcB	QT corrected for heart rate using Bazett's formula
QTcF	QT corrected for heart rate using Fridericia's formula
QTcS	QT corrected for heart rate using estimated study specific correction
R _{ac}	Accumulation Ratio
Rb	Retinoblastoma
RECIST	Response Evaluation Criteria In Solid Tumours
RP2D	Recommended Phase II dose
RR	Time interval from one QRS interval to the beginning of the next QRS interval that is, time interval between consecutive heart beats
RR-C	Concentration-RR relationship
SAE	Serious adverse event
SCLC	Small Cell Lung Carcinoma
SCM	Stepwise Covariate Modelling
SOC	System Organ Class
StD	Stable Disease
SULT	Sulfotransferase
SULT2A1	Sulfotransferase Family 2A Member 1
SUV	Standard uptake value
SUVmax	Maximum standard uptake value
SVPC	Standardized Visual Predictive Check
t _{1/2}	Half-Life
TBR	Tumour Background Ratios
TEAE	Treatment-Emergent Adverse Events

Abbreviation	Meaning
TTP	Time to tumour progression
ULN	Upper limit of normal
UM	Ultra-rapid metaboliser
VPC	Visual predictive check
V ₂ /F	Apparent volume of distribution in the central compartment
V ₃ /F	Apparent volume of distribution in the peripheral compartment
V _{ss}	Apparent volume of distribution at steady state
V _z /F	Apparent volume of distribution

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	28 April 2017
<i>Date of entry onto ARTG</i>	3 May 2017
<i>Active ingredient(s):</i>	Palbociclib
<i>Product name(s):</i>	Ibrance
<i>Sponsor's name and address:</i>	Pfizer Australia Pty Ltd 38 - 42 Wharf Road West Ryde NSW 2114
<i>Dose form(s):</i>	Hard gelatin capsules
<i>Strength(s):</i>	75 mg, 100 mg and 125 mg
<i>Container(s):</i>	Blister pack and bottle
<i>Pack size(s):</i>	21 tablets
<i>Approved therapeutic use:</i>	<p><i>Ibrance is 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:</i></p> <ul style="list-style-type: none"><i>an aromatase inhibitor as initial endocrine-based therapy</i><i>fulvestrant in patients who have received prior therapy.</i>
<i>Route(s) of administration:</i>	Oral (PO)
<i>Dosage:</i>	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. For further details see Pi Attachment 1.
<i>ARTG number (s):</i>	274624, 274623, 274622, 274621, 274620 and 274619

Product background

This AusPAR describes the application by the sponsor to register the new chemical entity palbociclib as Ibrance and is proposed to be used in combination with endocrine therapy for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

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 sponsor's 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*

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.

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

Continue the treatment as long as the patient is deriving clinical benefit from therapy.

Background

Palbociclib is the first CDK4/6 inhibitor to be evaluated for registration by the TGA.

It is approved by the FDA and by the European Medicines Agency (EMA), in first and second line settings. In the US, approval in the first-line setting is 'accelerated', that is, based on surrogate endpoints and subject to confirmation by a separate study. Evaluation of palbociclib for first-line use by these agencies did not include evaluation of Study 1008's full Clinical Study Report (Study 1008, or PALOMA-2, is the confirmatory study for the FDA's accelerated approval. First-line use was based on Study 1003).

No major manufacturing, quality control or nonclinical issues have been identified in the TGA evaluation process to date. Key issues are clinical in nature. Initial advice has been received from discussion at the Oncology Working Group (Meeting #2; 2 March 2016).

Mechanism of action

Palbociclib is a reversible inhibitor of CDK4 and CDK6. The Clinical Study Report (CSR) for PALOMA-2 states:

The compound prevents cellular deoxyribonucleic acid (DNA) synthesis by prohibiting progression of the cell cycle from G1 into the S phase...

Upon binding to D-type cyclins, cyclin-dependent kinase (CDK) 4 and CDK6 regulate cell cycle G1 to S phase transition. The CDK4/6/Cyclin D1 (CCND1) complex phosphorylates the retinoblastoma susceptibility (RB1) gene product (Rb), releasing the E2F and DP transcription factors that drive expression [of] genes required for S phase entry.

CDK activity and G1 progression is negatively regulated by CDK interacting protein-kinase inhibitory protein (Cip-Kip) and inhibitor of the cyclin-dependent kinase (INK) 4 family, typified by p16. Overexpression of p16 in cells with normal Rb

inhibits both CDK4- and CDK6-associated kinase activity and Rb phosphorylation, with subsequent cell cycle arrest.

There is a strong link between the actions of estradiol and the G1-S phase transition, where the estradiol effector is the cyclin D1-CDK4/6-Rb complex. Cyclin D1 is a direct transcriptional target of ER and microinjection of antibodies to cyclin D1 inhibits estrogen-induced S phase entry. In addition, anti-estrogen-induced growth arrest of ER-positive BC cells is accompanied by decreased cyclin D1 expression while endocrine resistance is associated with persistent cyclin D1 expression and Rb phosphorylation.

Consistent with the notion that the main function of cyclin D1 is to activate CDK4/6, its oncogenic activity is dependent on CDK4/6-associated kinase activity and CDK4/6 inhibitors are most effective in tumors with gene amplification and overexpression of cyclin D1, which is common in ER-positive BC. For example, palbociclib was most effective for ER-positive BC in a cell line panel, including those that exhibit anti-estrogen resistance. Genetic aberrations leading to hyperactivation of cyclin D1-CDK4/6 are particularly common in ER-positive BC, consistent with its critical role in the tumorigenesis of this cancer subtype, making CDK4/6 inhibitors particularly attractive agents for ER positive BC.

The same CSR also asserts that palbociclib may have cytoreductive as well as cytostatic effects on tumour cells.

Regulatory guidelines

The TGA has adopted the following relevant EU guidelines (amongst others):

- Evaluation of anticancer medicinal products, EMA/CHMP/205/95/Rev.4 (and relevant appendices).
- Data Monitoring Committees, EMEA/CHMP/EWP/5872/03 Corr.
- Points to consider on application with 1) meta-analysis; 2) single pivotal study (CPMP/EWP/2330/99).

Guidelines are not binding but variation from their recommendations may suggest a need for close examination of particular quality, efficacy and / or safety issues.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 3 May 2017.

USA

Palbociclib is currently approved in the USA with the following indications:

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.

The FDA received an initial application in August 2014, leading to 'accelerated' approval¹ on 3 February 2015 of the first-line indication based on PALOMA-1. An FDA advisory committee was not used. The post-marketing requirement was:

Submit the progression free survival (PFS) and overall survival (OS) data and results from the ongoing Trial A5481008, PALOMA-2, 'A Randomized, Multicenter, Double-blind Phase 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' when supplemental application for regular approval is submitted. In addition, submit OS data and results at trial completion.

Trial Completion: 12/2016

Final PFS Report Submission: 06/2017

Final OS Report Submission: 11/2020

Other post-marketing requirements/commitments accompanying initial approval were to submit:

- Study A5481013 (PK in subjects with impaired hepatic function) by December 2017
- Study A5481039 (DDI study with modafinil and pioglitazone) by October 2015
- Analyse PALOMA-2 to determine prognostic/predictive significance of genetic alterations in cyclin D1/CDK4/6/p16/ Rb pathway for safety and efficacy of palbociclib (by June 2017)

The sponsor submitted an efficacy supplement in October 2015 for use in combination with fulvestrant on progression following endocrine therapy. This was approved in February 2016, as a standard approval, with a post-marketing commitment to submit final OS analysis of PALOMA-3, by June 2018.

EU

Palbociclib is approved for use in the EU with the following indication:

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

in combination with an aromatase inhibitor;

in combination with fulvestrant in women who have received prior endocrine therapy (see section 5.1).

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

The EMA received an initial application on 30 July 2015, covering both first and second line uses. Full approval was given on 9 November 2016; a European Public Assessment Report (EPAR) is available².

The following table summarises the international regulatory status of Ibrance.

¹ Accelerated approval is approval based on a surrogate or an intermediate clinical endpoint; studies using these endpoints need to be adequate and well-controlled; confirmation of clinical benefit is still required, e.g. in confirmatory clinical trials.

² http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003853/WC500217198.pdf

Table 1: International regulatory status

Country	Status	Regulatory Actions	Indications
United States of America	Approved	NDA 3 February 2015 sNDA 19 February 2016	Ibrance is indicated for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with: letrozole as initial endocrine based therapy in postmenopausal women, or fulvestrant in women with disease progression following endocrine therapy. <i>The indication in combination with letrozole is approved under accelerated approval based on progression-free survival (PFS) [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.</i>
	Under evaluation	sNDA 26 October 2016	Ibrance is indicated for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with:
	(Priority Review Designation)	Action date: 27 April 2017	an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or fulvestrant in women with disease progression following endocrine therapy.
European Union (CP)	Approved	9 November 2016	Ibrance is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer: in combination with an aromatase inhibitor; in combination with fulvestrant in women who have received prior endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.
Canada	Approved	16 March 2016	Ibrance in combination with letrozole for the treatment of

Country	Status	Regulatory Actions	Indications
			<p>postmenopausal women with ER+, HER2- advanced breast cancer as initial endocrine-based therapy for their metastatic disease.</p> <p><i>This Conditional Marketing authorization is based on progression free survival (PFS) benefit observed in PALOMA-1 study. Continued approval for this indication is contingent upon verification and description of clinical benefit in PALOMA-2 study.</i></p>
	Submitted	29 November 2016	<p>For the treatment of hormone receptor (HR) positive, HER2 negative advanced or metastatic breast cancer:</p> <p>-in combination with an aromatase inhibitor as initial endocrine- based therapy in postmenopausal women</p>
Singapore	Approved	21 July 2016	Ibrance in combination with letrozole for the treatment of postmenopausal women with ER+, HER2- advanced breast cancer as initial endocrine-based therapy for their metastatic disease
Switzerland	Approved	31 January 2017	Ibrance is 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 fulvestrant in pre-/peri- (combined with LHRH analogs) or postmenopausal women who have received prior endocrine therapy
	Submission	First quarter 2017	Ibrance is 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 in pre-/peri- (combined with LHRH analogs) or postmenopausal women
New Zealand	Under evaluation (granted Full Priority Review)	Abbreviated NMA ref. EU consent submitted 31 October 2016	Ibrance is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or

Country	Status	Regulatory Actions	Indications
			<p>metastatic breast cancer:</p> <p>in combination with an aromatase inhibitor;</p> <p>in combination with fulvestrant in women who have received prior endocrine therapy.</p> <p>In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.</p>

Product Information

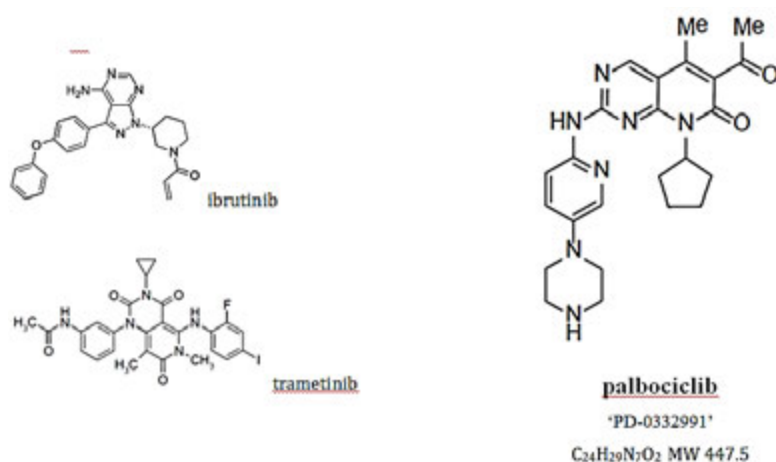
The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the [TGA website](https://www.tga.gov.au/product-information-pi) at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Drug substance (active ingredient)

Palbociclib is a synthetic drug. It is not chiral and does not show isomerism. The structure is not very closely related to other drugs. The chemical structure of palbociclib is compared to that of ibrutinib and trametinib in Figure 1 below.

Figure 1: Chemical structures



Palbociclib is a yellow to orange crystalline powder. It is basic (pKa values 7.4 [piperazine] and 3.9 [pyridine]). Palbociclib is very soluble in acid up to about pH 4. Under less acidic conditions, the solubility of the drug substance is markedly lower. Thus there is some chance of lower bioavailability in achlorhydric patients. (The sponsor however argues that population pharmacokinetic analysis shows acid-reducing agents, including proton pump inhibitors (PPIs), histamine subtype 2 (H₂) receptor antagonists and antacids did not significantly affect exposure under fed conditions, although rabeprazole did substantially

reduce absorption under fasting conditions. Curiously there is a low-exposure cohort in some pharmacokinetic studies.).

The particle size of palbociclib is controlled but does not appear to affect dissolution from the capsules, at least in acid as used in in vitro testing. Impurity limits are considered acceptable.

Drug product

The recommended dose is a 125 mg taken once daily for 21 days, followed by 7 days off. Capsules are taken with food and swallowed whole. Dose reductions are recommended based on tolerability.

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

The capsules are opaque and are distinguished by size, colour and printing (75 mg: light orange body/light orange cap; 100 mg: light orange body/caramel cap; 125 mg: caramel body/caramel cap; these are all printed with 'Pfizer' along with 'PBC 75' or 'PBC 100' or 'PBC 125' corresponding to the dose in white lettering). Both bottles and blister packs containing 21 capsules for all strengths are proposed.

The three strengths are made using a common blend (that is, the same capsule fill). There is one specified impurity in the capsule specification. This is toxicologically qualified, as a metabolite.

Batches of capsules are routinely assessed using an in vitro dissolution test.

There were no significant changes detected in stability trials in either bottles or blisters, with only a small increase in levels of the formyl adduct notable. Packed capsules are stored below 30°C with no special warnings.

Biopharmaceutics

Absolute bioavailability

Study A5481501 was an open-label, fixed-sequence, 2-period, 2-treatment, crossover, single dose study conducted to assess the absolute bioavailability of palbociclib from the initial Phase III capsule formulation relative to an intravenous (IV) infusion after administration to healthy volunteers in the fasted state. This study has not been evaluated in detail but is summarised here. Subjects were administered one palbociclib 125 mg capsule with 240 mL of water after an overnight fast, followed 10 days later by a palbociclib 50 mg infusion. The mean plasma profiles, reported data, and statistical analyses are as shown below.

Formulations

Early clinical studies used palbociclib (as isethionate = 2-hydroxyethanesulfonic acid) 5 mg, 25 mg, and 100 mg capsules, however, the physical properties of both the drug substance and the drug product were unsuitable for commercial production. The isethionate capsules were used in early Phase I Studies 1001 and 1002, Phase I/II Studies 1003, 1004 and Phase I of 1010 in patients with cancer and BE studies 1009, 1020 and 1036.

After extensive salt screening, the free base was chosen for development of Phase III formulations. The initial Phase III capsule was formulated using the free base form of palbociclib. This capsule formulation also contained microcrystalline cellulose, lactose

monohydrate, sodium starch glycolate, colloidal anhydrous silica and magnesium stearate. Three strengths: 75 mg, 100 mg and 125 mg, were developed using a common fill.

The final Phase III free base capsule contains the same concentrations of drug substance, disintegrant (sodium starch glycolate) and lubricant (magnesium stearate) as the initial Phase III drug product. However this formulation contains a slightly higher level of colloidal anhydrous silica in order to improve the flow properties of the intragranular blend and adjustments to the quantities of the diluents. The formulation used in the later Phase III studies is identical to that proposed for commercial production.

Preliminary analysis of the available data in healthy volunteers over several studies showed that significant lower exposure (peak plasma concentration (C_{max}) and area under the concentration versus time curve (AUC)) occurred in approximately 13% of the profiles across palbociclib treatments when a free base formulation was used under fasted conditions.

Food

Study A5481021 was a crossover study of the effect of food on the pharmacokinetics of palbociclib in healthy volunteers taking the Phase III capsule formulation. The food effect study demonstrated that administration of the commercial capsule with or in-between meals (moderate fat meal 1 h before and 2 h after dosing) eliminated the occurrence of 'low-liers' without affecting the palbociclib exposure of subjects who were not low-liers. Based on these findings, it is recommended that palbociclib free base formulations should be taken with food.

Quality summary and conclusions

Registration is recommended with respect to chemistry, quality control and biopharmaceutic aspects.

III. Nonclinical findings

Introduction

The main body of this evaluation report was largely based on the FDA assessment report which is available from the public domain. Wherever possible, efforts were made to verify the accuracy of statements made therein.

The proposed dosing regimen involves oral administration of one capsule (125 mg) once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Treatment is to continue as long as the patient is deriving clinical benefit from therapy.

The submitted nonclinical data was in accordance with the relevant International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline for the nonclinical assessment of anticancer pharmaceuticals.³ The overall quality of the dossier was reasonable with all pivotal safety studies conducted under GLP conditions.

³ ICH Topic S 9 Nonclinical Evaluation for Anticancer Pharm

Pharmacology

Primary pharmacology

Rationale and mechanism of action

Cyclins and cyclin-dependent protein kinases (CDKs) are important components required for passage through the cell division cycle. CDK4 and CDK6 are key regulators of the G1-S transition in the cell cycle. Compared with other CDK enzymes, CDK4 and CDK6 have a narrow substrate range, catalysing the phosphorylation of retinoblastoma (Rb) and two other Rb-like family proteins. Treatment with palbociclib is expected to inhibit the proliferation of rapidly dividing cells containing Rb, such as those in tumours. In hormone-receptor (HR)-positive breast cancer cells, 17- β -oestradiol binds to the nuclear ER- α , resulting in the expression of several genes, including the gene encoding cyclin D1, thereby resulting in CDK4/6 activation.⁴ Therefore, the combination of palbociclib and an anti-oestrogen may have greater anti-tumour efficacy in patients with HR-positive breast cancer than either agent alone.

In vitro

Palbociclib inhibited CDK4/cyclinD1/3 and CDK6/cyclinD2 kinase activities with nanomolar potency (50% inhibitory concentration (IC₅₀) 9–15 nM; 0.22 times the clinical free C_{max}⁵). The selectivity for palbociclib on CDK4/6/cyclin activity was at least 28 times higher than on other CDK/cyclin activities (CDK1/cyclinB, CDK2/cyclinA, CDK2/cyclinE, CDK3/cyclinE, CDK5/p25, CDK7/cyclinH/MAT1, CDK9/cyclinT, CDC7/ASK). Inhibition of other CDK/cyclin complexes is not expected to occur with the proposed clinical use of palbociclib. Palbociclib treatment resulted in a reduction of retinoblastoma (Rb) phosphorylation at Ser780 and Ser795 in human breast cancer cells and inhibited the cell proliferation of these Rb positive cells (IC₅₀ 32–66 nM; approximately equivalent to the clinical free C_{max}), with an increase in the percentage of cells in the G1 phase of the cell cycle (at ≥ 4 nM). Palbociclib had no significant antiproliferative activity on Rb-negative tumour cells, confirming the antiproliferative activity of palbociclib is through its action on CDK4 and CDK6 kinase activities.

When compared with palbociclib alone, the combination of palbociclib with an anti-oestrogen (fulvestrant or letrozole) had an additive antiproliferative effect, with additional inhibition of DNA synthesis and an increase in senescence in ER-positive breast cancer cell lines. Combination treatment of palbociclib with an anti-oestrogen (fulvestrant or tamoxifen) yielded more significant and sustained inhibition of Rb phosphorylation than either agent alone. There was also a decrease in E2F transcription factor levels. The effects of the combination treatment (palbociclib and an anti-oestrogen) on Rb phosphorylation status and deoxyribonucleic acid (DNA) synthesis displayed a durable response following removal of the drug treatment as compared to single agent treatment only.

A number of palbociclib metabolites also had nanomolar inhibitory activity on CDK4 and CDK6. However, given the low levels of these circulating metabolites ($\leq 20\%$ of palbociclib levels), they are unlikely to contribute to the efficacy of the drug. The pharmacological activity of the main circulating metabolite in human plasma was not evaluated.

⁴ O'Sullivan, C.C. (2016). CDK4/6 inhibitors for the treatment of advanced hormone receptor positive breast cancer and beyond: 2016 update. *Expert Opinion on Pharmacotherapy* 17: 1657–1667.

⁵ Based on a C_{max} of 416 nM and a free fraction of 15%.

In vivo

Palbociclib (when provided alone) had anti-tumour activity against multiple human Rb-positive tumour xenograft models in SCID mice⁶. Doses ≥ 77 mg/kg PO (steady state C_{max} approximately 1 $\mu\text{g/mL}$ [free fraction approximately 160 ng/mL] compared to clinical free fraction C_{max} 62 ng/mL) significantly delayed tumour growth in mice bearing Rb-positive breast cancer xenografts, though tumour size rarely decreased to levels below the original tumour size. The anti-tumour activity correlated with the percentage reduction in Rb phosphorylation.

In an oestrogen dependent patient derived xenograft breast cancer model (HBCx-34), the combination of palbociclib (≥ 75 mg/kg; 225 mg/m²) with letrozole (2 mg/kg; 6 mg/m² compared to a clinical dose of 1.65 mg/m²) had greater anti-tumour activity than either agent alone. There was also a greater inhibition of Rb phosphorylation, downstream effects on signalling were more significant and the extent of senescence was increased. A trend to tumour volume reduction was observed when both agents were applied.

Overall, the submitted pharmacology studies support the proposed use of palbociclib with fulvestrant or letrozole to treat patients with Rb-positive, ER-positive breast cancers. Based on plasma levels of the active agent, the proposed dose is supported.

Secondary pharmacodynamics and safety pharmacology

Palbociclib was assessed for inhibitory activity against over 800 kinases covering the majority of the human kinome. The only notable inhibitory activities at potentially clinically relevant concentrations (IC₅₀ values were 3–6 times the clinical free C_{max}) were observed at CLK, CLK2 and MPSK1/STK16. There was no obvious evidence of inhibition of these kinases in the submitted toxicity studies⁷ at exposures exceeding the clinical exposure. Therefore, inhibition of these off-target sites is unlikely to occur during clinical use.

Palbociclib and its lactam metabolite were assessed for secondary activity against an acceptable panel of receptors, ion channels, transporters and enzymes. The only notable affinity was for the rat neuronal nicotinic receptor (binding affinity constant (K_i) 290 nM palbociclib; approximately 4 times the clinical free C_{max}). However, given the low penetration of the blood-brain barrier (see below), significant activity at this receptor is not expected to occur in patients. No clinically-relevant inhibitory activity at off-target sites was observed with the lactam metabolite.

Dedicated safety pharmacology studies examined effects on neurofunction in male rats, pulmonary function in dogs and effects on the cardiovascular system (in vitro and in vivo in dogs). Aside from a slight decrease in activity at ≥ 30 mg/kg PO (at plasma concentrations ≥ 1.15 $\mu\text{g/mL}$; approximately 6 times the clinical C_{max}), there were no other effects on neurofunction in rats. A No observable effect level (NOEL) was not established for hypoactivity, therefore, it cannot be dismissed that lethargy may be seen in patients.

Respiratory depression (increases in minute volume and respiratory rate and decreases in compliance, peak expiratory flow and tidal volume) were seen in dogs given an IV infusion of 5 mg/kg palbociclib. The respiratory effects were transient, subsiding when plasma

⁶Mice homozygous for the severe combined immune deficiency spontaneous mutation Prkdcscid, commonly referred to as scid. These mice are characterised by an absence of functional T cells and B cells, lymphopenia, hypogammaglobulinemia, and a normal hematopoietic microenvironment.

⁷Based on data contained in:

In *et al.* (2014) Serine/threonine kinase 16 and MAL2 regulate constitutive secretion of soluble cargo in hepatic cells. *Biochem. J.* **463**: 201-213.

Tabata *et al.* (2014) Cdc2-like kinase 2 suppresses hepatic fatty acid oxidation and ketogenesis through disruption of the PGC-1 α and MED1 complex. *Diabetes* **63**: 1519-1532.

Vitaterna *et al.* (1994) Mutagenesis and mapping of a mouse gene, Clock, essential for circadian behavior. *Science* **264**: 719-725.

concentrations were reduced to <2 µg/mL (29 times the clinical free C_{max} ⁸). These respiratory effects are unlikely to be seen in patients.

An increase (by 8%) in action potential duration at 90% repolarisation was observed in dog Purkinje fibres with 10 µM palbociclib in vitro. No effect was observed at ≤ 1 µM (16 times the clinical free C_{max}). In vitro, there was a concentration-dependent inhibition of hERG⁹ potassium (K⁺) tail current with an IC₅₀ value of 3.2 µM (51 times the clinical free C_{max}). In a definitive, dedicated study assessing effects on the cardiovascular system in dogs, a dose-related prolongation of the QTc interval¹⁰ (by 5-10 ms) was observed at ≥ 3 mg/kg PO (associated with a free C_{max} approximately 2 times the clinical free C_{max}) with a small decrease in heart rate (by 6-8 beats per minute (bpm)) and slight increases in RR-interval and systolic blood pressure (by 3-6 mmHg) at higher doses (≥ 10 mg/kg PO; associated with a plasma concentration approximately 4 times the clinical C_{max}). While the margins from in vitro studies suggest prolongation of the QTc interval is unlikely during clinical use, the findings in dogs at clinically-relevant plasma concentrations (QTc prolongation, decreased heart rate, increased blood pressure and increased RR-interval) suggests an effect in patients cannot be completely dismissed.

Pharmacokinetics

The rate of absorption by the oral route was moderate in rats, dogs, Cynomolgus monkeys and human subjects (T_{max} 2.7–12 h). Oral bioavailability was low to moderate (23–53%). The mean terminal half-life was moderate-long in animals (ranging from 2.4–10.8 h) but even longer in humans subjects (half-life (t_{1/2}) of approximately 24 h). Consistent with this, there was no consistent evidence of accumulation with repeated dosing to either rats or dogs, but median accumulation ratios of 1.9–2.4 (based on AUC) were observed in clinical studies. Higher exposures (AUC; 1.4–22 times higher) were consistently seen in male rats as compared to female rats at equivalent doses. This might be attributable to greater metabolism of palbociclib, specifically to the sulfamic acid conjugate in female rats since significantly more sulfamic acid metabolite was excreted in bile and faeces in females than in males. No sex differences were evident in dogs.

Protein binding by palbociclib was moderate in the plasma of mice, rats and humans (84%, 88% and 85% bound fraction, respectively) with lower binding seen in the plasma of dogs (59% bound fraction). The extent of protein binding in human plasma was only partially attributable to human serum albumin and α₁-acid glycoprotein, suggesting other components are responsible for some of the binding. As there are significant differences in the extent of protein binding in the plasma of dogs and humans, exposure ratios were calculated using the free fraction, rather than total plasma, for studies conducted in dogs. Palbociclib preferentially distributes to red blood cells, relative to plasma. Following IV dosing to animal species (rats, dogs and Cynomolgus monkeys) and following oral dosing to human subjects, the volume of distribution was larger than total body water (5.1–7.0 L/kg and 52 L/kg, respectively), suggesting extensive tissue distribution. Consistent with this, tissue distribution of radioactivity was wide and extensive in Long Evans rats following oral administration of radiolabelled palbociclib. Exposures in most tissues were higher than

⁸ For comparison of plasma concentrations between humans and dogs, free fractions were used due to the significant difference in protein binding in the two species (41% free fraction in dogs, 15% free fraction in humans).

⁹ hERG is a gene that codes for a protein known as K_v11.1, the alpha subunit of a potassium ion channel. This ion channel is best known for its contribution to the electrical activity of the heart that coordinates the heart's beating.

¹⁰ QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarisation and repolarisation of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like Torsades de pointes and a risk factor for sudden death.

those in blood. Excluding tissues involved in excretion, high exposures (AUC) were seen in the adrenal gland, Harderian gland, lacrimal glands, lungs, lymph nodes, meninges, pituitary, preputial gland, prostate, salivary glands, skin, spleen, uvea and thyroid. Clearance from some tissues (Harderian gland, lacrimal glands, meninges, preputial gland and uvea) was noticeably slower (as characterised by the long half-lives in these tissues). There was minimal penetration of the blood-brain barrier. The slow clearance from the uvea was suggestive of an affinity for melanin, but palbociclib was not phototoxic in an in vitro assay (see *Phototoxicity* below).

The metabolism of palbociclib involved glucuronidation, sulfonation, acetylation, formylation, oxidation and reduction. SULT2A1 was the main enzyme involved in the sulfonation of palbociclib, while cytochrome P450 (CYP) isozyme CYP3A was the main enzyme involved in the oxidative metabolism of palbociclib. Unchanged palbociclib was the dominant circulating drug-related species in rats, dogs and humans. The glucuronide was detected in in vitro incubations of palbociclib with hepatocytes from rats and was found in trace amounts in this species in vivo, suggesting rats are capable of forming this metabolite. The glucuronide was the predominant metabolite in human plasma, comprising approximately 15% of drug-related material in plasma. Given the chemical nature of this metabolite, it is not expected to raise a safety concern and no additional safety examinations are required.¹¹

Excretion of palbociclib and/or its metabolites was predominantly via the faeces in rats, dogs and humans. There was significant excretion of radioactivity into bile in bile duct cannulated rats (50% of the dose in males and 81% of the dose in females).

Overall, the pharmacokinetic profile of palbociclib was adequately similar in rats, dogs and humans, thus supporting the choice of animal species for toxicity studies.

Pharmacokinetic drug interactions¹²

CYP3A is involved in the oxidative metabolism of palbociclib. Therefore, inducers/inhibitors of CYP3A may alter palbociclib exposures. Clinical data suggest that this is the case for strong CYP3A inducers/inhibitors.

In vitro, palbociclib was a weak substrate for P glycoprotein and a moderate substrate for breast cancer resistance protein (BCRP), but was not a substrate for organic anion transporter proteins (OATP) OATP1B1 or OATP1B3. Inhibitors of P glycoprotein are unlikely to significantly affect palbociclib exposures. Based on the nonclinical data submitted, it is possible that BCRP inhibitors may alter palbociclib exposures but the effect is expected to be minimal.

Palbociclib did not induce CYP1A2, 2B6, 2C8 or 3A4 activities in human hepatocytes in vitro.

No clinically-relevant reversible or time-dependent inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19 and 2D6 was observed with palbociclib in in vitro studies. Palbociclib was not a

¹¹ Guidance for Industry: Safety testing of drug metabolites. US Department of Health and Human Services, FDA, CDER. Stachulski, AV & X. Meng. (2013) Glucuronides from metabolites to medicines: a survey of the *in vivo* generation, chemical synthesis and properties of glucuronides. *Nat. Prod. Rep.* **30**: 806-848.

¹² The following assumptions were made:

- molecular weight, 447.5; dose, 125 mg; C_{max}, 186 ng/mL (total); free fraction, 15%; intestinal volume, 0.25 L; absorption rate constant, 0.1 min⁻¹; fraction absorbed from gut, 100%; k_{deg} for CYP3A, 0.0005 min⁻¹
- for intestinal CYP (CYP3A) and intestinal transporters (P-glycoprotein and BCRP): if the IC₅₀ is ≤0.1-fold the intestinal concentration, an in vivo interaction is considered possible
- for systemic CYP, renal uptake and efflux transporters, and hepatic efflux transporters (OAT1, OAT3, OCT2, BCRP, BSEP and P-glycoprotein): if the IC₅₀ is ≤50-fold the unbound clinical C_{max}, an in vivo interaction is considered possible
- for hepatic uptake transporters (OCT1, OATP1B1 and OATP1B3): if the IC₅₀ is ≤25-fold the unbound hepatic inlet concentration, an in vivo interaction is considered possible.

notable reversible inhibitor of CYP3A but palbociclib was a time-dependent inhibitor of this enzyme. Based on the KI (10-19 μM) and k_{inact} (0.036-0.087) values, this inhibition is predicted to be clinically-relevant.

Palbociclib was a weak inhibitor of UDP-glucuronosyltransferase (UGT) enzymes (UGT1A1, 1A4, 1A6, 1A9 and 2B7; free fraction $\text{IC}_{50} > 10 \mu\text{M}$) but is not expected to cause clinically relevant inhibition of these enzymes.

In *in vitro* assays, there was no clinically-relevant inhibition of systemic BCRP, systemic P glycoprotein, Bile Salt Export Pump (BSEP), OATP1B1, OATP1B3, OAT1, OAT3 or organic cation transporter 2 (OCT2). The concentrations of palbociclib tested were too low to rule out the possibility of inhibitory activity on intestinal BCRP and intestinal P glycoprotein. Therefore, no comment can be made on the likelihood of palbociclib inhibiting these intestinal transporters. Palbociclib was an inhibitor of OCT1 and, based on the low IC_{50} value (0.72 μM); this activity is expected to be clinically relevant.

There were no nonclinical data on the potential pharmacokinetic interactions between palbociclib and letrozole or fulvestrant. The draft PI document states that no meaningful pharmacokinetic drug interactions were observed when letrozole was coadministered with palbociclib or when fulvestrant was coadministered with palbociclib in clinical studies.

Toxicology

Acute toxicity

A single-dose toxicity study was conducted in rats, and an exploratory, escalating dose study was conducted in dogs. The gastrointestinal and haematolymphopoietic systems were target organs for toxicity. The maximum non-lethal dose by the oral route was 500 mg/kg in male rats and 2000 mg/kg in female rats (approximately 50 times the clinical C_{max} and AUC at 125 mg/day based on Day 1 toxicokinetic data in the 2 week repeat dose toxicity study at 300 and 600 mg/kg/day) and, based on data from repeat-dose toxicity studies, 3 mg/kg in dogs (approximately 2 times the clinical free fraction C_{max} and AUC), indicating a low order of toxicity in rats but a high order of toxicity in dogs.

Repeat-dose toxicity

Repeat-dose toxicity studies by the oral route (also the clinical route) were conducted in rats (up to 27 weeks) and dogs (up to 39 weeks). All pivotal studies were Good Laboratory Practice (GLP) compliant. The duration of the pivotal studies, group sizes and the use of both sexes were consistent with ICH guidelines.¹³ Dosing was daily in the shorter term studies (2–3-week studies) while the clinical dosing regimen was used in the longer term studies (15, 27 and 39 week studies).

Relative exposure

Free fractions were compared between dog and human exposures due to significant differences in plasma protein binding between these two species. Exposure ratios in male and female rats were calculated separately due to significant differences in exposure between the two sexes at equivalent doses. At the highest tested doses, exposures achieved in male rats were high with moderate exposures achieved in female rats (Table 2). At the

¹³ICH M3(R2): Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals; Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1); TGA Amendment: Note for Guidance on duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing); ICH S9: Nonclinical evaluation for anticancer pharmaceuticals

highest tested doses, exposures achieved in dogs were marginally above the clinical exposure (Table 2).

Table 2: Relative exposure in repeat-dose toxicity studies

Species							
				Total	Free		
Rat (SD)	3 weeks ^a [Study RR-745-03731]	50	♂	17300	–	6	
		100	♂	45300	–	16	
			♀	2530	–	0.9	
		200	♂	46600	–	16	
			♀	5930	–	2.1	
		400	♀	11100	–	4	
	15 weeks ^b [Study 20026125]	10	♂	3770	–	1.3	
		30	♂	18300	–	6	
		50	♀	1710	–	0.6	
		100	♂	41600	–	15	
			♀	2820	–	1.0	
		200	♀	7050	–	2.5	
	27 weeks ^b [Study 8282224]	10	♂	6000	–	2	
		30	♂	21300	–	8	
		50	♀	2650	–	0.9	
		100	♂	29300	–	10	
			♀	4450	–	1.6	
		300	♀	12800	–	5	
Dog (Beagle)	3 weeks ^a [Study RR 745-03781 Dog]	0.2		205.5	84.3	0.2	
		0.6		581	238	0.6	
		2		3260	1337	3.1	
	15 weeks ^b [Study 20026126]	0.2		141	57.8	0.1	
		0.6		532	218	0.5	
		2		1655	679	1.6	
	39 weeks ^b [Study 8282225]	0.2		90	36.9	0.1	
		0.6		271	111	0.3	
		3		2315	949	2.2	
	Human	[Studies 1001, 1003, 1010]	[125 mg]		2838	426	–

= animal:human plasma AUC_{0-24h}; ^adaily dosing; ^bCycles of 3 weeks daily dosing + 1 week off; 41% free fraction in dogs and 15% free fraction in humans

Major toxicities

The target organs for toxicity in both species were the bone marrow and haematolymphopoietic system, the male reproductive organs and to a lesser extent, the gastrointestinal tract. Additional organs for toxicity in rats included lungs, adrenal, bone, kidney and pancreas (with secondary effects on the eye, kidney and teeth).

Male reproductive organs

Lower testicular and/or epididymal weights were seen in male rats treated with 100 mg/kg/day PO palbociclib for 27 weeks and male dogs treated with 3 mg/kg/day PO palbociclib for 39 weeks, with microscopic evidence of testicular degeneration and hypospermia at ≥ 30 mg/kg/day PO in rats (NOEL 10 mg/kg/day PO; Exposure ratio for

AUC (ER_{AUC} approximately 2) and ≥ 0.2 mg/kg/day PO in dogs (ER_{AUC} 0.1; NOEL not established). Intraductal cellular debris in the epididymis was also evident in rats at ≥ 30 mg/kg/day and dogs at 2 mg/kg/day (15 week study). Effects on male reproductive organs were reversible or showed a trend to reversion after a 12 week treatment-free period in both rats and dogs. Reversibility was not evident in either species after a 4 week treatment-free period, likely as a full spermatogenesis cycle had not been completed within that time period. The effects of palbociclib on the male reproductive organs can be attributed to the pharmacological action of the drug. Male cell division protein kinase 4 (CDK4) knockout mice were infertile with defective spermatogenesis and reduced size and weight of the testes.¹⁴ While there were no obvious drug-related effects on functional fertility when treated male rats were mated with untreated females, the reduction in sperm motility and sperm density following palbociclib treatment, and the reported findings of male infertility in CDK4 knockout mice suggest that male fertility is likely to be affected with palbociclib treatment (see *Reproductive toxicity* below). However, this is not relevant for the currently proposed patient group.

Bone marrow and haematolymphopoietic system

Bone marrow hypocellularity (affecting all cell lines, including myeloid, erythroid and megakaryocytic cell lines) was observed in rats (males at ≥ 30 mg/kg/day in the 27 week study and females in the shorter term studies; exposure ratio based on AUC [ER_{AUC}] at the NOEL, 2) and dogs (females at 3 mg/kg/day in the 39-week study, also seen in males in the shorter term studies; ER_{AUC} at the NOEL, 0.2). An in vitro mechanistic study confirmed that palbociclib inhibited the proliferation of human bone marrow mononuclear cells (not lineage-specific) but did not cause senescence, confirming a direct effect of palbociclib on haematopoietic bone marrow cells. Lymphoid depletion was seen in the thymus, spleen, lymph nodes and gut associated lymphoid tissue in male rats at ≥ 30 mg/kg/day and female rats at 300 mg/kg/day in the 27 week study (ER_{AUC} at the NOEL 2) and dogs at ≥ 0.6 mg/kg/day (39-week study; ER_{AUC} at the NOEL 0.1). Reduced erythrocyte numbers were seen in the spleen of male rats at 100 mg/kg/day (ER_{AUC} at the NOEL 8) (also seen in females in the short term studies). Consequential of the bone marrow and lymphoid tissue effects, pancytopenia (reduced red blood cells, leukocytes and platelets) was seen in both species (≥ 10 mg/kg/day in male rats, ≥ 50 mg/kg/day in female rats and ≥ 0.2 mg/kg/day in dogs; NOEL not established). All effects were reversible.

Most, if not all, of these findings can be attributed to the pharmacological action of palbociclib. CDK4 knockout mice had hypoplastic thymuses with decreased total thymocyte cell numbers¹⁵. CDK6 knockout mice also had lower thymic weights with decreased cellularity. Splenic weights with decreased cell density and pancytopenia were also observed in CDK6 knockout mice.¹⁶ While no bone marrow abnormalities were observed in either CDK4 or CDK6 knockout mice, it may be that CDK6 can compensate for a lack of CDK4 in this tissue, and vice versa. No conclusive information can be gained from CDK4/CDK6 knockout mice, as the double knockout animals die during the late stages of embryonic development due to severe anaemia¹⁷, though this finding may suggest a requirement for both CDK4 and CDK6 in bone marrow haematopoiesis.

Given the low exposures at which effects on the bone marrow and lymphoid tissues occurred, myelosuppression, immunosuppression and pancytopenia may be seen in human subjects receiving palbociclib.

¹⁴ Rane et al. (1999) Loss of CDK4 expression causes insulin-deficient diabetes and CDK4 activation results in β -islet cell hyperplasia. *Nature Genetics* 22: 44-52.

¹⁵ Chow et al. (2010) Role of CDK4 in lymphocyte function and allergen response. *Cell Cycle* 9: 4922-4930.

¹⁶ Malumbres et al. (2004) Mammalian cells cycle without the D-type cyclin-dependent kinases CDK4 and CDK6. *Cell* 118: 493-504.

¹⁷ Rane et al. (1999) Loss of Cdk4 expression causes insulin-deficient diabetes and Cdk4 activation results in β -islet cell hyperplasia. *Nature Genet.* 22 44-52

Pancreas and related effects

Pancreatic islet cell vacuolation was seen in male rats treated with ≥ 30 mg/kg/day PO palbociclib for 27 weeks (ER_{AUC} at the NOEL 2 in males and 5 in females). There was a clear decrease in the absolute and relative numbers of beta cells. Hyperglycaemia, with reduced levels of serum insulin and C peptide were seen in male rats treated with ≥ 30 mg/kg/day palbociclib and female rats treated with ≥ 100 mg/kg/day palbociclib for 27 weeks (ER_{AUC} at the NOEL, approximately equivalent to the clinical AUC). CDK4 knockout mice develop an insulin deficient diabetic phenotype¹⁸, similar to that described above, suggesting the effects are pharmacologically mediated. While pancreatic cell vacuolation was not evident in animals after a 12 week treatment-free period (suggesting reversibility), some previously-treated males (at 100 mg/kg/day) still had glucosuria and lower insulin levels and hyperglycaemia was still present in males at ≥ 30 mg/kg/day after a 12 week treatment free period, suggesting the effects on pancreatic islet cell function had not reversed in the treatment-free period. In the submitted toxicity studies, this diabetic state correlated with lens degeneration, pancreatic islet cell vacuolation (including a reduction in the relative percentage and total number of beta cells), ameloblast degeneration and/or renal tubuloepithelial cell vacuolation.

Likely as a consequence of the diabetic state, glucosuria was noted in male rats given ≥ 30 mg/kg/day palbociclib. Renal tubular vacuolation was observed at these doses in rats, with this change likely associated with the increase in glucose excretion. Glucosuria and renal tubular vacuolation were still present after a 12 week treatment-free period, suggesting a lack of reversibility.

Lens degeneration was seen in male rats at ≥ 10 mg/kg/day palbociclib and female rats at ≥ 50 mg/kg/day with irreversible cataracts seen in males at ≥ 30 mg/kg/day. Lens opacification and cataracts have been shown to occur in rats with sustained hyperglycaemia.¹⁹ With lens degeneration and cataracts observed in some animals after a 12-week treatment-free period, the ocular effects appeared to be non-reversible.

Discoloured incisors and ameloblast degeneration/necrosis were seen in male rats treated with 100 mg/kg/day PO palbociclib for 27 weeks. These effects are likely secondary to a hyperglycaemic state.²⁰

Adrenal gland

Hypertrophy of cortical cells, generally within the zona fasciculata, was observed in male rats treated with ≥ 10 mg/kg/day PO palbociclib for 27 weeks (ER_{AUC} 2; NOEL not established). Similar findings were not seen in female rats (ER_{AUC} at the NOEL 5) or dogs (ER_{AUC} at the NOEL approximately 2). Adrenal changes were not evident after a 12 week treatment-free period. The underlying cause for the adrenal effects is unknown but is not considered to be related to stress. Inactivation of CDK4 appears to induce endocrine changes^{19,21} which may lead to effects on the adrenal gland. Such a scenario may explain the sex-specific findings in rats. However, this is just speculation at this stage. Given the low margins at which adrenal changes were observed, adrenal effects may be seen in (male) patients who receive palbociclib. The adrenal hypertrophy was reversible, and when

¹⁸ Rane et al. (1999) Loss of Cdk4 expression causes insulin-deficient diabetes and Cdk4 activation results in β -islet cell hyperplasia. *Nature Genet.* 22 44-52.

¹⁹ Swamy-Mruthinti et al. (1999) Evidence of a glycemic threshold for the development of cataracts in diabetic rats. *Current Eye Res* 18: 423-429.

²⁰ Silva-Sousa et al. (2003) Are there structural alterations in the enamel organ of offspring of rats with alloxan-induced diabetes mellitus? *Braz. Dent. J.* 14: 162-167.

Yeh et al. (2012) Hyperglycemia and xerostomia are key determinants of tooth decay in type 1 diabetic mice. *Lab. Investigat.* 92: 868-882.

²¹ Jirawatnotai et al. (2004) Cdk4 is indispensable for postnatal proliferation of the anterior pituitary. *J. Biol. Chem.* 279: 51100-51106.

considered in isolation and due to an absence of any degenerative lesions in the adrenal glands, is not considered adverse.²² However, the underlying mechanism behind the hypertrophy should be investigated to confirm that this is indeed the case.

Gastrointestinal (GI) effects

Gastric and intestinal erosions were seen in male rats treated with 200 mg/kg/day PO palbociclib for 3 weeks (ER_{AUC} 16) and female rats treated with \geq 200 mg/kg/day PO palbociclib for 3 weeks (ER_{AUC} 2). Stomach (non-glandular) ulcers/erosions and mucosal inflammation (epithelial degeneration, hyperplasia/hyperkeratosis, neutrophilic infiltration) and decreased mucus in gastric glands of the glandular stomach were seen in male rats treated with \geq 30 mg/kg/day PO palbociclib for 27 weeks (ER_{AUC} at the NOEL, 2). No GI tract effects were seen in female rats in this longer term study (ER_{AUC} 5). Emesis and/or faecal changes were seen in dogs treated with \geq 0.2 mg/kg/day PO palbociclib for 3 weeks (ER_{AUC} 0.2) with enlarged nuclei and basophilic cytoplasm seen microscopically in intestinal glands/crypts of dogs treated with 1–10 mg/kg/day PO palbociclib for 2 weeks. Aside from soft stools in the 15 week study, there was no evidence of GI tract disturbances in the longer term dog studies. For both species, GI tract changes appeared more evident and severe in the short-term studies, suggesting some adaptation may have occurred in the longer term studies. The effects appeared reversible. Given the low relative exposures at which effects were seen in female rats and dogs in the short term studies, some GI upset may be experienced in patients, particularly during the early stages of dosing.

Bone effects

A decrease in trabeculae (characterised by thickness of the physis, decreased segmental loss of primary and secondary spongiosa and/or decreased trabeculae within the metaphysis) was seen in the femur of male rats treated with \geq 10 mg/kg/day PO palbociclib for 27 weeks (ER_{AUC} 2; NOEL not established). The effects had not reversed after a 12 week treatment-free period. No palbociclib related bone effects were observed in female rats in this study (ER_{AUC} at the highest tested dose, 5) or in dogs after 39 weeks treatment (ER_{AUC} at the highest tested dose, 2). However, dogs were 14–15 months old at the initiation of treatment and the majority of bone growth was already completed, while rats were 6–7 weeks old at the initiation of dosing, with significant bone growth occurring during the study and lifetime bone remodelling²³, which may account for species differences in the effects. The bone effects may be associated with the pharmacological action of palbociclib²⁴ but are unlikely to be a concern for an adult patient group.

Lungs and phospholipidosis

Alveolar infiltration of vacuolated macrophages was seen in the lungs of male rats treated with 100 mg/kg/day palbociclib (27 week study; ER_{AUC} at the NOEL 8). Vacuolated macrophages were also seen in multiple organs (heart, bone marrow, foot and tongue) and were consistent morphologically with phospholipidosis, possibly associated with the cationic amphiphilic chemical nature of palbociclib. These effects were reversible. No such findings were seen in female rats or dogs but maximum exposures achieved in these animals were lower than that at the NOEL in male rats. It is uncertain if phospholipidosis in animals is predictive for humans and it is also uncertain if it is merely an adaptive response

²² Harvey & Sutcliffe. (2010) Adrenocortical hypertrophy: establishing cause and toxicological significance. *J. Appl. Toxicol.* 30: 617-626.

²³ Zoetis, T. *et al.* (2003) Species comparison of postnatal bone growth and development. *Birth Defects Research (Part B)* 68: 86-110.

²⁴ Altenburg & Farag. (2015) The potential role of PD0332991 (Palbociclib) in the treatment of multiple myeloma. *Expert Opin. Investig. Drugs* 24: 261-271

or has toxicological implications.²⁵ Nonetheless, given the exposure at the NOEL was significantly above the expected clinical exposure, the observed phospholipidosis in male rats is not expected to be clinically-relevant.

Additional kidney changes

An increased incidence and severity of chronic progressive nephropathy (CPN) was seen in male rats treated with ≥ 10 mg/kg/day PO palbociclib for 27 weeks (ER_{AUC} 2; NOEL not established) which did not appear to be reversible. No such findings were seen in female rats, which is consistent with reports that this spontaneous disease is more severe in male rats than female rats.²⁶ While the increase in incidence/severity of CPN may be drug-related, such an effect in rats is not generally considered a predictor of renal toxicity in humans²⁰.

Other effects

Tracheal mucosal atrophy was seen in male and female rats treated with ≥ 50 mg/kg/day and ≥ 100 mg/kg/day, respectively, palbociclib for 3 weeks. This finding was not seen in any other toxicity studies in rats (even at higher exposures), nor was it seen in treated dogs of any study duration. The clinical relevance of this finding is likely low, given that the findings were only observed in one study.

Single cell necrosis of hepatocytes was seen in male rats (generally premature decedents) treated with ≥ 100 mg/kg/day PO palbociclib for 3 weeks (ER_{AUC} at the NOEL, 6). Elevated aspartate aminotransferase (AST) (up to 2 \times), alanine aminotransferase (ALT) (up to 3 \times) and alkaline phosphatase (ALP) (up to 0.6 \times) was seen in male rats treated with 100 mg/kg/day PO palbociclib for 15 or 27 weeks (ER_{AUC} at the NOEL, 8), but in the absence of any degenerative changes in the liver. There was no clear evidence of hepatic damage in treated female rats or in treated dogs, though maximum exposures were below those achieved at the NOEL in male rats, therefore, no conclusions can be drawn from the absence of findings in these animals. Given the safety margin at the NOEL and the mildness of the hepatic effects²⁷, hepatic damage is not expected to be of concern with the proposed clinical use of palbociclib.

Skin/subcutis and/or thymic adipose atrophy were seen in male rats treated with 100 mg/kg/day PO palbociclib for 27 weeks (ER_{AUC} at the NOEL, 8). It is unclear if this is a result of the pharmacological action of the drug or was secondary to the significantly reduced bodyweight gain in these animals. Nonetheless, given the margin at the NOEL, the effects are unlikely to be seen in patients.

Toxicities with the proposed combinations

Shared target organs of toxicity for palbociclib and letrozole include the eyes (corneal opacity and cataracts) and adrenal gland (vacuolation of cortical cells). Shared target organs of toxicity for palbociclib and fulvestrant include the adrenal gland (cortical congestion, haemocysts and atrophy) and the kidney (vacuolation of proximal and cortical tubules). Therefore, effects on the kidney (when used in combination with fulvestrant), eyes (when used in combination with letrozole) and adrenals (when used in combination with either

²⁵ Reasor et al. (2006) Drug-induced phospholipidosis: issues and future directions. *Expert Opin. Drug Saf.* 5: 567-583.

Reasor, M.J. & S. Kacew. (2001) Drug-induced phospholipidosis: are there functional consequences? *Exp. Biol. Med.* 226: 825-830.

Alakoskela et al. (2009) Screening for the drug-phospholipid interaction: correlation to phospholipidosis. *ChemMedChem* 4: 1224-1251.

²⁶ Hard G.C., Johnson K.J. and Cohen S.M. (2009) A comparison of rat chronic progressive nephropathy with human renal disease – implications for human risk assessment. *Crit. Rev. Toxicol.* 39: 332-346.

²⁷ EMEA/CHMP/SWP/150115/2006: *Reflection paper on non-clinical evaluation of drug-induced liver injury (DILI)*.

letrozole or fulvestrant) may be greater with the proposed combinations than monotherapy.

Genotoxicity and carcinogenicity

The potential genotoxicity of palbociclib was assessed in a bacterial mutagenicity assay, an in vitro clastogenicity assay with human peripheral blood lymphocytes and a rat micronucleus test (assessed as part of a repeat-dose toxicity study). The conduct was in accordance with the relevant guideline.²⁸ Negative results were returned in the in vitro assays but a clear increase in micronucleated PCE (mnPCE) was seen in male rats treated with ≥ 100 mg/kg/day PO palbociclib, respectively. Equivocal results were seen in males at 50 mg/kg/day and females at 400 mg/kg/day PO palbociclib (individual animals had %mnPCE values outside of the concurrent control range; mean values were not statistically significantly different from the mean negative control value). An exploratory in vitro study in CHO-WBL cells provided some evidence to indicate that palbociclib induces micronuclei through an aneugenic mechanism. A clear NOEL was not established in males, and the exposure at the NOEL in female rats was approximately 2 times the clinical AUC. Given the role of CDK4 and CDK6 in cell cycle division, it is possible that the observed aneugenic activity with palbociclib is pharmacologically mediated.²⁹

No carcinogenicity studies were conducted, which is considered acceptable given the indication (ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals).

Reproductive toxicity

Reproductive toxicity studies investigated effects on fertility in rats (male and female) and embryofetal development in rats and rabbits. The lack of a postnatal development study is considered acceptable given the indication.³⁰ Dosing in the female fertility study and the embryofetal development studies was once daily, consistent with the daily dosing in the 3 week on/1 week off clinical dosing regimen. Given the longer duration of dosing in the male fertility study, the clinical dosing regimen was used. Adequate animal numbers were used in the pivotal studies. Selected doses were acceptable based on reasonable exposures achieved (male fertility study) or based on findings in dose-ranging or repeat-dose toxicity studies (female fertility and embryofetal development studies). At the highest tested doses, reasonable exposures were achieved in male rats with low to moderate exposures achieved in female rats and rabbits (Table 3).

Table 3: Relative exposure in reproductive toxicity studies

Species				
Rat	Male fertility	10	3770	1.3

²⁸ ICH S2(R1): Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use.

²⁹ Lentini *et al.* (2006) Centrosome amplification induced by hydroxyurea leads to aneuploidy in pRB deficient human and mouse fibroblasts. *Cancer Lett.* **238**: 153-160.

Iovino *et al.* (2006) RB acute loss induces centrosome amplification and aneuploidy in murine primary fibroblasts. *Molecul. Cancer* **5**: 38 doi:10.1186/1476-4598-5-38.

Takayasu *et al.* (2015) p16 gene transfer induces centrosome amplification and abnormal nucleation associated with survivin downregulation in glioma cells. *Pathobiol.* **82**: 1-8.

Krämer *et al.* (2002) Centrosome replication, genomic instability and cancer. *Leukemia* **16**: 767-775.

³⁰ ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals

Species	Study [Study no.]	Dose (mg/kg/day PO)	AUC _{0-24h} (ng·h/mL)	Exposure ratio [#]
(SD)	[Study 20057548] ^a	30	18300	6
		100	41600	15
	Female fertility [Study 20037853]	30	740	0.3
		100	3040	1.1
		300	8010	3
	Embryofetal development [Study 20039574]	30	836	0.3
		100	2960	1
		300	7310	3
	Rabbit (NZW)	Embryofetal development [Study 20039575]	2	924
10			7460	3
20			17200	6
Human	[Studies 1001, 1003, 1010]	[125 mg]	2838	-

[#] = animal:human plasma AUC_{0-24h}; ^ano toxicokinetic data were collected in this study, data from the 15-week repeat-dose toxicity study was used as an estimate

As stated in the Repeat-dose toxicity section, palbociclib treatment had adverse effects on the male reproductive system of animals. Similar effects (hypospermia, reduced sperm motility and density, seminiferous tubular degeneration in the testes) were observed in a dedicated male fertility study in rats at ≥ 30 mg/kg/day. However, there was no effect on functional fertility when male rats treated with ≤ 100 mg/kg/day PO palbociclib (estimated ER_{AUC}, 15) were mated with untreated females. The lack of functional effects on male fertility needs to be interpreted cautiously as sperm production may have to be decreased by 80% to 90% in adult male rats in order to affect fertility with routine mating procedures. In contrast, human males have substantially less epididymal sperm reserves compared to species routinely used for toxicity testing.³¹ Palbociclib is likely to adversely affect male fertility.

There was no effect on female fertility (or early embryonic development) when treated female rats (at ≤ 300 mg/kg/day PO palbociclib; ER_{AUC} 3) were mated with untreated males. Given the low exposure margins at the tested doses, the aneugenic properties of palbociclib and the published reports that inactivation of both CDK4 and CDK6 leads to late embryonic death¹⁸, the absence of an effect should be considered cautiously.

No submitted studies assessed the placental transfer of palbociclib and/or its metabolites. When pregnant rats were treated during the period of organogenesis, reduced fetal weights were observed, but only at a maternotoxic dose (300 mg/kg/day; ER_{AUC} at the NOEL, 1), while an increased incidence of cervical ribs at the 7th vertebra (a skeletal variation) was seen at non-maternotoxic doses (≥ 100 mg/kg/day; ER_{AUC} at the NOEL, 0.3). This variation

³¹ Hayes, A.W. (1994) *Principles and Methods of Toxicology*, Third Edn, Raven Press, New York.

was considered to have a minimal consequence postnatally. Skeletal effects were also seen in rabbit fetuses following maternal exposure (≥ 10 mg/kg/day; ER_{AUC} at the NOEL, 0.3), including an increased incidence of small phalanges (at 20 mg/kg/day; a maternotoxic dose), other skeletal variations in the forelimbs (at ≥ 10 mg/kg/day; a non-maternotoxic dose), and changes in skeletal ossification (an increase in the average number of ossified rib pairs; ≥ 10 mg/kg/day). While only relatively minor effects were seen in the submitted rat and rabbit embryofetal development studies, the tested exposures were low. Based on the pharmacological action of palbociclib (effect on bone growth, haematopoiesis, and inactivation of both CDK4 and 6 results in embryofetal lethality), adverse effects on embryofetal survival and development may be possible if taken during pregnancy.

Excretion of palbociclib and/or its metabolites into milk has not been assessed in animals.

Pregnancy classification

The sponsor has proposed Pregnancy Category D.³² Based on the pharmacology of palbociclib, this Category is considered appropriate.

Immunotoxicity

As palbociclib has myelosuppressive activity, the clinical use of palbociclib may be associated with an increased risk of infection.

Phototoxicity

As palbociclib absorbs light in the 290–700 nm range with a maximum molar extinction coefficient of $16751 \text{ M}^{-1}\text{cm}^{-1}$ at 355 nm, its phototoxic potential was assessed in a standard in vitro assay. Palbociclib was determined to be non-phototoxic in this assay.

Impurities

The proposed specifications for impurities/degradants in the drug substance/product are below the ICH qualification thresholds or have been adequately qualified.

Paediatric use

Palbociclib is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- The submitted nonclinical data were in accordance with the relevant ICH guideline for the nonclinical assessment of anticancer pharmaceuticals.³ The overall quality of the dossier was reasonable with all pivotal safety studies conducted under GLP conditions.
- In vitro, palbociclib inhibited CDK4 and 6 kinase activities at clinically relevant concentrations. Reasonable selectivity over other CDK kinase activities was demonstrated. Palbociclib treatment resulted in a reduction of retinoblastoma (Rb) phosphorylation in human breast cancer cells with inhibition of cell proliferation and cell cycle arrest at G1. The combination of palbociclib with fulvestrant or letrozole had an additive and more sustained antiproliferative effect. In vivo, the combination of

³² Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

palbociclib with letrozole had greater anti-tumour activity than either agent alone in an oestrogen-dependent patient derived xenograft breast cancer model.

- Based on a comprehensive screen against kinases, receptors, ion channels and transporters, as well as findings in toxicity studies, no off-target effects are anticipated with palbociclib.
- Safety pharmacology studies assessed effects on the cardiovascular, respiratory and central nervous systems. Hypoactivity was seen in rats at clinically-relevant exposures. In vitro, palbociclib inhibited hERG K⁺ channel tail current, and QTc prolongation, decreased heart rate and increased blood pressure were seen in dogs at clinically-relevant exposures. Respiratory depression was observed in dogs but only at high exposures. Lethargy and QT prolongation may be seen in patients.
- The rate of oral absorption was moderate in rats, dogs, Cynomolgus monkeys and human subjects, with low to moderate bioavailability. Higher exposures were seen in male rats as compared to female rats at equivalent doses. No sex differences were evident in other species. The extent of protein binding was moderate in the plasma of mice, rats and humans but lower in the plasma of dogs. Tissue distribution of drug-related material was wide and extensive in rats but there was minimal penetration of the blood-brain barrier. Slow clearance from the uvea was suggestive of an affinity for melanin. Palbociclib is mainly metabolised by SULT2A1 and CYP3A. Unchanged palbociclib was the dominant circulating drug related species in rats, dogs and humans. The glucuronide was the predominant metabolite in human plasma but was either not detected or was a trace metabolite in animal samples. This metabolite is not expected to raise a safety concern. Excretion of palbociclib and/or its metabolites was predominantly via the faeces in rats, dogs and humans. Excretion of drug-related material into bile was demonstrated in rats. The pharmacokinetic profile of palbociclib was considered adequately similar in rats, dogs and humans.
- Inducers/inhibitors of CYP3A may alter palbociclib exposures. Palbociclib may alter the exposure of co-administered drugs that are substrates for the CYP3A enzymes or the OCT1 transporter.
- Palbociclib had a low order of acute oral toxicity in rats but a very high order of oral toxicity in dogs.
- Repeat-dose toxicity studies by the oral route were conducted in rats (up to 27 weeks) and dogs (up to 39 weeks). Target organs for toxicity in both species were the bone marrow and haematolymphopoietic system (bone marrow hypocellularity, lymphoid depletion, reductions in splenic red blood cells, pancytopenia), the male reproductive organs (testicular degeneration and hypospermia) and the gastrointestinal tract (gastric and intestinal erosions/ulcers and enlarged nuclei and basophilic cytoplasm in intestinal glands/crypts). Additional organs for toxicity in rats included lungs (phospholipidosis), bone (decrease in trabeculae in femur), adrenal gland (hypertrophy of cortical cells), kidney (increased incidence/severity of chronic progressive nephropathy in males) and pancreas (insulin-deficient diabetic state as a result of effects on beta cells [vacuolation and decreased numbers], with secondary effects on the eye, kidney and teeth). Aside from the diabetic state (and its secondary effects) and the effects on bone and the kidneys, all other toxicity findings were reversible.
- Palbociclib was not mutagenic in the bacterial mutation assay or clastogenic in vitro (in human lymphocytes) but induced micronuclei in the bone marrow of treated rats via an aneugenic mechanism.
- Palbociclib is likely to adversely affect male fertility. There was no effect on female fertility (or early embryonic development) when treated female rats were mated with untreated males. The absence of an effect should be considered cautiously. While only

relatively minor effects (fetal skeletal variations) were seen in the submitted rat and rabbit embryofetal development studies, the tested exposures were low. Based on the pharmacological action of palbociclib (effect on bone growth, haematopoiesis, and inactivation of both CDK4 and 6 results in embryofetal lethality), adverse effects on embryofetal survival and development may be possible if taken during pregnancy.

- Palbociclib was not phototoxic in vitro.

Nonclinical conclusions and recommendation

- The pharmacology studies support the proposed use of palbociclib with fulvestrant or letrozole to treat patients with Rb-positive, ER-positive breast cancers. Based on plasma levels of the active agent, the proposed dose is supported.
- The combined animal safety studies revealed the following findings of potential clinical relevance:
 - Lethargy and QT prolongation
 - Alterations in haematological parameters (pancytopenia)
 - Reduced immunity as a result of lymphoid depletion
 - Diabetes due to effects on pancreatic β -cells
 - Gastrointestinal disturbances
 - Inducers/inhibitors of CYP3A may alter palbociclib exposures
 - Palbociclib may alter the exposure of coadministered drugs that are substrates for the CYP3A enzymes or the OCT1 transporter
- The safety of the combination of palbociclib with letrozole or fulvestrant has not been assessed in submitted nonclinical studies. Provided adequate clinical safety data are available for the combination use, there are no objections on nonclinical grounds to the registration of palbociclib for the proposed indication.
- Amendments to the draft PI were recommended to the Delegate.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The clinical evaluator has considered the sponsor's proposed indication as in the Letter of Application and draft PI (see Product background above).

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 to 24 months.³³ The goal of therapy in any setting is

³³ 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.

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 years³⁴, 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 IV 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+ 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-negative) 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+, HER2-negative advanced breast cancer (that is, locally advanced and metastatic disease). 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; this product gives a novel treatment approach for women diagnosed with metastatic HR-positive breast cancer.

Guidance

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.

³⁴Harvey M, Clark GM, Osborne CK and Allred DC. Estrogen Receptor Status by Immunohistochemistry Is Superior to the Ligand-Binding Assay for Predicting Response to Adjuvant Endocrine Therapy in Breast Cancer. *J Clin Oncol* 17:1474-1481

- 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.
- Howlander 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>.

Contents of the clinical dossier

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.

The following clinical studies were submitted:

- 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 December 2014, and 2 updates of efficacy with data cut-off dates of 16 March, 23 October 2015; 1 safety update (90-day safety update as of cut-off date of 31 July 2015 which updates the data in CSR and SCS)
- Top line summary and Tables from 1 Phase III Study A5481008 (Study 1008) (cut-off 26 February 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 were provided for some of these adverse events.

No Integrated Safety Summary was provided.

Postmarketing data

- The first annual Periodic Safety Update Report 03 February 2015 to 02 February 2016;
- Safety specification of the Risk Management Plan

Product Information

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

Further details of clinical information provided by the sponsor in additional safety data, summary of Clinical Safety (SCS) and Safety narratives/ Council for International Organizations of Medical Sciences (CIOMS) are detailed in Attachment 2.

Paediatric data

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

Good clinical practice

This sponsor has stated that the studies were designed and monitored in accordance with the contract research organisation's (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.

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 ...'³⁵.

Pharmacokinetics

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

³⁵ FDA Medical review, p18, Supplement Number 000 accessed online 28 July 2016

PK topic	Subtopic	Study ID	*
			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 pop ⁿ	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 patients with advanced 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-	Rifampin	A5481017	Effect of multiple doses of rifampin on the PK of a single oral 125 mg dose of

PK topic	Subtopic	Study ID	*
actions			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

Evaluator's overall conclusions on pharmacokinetics

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.

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?

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.

For further details of the evaluator's summary of the PK findings see Attachment 2.

Pharmacodynamics

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.

Table 5: 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-	To describe the effect of palbociclib on absolute

PD Topic	Subtopic	Study ID	*
		286	thrombocyte count
		PMAR-EQDD-A548b-DP4-287	To characterise the effects of palbociclib exposure on the QT interval

Evaluator's overall conclusions on pharmacodynamics

For further details of the evaluator's summary of pharmacodynamics see Attachment 2.

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.

Questions regarding the PD studies

Given that at the mean and median $C_{max,ss}$ 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?

For further details of the evaluator's summary of pharmacodynamics see Attachment 2.

Dosage selection for the pivotal studies

Pharmacokinetics and pharmacodynamics: dose finding studies

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).

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 Maximum Tolerated Dose (MTDs), were determined to be 125 mg once a day (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 anti-tumour activity observed on Schedule 3/1, led to the selection of this treatment schedule for the advanced breast cancer study.

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.

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

Phase III pivotal studies investigating more than one dose regimen

None provided.

Efficacy

Studies providing efficacy data

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, multicentre 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 Statistical Analysis Plan), information on the patient population, primary and 3/11 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.

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 October 2015 and updated progression free survival (PFS) analyses reports for the 16 March 2015 and 23 October 2015 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.

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.

Evaluator's conclusions on 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 medicines 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+ 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.

Safety

Studies providing 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.

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.

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 (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 Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) reported as of 31 July 2015 in Studies 1003, 1034, 1008, 1027' (90-day safety update)
 - 1010 PhIP2 and Phase II, 1013, and IIR studies.
 - Study 1010 Phase I Part 2 (PhIP2) 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 superseded for Study 1023, partly superseded 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 (see Clinical questions Attachment 2).

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 summarized 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.

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.

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.'

Clinical evaluator comments that³⁶:

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.

³⁶ 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:

3. There can be inter-investigator variability in reporting of outcomes, as well as potentially introducing bias where a study is open label (Study 1003) and within blinded studies where distinct toxicity profiles will lead to assumptions about treatment allocation effectively unblinding treatment (palbociclib causes significant neutropenia).

Pivotal studies that assessed safety as the sole primary outcome

No pivotal studies were provided that assessed safety as the sole primary outcome.

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 Attachment 2)

Study 1023 is the pivotal study for the proposed combination of palbociclib and fulvestrant. No other studies examined this combination for the proposed usage.

Patient exposure

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 PhIP2 portion
 - 32 patients in the ongoing Phase II portion of the study);
 - 444 (based on a 2:1 patient randomization ratio for palbociclib versus placebo [666 times 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.

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.

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.

From the main CSR (data cut-off 5 December 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 Case Report Form (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).

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.

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.

Study 1008 – topline 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 or dose reductions were provided for either arm for this pivotal study.

Study 1003 – Phase I/II study as of data cut-off 31 July 2015

Phase I PK/safety

12 postmenopausal women with ER-positive, HER2-negative advanced breast cancer were assigned to palbociclib plus letrozole treatment of who 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.

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%).

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.

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.

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

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 injury³⁷' reported that was not classified as meeting the criteria for an SAE. These cases are discussed in detail in the SAE section in Attachment

³⁷ 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.

2 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.

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.

No information is provided about the case of increased bilirubin for the patient and details of this are requested (Clinical questions Attachment 2).

Combination of palbociclib and letrozole Study 1008

No evaluable data provided as the full CSR is required.

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 patients had elevated liver enzymes (≥ 3 times upper limit of normal (xULN)) for AST and ALT and at a different time, bilirubin ≥ 2 xULN 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 but it is not clear if these are from the aforementioned patient.

A review of the liver function tests does not reveal any consistent pattern or abnormalities to suggest a treatment-related effect.

Renal function and renal toxicity

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 System Organ Class (SOC) Medical Dictionary for Regulatory Activities (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 as the full CSR is required.

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).

Treatment-emergent AEs (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 hospitalised.³⁸

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 (see Clinical questions Attachment 2).

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.

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.

Other clinical chemistry

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.

Combination of palbociclib and letrozole-Study 1008

No data, analyses or discussion provided for evaluation.

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 \leq 2 at baseline to Grade \geq 3 postbaseline 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 \leq 2 at baseline to Grade \geq 3 post baseline in AP were observed for 4/77 patients (5.2%); in

³⁸ 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).

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.

Haematology and haematological toxicity

The events of neutropenia and thrombocytopenia are discussed in detail in the section on *Adverse events of special interest* in Attachment 2.

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 questions Attachment 2). 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.³⁹

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.

The evaluator commented that:

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 Common Terminology Criteria for Adverse Events (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 questions Attachment 2 Safety Question 17).
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 request 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.

³⁹ Clarification: These are laboratory abnormalities not treatment-emergent adverse events.

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.

In a table of TEAEs anaemia listed as occurring in 23.2%, including a Grade 4 frequency of 0.2%, Grade 3, 5.2%.

Another table lists the frequency of TEAEs of anaemia as 24.1%.

No specific data, analyses or discussion in the top-line summary were provided for evaluation and 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.

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.

Table 6: 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 100mg 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 post baseline occurred for 5 patients (83.3%), while shifts in white blood cell counts from Grade ≤ 2 at baseline to Grade ≥ 3 post baseline were observed for 3 patients (50.0%).

Clinical commented that:

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 questions Attachment 2).

Electrocardiograph (ECG) findings and cardiovascular safety

Combination of palbociclib and fulvestrant-Study 1023

ECG abnormalities (QT prolongation) and cardiovascular AEs are 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 as the full CSR is required.

Vital signs and clinical examination findings

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%).

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 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 arm (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.

Immunogenicity and immunological events

This is not considered relevant to this application and there are no data provided which is considered acceptable.

Serious skin reactions

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 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.

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.

On the information provided to date, rash appears to be a common but generally mild adverse event.

Postmarketing data

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.

The evaluator noted that 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.

Eight 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 one subject 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 deep vein thrombosis (DVT). One case each of peripheral motor neuropathy and asthenia were also included. Of these, the febrile neutropenia and pancytopenia were considered treatment-related.

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.

Periodic Safety Update Report 03 February 2015-02 February 2016

Cumulative Subject Exposure in Clinical Trials

Cumulatively, it is estimated that 2,461 subjects have participated in the palbociclib clinical development program as of the data lock point (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).

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.

Events noted

QT prolongation was noted in one patient (QTc 700 ms) 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.

Clinical evaluator commented:

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.' 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.

The clinical evaluator notes that 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.

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.

Use in the Elderly

The Periodic Safety Update Report (PSUR) did not provide information that could be evaluated and no additional changes for the Risk Management Plan (RMP) or PI can be made.

Evaluator's conclusions on safety

No integrated summary was provided.⁴⁰

⁴⁰ Sponsor clarification: The safety summaries for all studies were updated by the 90-day safety update which complements the safety information provided in the SCS for Study A5481003 and updates the data presented for Study A5481023. The safety information for Study A5481008 in the SCS was updated by the top line summary.

The sponsor has been requested to provide a single, up to date comprehensive summary integrating the safety data from all studies rather than 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 includes neutropenia. This occurs in the vast majority of patients and is often of 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.

Leukopenia was common and often prolonged, and the potential clinical impact Progressive multifocal leukoencephalopathy (PML), viral reactivation, opportunistic infection and risks with live vaccines) is not currently addressed in the dossier (see Clinical questions Attachment 2). 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 that 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 also been one case reported of ischaemic colitis in patients receiving palbociclib.

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 $\geq 5\%$ 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 questions Attachment 2)⁴¹One 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 questions Attachment 2).

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 questions Attachment 2).

First Round Benefit-Risk Assessment

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 (BICR) 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. 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.

⁴¹ 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.

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+ metastatic breast cancer (Clinical questions Attachment 2). Similarly, the number of patients with locoregional or locally advanced inoperable disease requires clarification (Clinical questions Attachment 2).

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 5 of 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 BICR 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 (Clinical Benefit Response (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.

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, DVT and one case 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 questions Attachment 2).

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 injury⁴², cataract formation, ischaemic colitis as well as suicidal ideation and behaviours.

⁴² 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

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 questions Attachment 2).

First round assessment of benefit-risk balance

The magnitude of the benefit on PFS is established and significant statistically and clinically relevant for the proposed usage in women with ER+ 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 top-line 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.

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 and 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.

Second Round Evaluation of clinical data submitted in response to questions

For details of the sponsor's responses to the Clinical questions and the evaluation of these responses please see Attachment 2.

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 Delegate reviewed additional data from PALOMA-2 and details of this evaluation is included in Attachment 2. The sponsor's responses to questions raised in this evaluation were considered in the Delegate's overview.

Second Round Benefit-Risk Assessment

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+ 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 Hazard Ratio (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.

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 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, in particular 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.

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.

Second round recommendation regarding authorisation

The second round evaluator is not able to make a recommendation regarding authorisation due to process related resource limitations.

V. Pharmacovigilance findings

Risk management plan

- Pfizer Australia Pty Ltd has submitted EU-RMP version 1.1 (19 April 2016; DLP. 15 May 2015) and ASA version 1.1 (19 April 2016) in support of this application. In its Section 31 response, the sponsor submitted EU-RMP version 1.3 (11 September 2016, DLP. 4 March 2016) and ASA version 1.3 (21 December 2016).
- The proposed Summary of Safety Concerns updated with changes agreed to by the sponsor in its response or changes made in EU-RMP version 1.3 (highlighted in yellow and underlined), as well as their associated risk monitoring and mitigation strategies are summarised below in Table 7.

Table 7: Summary of ongoing safety concerns

R=Routine and A=Additional

Summary of safety concerns		Pharmacovigilance		Risk Minimisation [#]	
		R	A	R	A
Important identified risks	<u>Myelosuppression*</u>	✓	-	✓	-
	<u>Neutropenia</u>				
	<u>Anaemia</u>				
	<u>Thrombocytopaenia</u>				
Important potential risks	QT prolongation	✓	✓	✓	-
	Interstitial lung disease/Pneumonitis	✓	-	-	-
	Hyperglycaemia	✓	✓	- [^]	-
	Reproductive and Developmental Toxicity	✓	-	✓	-
	<u>Hepatic failure and drug-induced liver injury** (ASA only)</u>	✓	-	-	-
Missing information	Male patients, <u>including-use in male breast cancer** (underlined wording ASA only)</u>	✓	-	-	-
	Hepatic impairment	✓	✓	✓	-
	Renal impairment	✓	✓	✓	-
	Long-term use	✓	-	-	-

*Added in EU-RMP version 1.3.

**Recommended by the Clinical Evaluator and agreed to by the sponsor in its Section 31 response for inclusion in the ASA only.

[^]ASA (version 1.3) states that text regarding hyperglycaemia observed in animals has been removed from the PI because, based on the extensive experience in humans, there are no evidence that the animal findings have any relevance for humans. The SmPC will be revised to remove this text.

[#] = The sponsor has agreed to implement a dosing reminder calendar.

- Additional pharmacovigilance activities include four ongoing clinical trials to address the safety concerns of hyperglycaemia and QT prolongation, and Missing Information for hepatic and renal impairment. A Post Authorisation Safety Study (PASS) is also being conducted but it is not intended to collect additional information against the safety concerns listed above. Study A5481064 is reported to be a 'retrospective assessment of treatment patterns and outcomes associated with palbociclib in combination with letrozole in postmenopausal women with HR+/HER2-advanced breast cancer'.
- Additional risk minimisation was not originally proposed. However, in response to recommendation made by the RMP evaluator the sponsor has stated it will be providing a Dosing Reminder Calendar to patients to support patients in their safe use of the product.

New and outstanding recommendations at second round

The sponsor has adequately addressed the first round recommendations. One new recommendation has arisen following the sponsor's response:

Recommendation 10: The sponsor should provide the Dosing Reminder Calendar to the TGA when available and clarify how it will be distributed to patients. When finalised, the Dosing Calendar should be attached to the ASA.

Advice to the Delegate

The sponsor has not specifically addressed the following issues raised by Advisory Committee on Safety of Medicines in its response:

- The committee advised that information in the PI on neutropenia could be simplified. The medicine will be prescribed by specialist medical oncologists who are familiar with neutropenia and its management in this context.

The wording in the PI regarding neutropenia is referred to the delegate for their consideration.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

- Implement EU-RMP (version 1.3, dated 11 September 2016, dated lock point 4 March 2016) with Australian Specific Annex (version 1.3, dated 21 December 2016) and any future updates as a condition of registration

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no outstanding issues and registration is recommended with respect to chemistry, quality control and bioavailability aspects.

Nonclinical

There were no nonclinical objections to registration. Of note:

- Palbociclib was relatively selective.
- There was a signal for QT prolongation.
- Tissue distribution of drug-related material was wide in rats but there was little penetration of the blood-brain barrier.
- In vitro, palbociclib was a weak substrate for P-glycoprotein and a moderate substrate for BCRP but was not a substrate for OATP1B1 or OATP1B3. Inhibitors of P-glycoprotein are unlikely to significantly affect palbociclib exposures. Based on the nonclinical data submitted, it is possible BCRP inhibitors may alter palbociclib exposures but the effect is expected to be minimal.
- Palbociclib may alter the exposure of co-administered drugs that are substrates for the CYP3A enzymes or the OCT1 transporter.
- Metformin, oxaliplatin, acyclovir and ganciclovir are some substrates of OCT1.
- Pregnancy Category D was supported by the nonclinical evaluator.

Clinical

Key efficacy / safety data

Key efficacy / safety data are summarised in the table below.

Table 8: Key efficacy and safety studies are summarised below

First-line (palbociclib + letrozole)	Study 1003 'PALOMA-1'	This supportive Phase I/II study compared palbociclib + letrozole versus letrozole alone in post-menopausal women who did not receive previous systemic treatment for their ER+ HER2- advanced breast cancer. There were n=165 in the randomised Phase II of the study.
	Study 1008 'PALOMA-2'	This Phase III, double-blind study compared palbociclib + letrozole versus placebo + letrozole in post-menopausal women who did not receive previous systemic treatment for their ER+ HER2- advanced breast cancer. There were n=666 randomised subjects.
Second-line (palbociclib + fulvestrant)	Study 1023 'PALOMA-3'	This Phase III, double-blind study compared palbociclib + fulvestrant versus placebo + fulvestrant in n=521 pre/post-menopausal women with HR+ HER2- advanced breast cancer, whose disease progressed after endocrine therapy regardless of their menopausal status.

Clinical evaluation reports (CERs)

There are multiple relevant clinical evaluations reports (CERs):

Table 9: Relevant TGA CERs

'Main CER'	Palbociclib (Ibrance)-Pfizer-Submission PM-2016-01317-1-4-Clinical Evaluation Report (CER) This CER includes the initial assessment of efficacy and safety, but not pharmacology. The Round 1 component was earlier labelled 'CER-ES' (ES for efficacy and safety). The main CER also includes second round review of answers to questions about efficacy, safety and pharmacology issues. The first and second rounds had different authors.
'CER-Ph'	Palbociclib (Ibrance)-Pfizer-Submission PM-2016-01317-1-4-Clinical Evaluation Report (CER)-Module 5 Round 1-pharmacology-TGA COPY This CER includes the initial assessment of pharmacology. Second round for this report is in the 'main CER'.
'CER for PALOMA-2'	Palbociclib (Ibrance)-Pfizer-Submission PM-2016-01317-1-4-separate Clinical Evaluation Report (CER) for Study A5481008 (PALOMA-2) This CER specifically examines the full CSR for PALOMA-2, although the 'main CER' has already examined the top-level summary (TLS).
EMA Second JRAR	Second Day 180 Joint Rapporteur's Assessment Report (authored by EMA evaluators; provided on 13 September 2016 by the sponsor to the TGA for consideration).

The TGA had access to reports generated earlier in the EMA evaluation process but the Second JRAR is considered more current (although it is acknowledged that it evaluates specific issues of concern rather than the dossier in its entirety).

The full CSR for PALOMA-2 (Study 1008; pivotal for 1L use) was submitted at the sponsor's response to TGA questions stage, and the CSR was evaluated after the normal evaluation period, but not by the author of the second round component of the main CER. So, recommendations from clinical evaluators (within the main CER and CER-Ph) do not take into account data from the full CSR for PALOMA-2.

Clinical pharmacology

Key PK considerations from the pharmacology evaluator are set out below:

- Scope of the PK data is set out on CER-Ph.
- 11/21 PK studies were in populations of solely or mainly Black subjects; in the 11 studies, almost all subjects were male.
- The formulation proposed for marketing is an immediate-release capsule; dose proportionality of 4 single dose levels has been assessed, but bioequivalence of the 3 dose strengths has not (CER-Ph and main CER).
- Tissue distribution is wide. Penetration through an intact blood-brain barrier is anticipated to be minimal based on the nonclinical evaluation report.
- Metabolism is mediated by CYP3A and sulfonylesterase (SULT) family 2A member 1 enzymes; <7% of palbociclib was excreted unchanged in urine.
 - Some SULTs can be inhibited by common foods (flavonoids in citrus fruits⁴³, wine, tea, chocolate and so on).

⁴³ It is noted that grapefruit juice already has PK interactions with palbociclib via CYP3A.

Question for sponsor

Can the sponsor discuss evidence for a clinical impact on palbociclib use of interactions with SULT inhibitors?

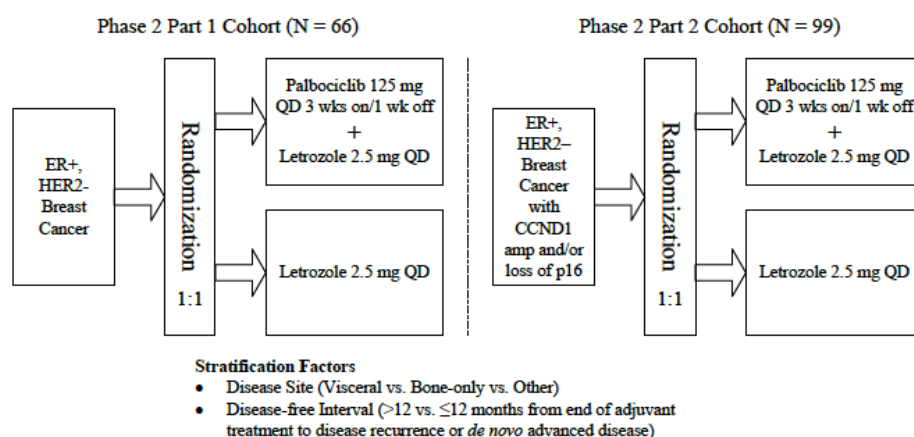
- Consistent with mediation by CYP3A enzymes:
 - concomitant itraconazole results in higher palbociclib exposure (1.87 fold higher AUC; 1.34 fold higher C_{max});
 - concomitant rifampicin results in much decreased exposure (CER-Ph); and
 - concomitant modafinil, a moderate CYP3A inducer, results in marginally lower exposure.
- Concomitant midazolam exposure rose in Study 1012 (C_{max} by 37.5%, AUC_{inf} by 61.1%), suggesting palbociclib inhibits CYP3A4.
- Assessment of PK in patients with impaired hepatic function relied on population PK analysis rather than outcomes of Study 1013 (it is expected the CSR for Study A5481013 will be available by December 2017); in the PopPK analysis, patients with more than mild impairment were not adequately represented.
- Assessment of the impact of race on PK is set out in CER-Ph; Study 1032 suggests approximately 1.3 fold higher exposure in Japanese subjects.
- Study 1003 also assessed possible interactions between palbociclib and letrozole but no significant PK effects were observed (CER-Ph).
- Interactions with gastric acid-suppressing agents were more prominent in the fasted conditions (CER-Ph). With regard to these interactions, it is noted in the proposed PI that:

At or below pH 4, palbociclib behaves like a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly.
- Various PK-PD analyses were presented (CER-Ph). Analysis of the relationship between exposure and PFS in Study 1003 suggested patients with higher exposure had higher median PFS than those with lower exposure (CER-Ph).

Clinical efficacy**Study A5481003 ('PALOMA-1')**

This study compared palbociclib + letrozole versus letrozole alone in post-menopausal women who did not receive previous systemic treatment for their ER+ HER2- advanced breast cancer (inclusion and exclusion criteria from main CER).

⁴⁴ It is noted that fulvestrant is metabolized in part by CYP3A4 based on in vitro studies, although DDIs with typical CYP3A4 inducers / inhibitors are not evident (FASLODEX PI)

Figure 2: Study schema

The evaluator noted major changes to the study protocol and statistical analysis plan (main CER) and described the study as having an 'adaptive course'.

Phase I (n=12) assessed safety / tolerability / interaction with letrozole.

Phase II (n=165) had two parts:

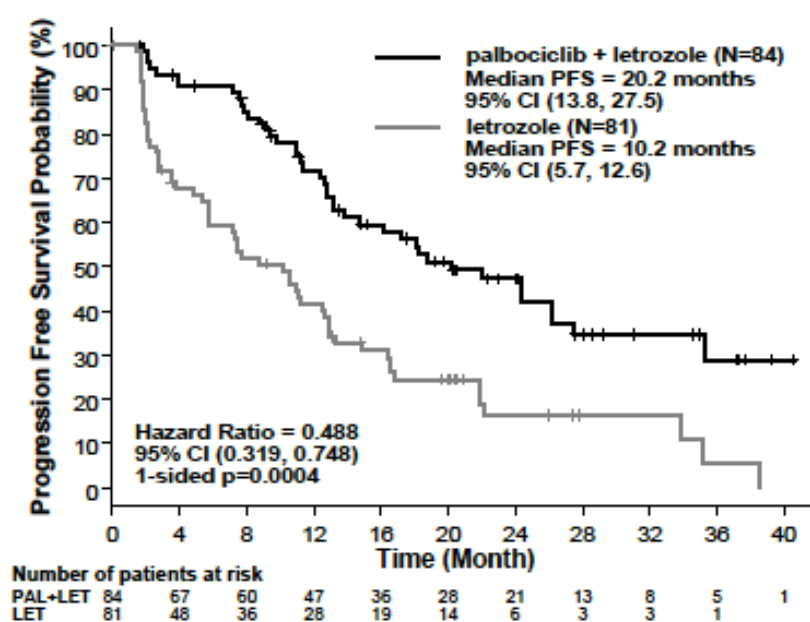
- 'Ph2P1' (n=66): efficacy and safety of palbociclib + letrozole versus letrozole in 1L use; and
- 'Ph2P2' (n=99): the same, but in biomarker-positive patients: their tumours showed CCND1 gene amplification and / or loss of CDKN2A / p16INK4A gene ('loss of p16').

This second part of Phase II was introduced as preclinical findings suggested patients whose tumours were positive for such biomarkers would be sensitive to palbociclib. Interim analysis of Ph2P1 showed the biomarker was not influential (a figure in the CER Attachment 2 shows the number of Ph2P1 patients by biomarker status and later on main CER shows PFS outcomes), so accrual to Ph2P2 was stopped after 99 patients had accrued and the protocol was amended to examine benefit in Ph2 *in toto* (main CER).

The study was open-label; primary analyses relied on investigator assessment (main CER). Randomisation was 1:1 and stratified. The evaluator (main CER) considered that a stratification factor (last disease-free interval) grouped together those least likely to respond (early relapsers) with those most likely to respond (*de novo* advanced). There was also stratification by enrolment in Part 1 versus Part 2 on Phase II of the study. There was no per protocol analysis.

Median age was 62.5-64 yrs across arms; one modest imbalance was in baseline weight (median 70 kg for the palbociclib-containing arm, 65.4 kg for the letrozole arm). Other more significant imbalances are noted and discussed in the main CER. The proportion of patients with *de novo* metastatic disease was far greater here (52% in the palbociclib-containing arm in Phase II; 46% in the control arm) than is generally seen (5-10% of newly diagnosed patients have metastatic disease at diagnosis, although this is distinct from the percentage of patients with advanced disease whose initial diagnosis was advanced disease).

The primary endpoint was PFS. In Phase II patients, PFS (investigator-assessed) was for a median of 20.2 months (palbociclib + letrozole) versus 10.2 months (letrozole); the PFS HR was 0.49 (95% CU 0.32-0.75); see main CER. The Kaplan-Meier plot follows (Figure 3):

Figure 3: Kaplan-Meier plot

By retrospective BICR, the PFS HR was 0.62 (95% CI 0.38-1.02). The discordance between investigator-assessed and BICR-assessed outcomes in the Ph2P1 (biomarker unselected) component was striking (for Ph2P2, less so):

- By investigator assessment, median PFS was 26.1 months (palbociclib + letrozole) versus 5.7 months (letrozole) (Kaplan-Meier (KM) curve in the main CER)
- By BICR assessment, median PFS was 31.6 months (palbociclib + letrozole) versus 38.6 months (letrozole) (KM curve in the main CER)

Overall survival outcomes were immature but the following was reported:

- 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).

Question for sponsor

An updated OS analysis is planned for inclusion in the Pre-ACM Response. Please include a subgroup analysis of OS by Ph2P1 versus Ph2P2.

Other efficacy outcomes are noted in the main CER.

Study 1003 has been described as supportive rather than pivotal. Sources of bias and limitations are noted in the main CER. Further supporting classification of Study 1003 as 'not pivotal' are these considerations:

- The formulation used in the study was the isethionate salt, which is not proposed for registration⁴⁵; and patients fasted for 1 h prior to / 2 h after dosing.
- The overall sample size is not large given the proposed use, and the overall sample is a mixture of different patient groups (Ph1, Ph2P1 and Ph2P2).

Some of these design limitations are more problematic than others:

⁴⁵ See CER-Ph

- One stratification factor grouped together ‘those likely to respond (de novo) with those least likely to respond (early relapse)’ which undermines the value of stratification (which aims to balance at least some baseline factors known to influence outcomes).
- Randomisation did not result in study arms with closely comparable baseline characteristics.
- A large proportion of patients had de novo metastatic disease.
- A protocol amendment resulted in the Phase II component including two patient groups (biomarker-unselected Ph2P1 and biomarker-selected Ph2P2). A subsequent amendment allowed determination of the clinical benefit in these P1 and P2 populations together. This undermines generalisability of outcomes. As noted on main CER and subsequently in discussion of BICR findings, outcomes differed in Ph2P1 and Ph2P2 patients.
- The combination of an open-label design and emphasis on investigator assessment may lead to bias (and large differences in PFS were seen in Ph2P1 depending on whether assessment was by investigator or by BICR).

Study A5481008 (‘PALOMA-2’)

Although top-level outcomes were evaluated in the main CER, the TGA evaluation of PALOMA-2 is considered to incorporate issues raised in the earlier report, so review is based on the CER for PALOMA-2; authored by the Delegate, as design and outcomes are not detailed here. In summary:

- PALOMA-2 was a randomised, double-blind study of palbociclib + letrozole (n=444) versus placebo + letrozole (n=222) in in post-menopausal women who did not received previous systemic treatment for their ER+ HER2- advanced breast cancer.
- Baseline factors were generally balanced across arms (CER for PALOMA-2). Median age was 62 years, higher than median age in PALOMA-3 (second-line use) at 57 yrs, consistent with enrolment only of post-menopausal women. A third of patients had de novo metastatic disease.
- The primary efficacy outcome was investigator-assessed PFS in the Intent-to-Treat (ITT) population. Median PFS was 24.8 months in the palbociclib + letrozole arm, and 14.5 months in the placebo + letrozole arm, with a PFS HR of 0.58 (95% CI 0.46-0.72). Subgroup analysis of investigator-assessed PFS presented a consistent picture.
- PFS based on BICR assessment was broadly consistent; mPFS was 30.5 months versus 19.3 months respectively, and the HR was 0.653. In subgroup analysis based on BICR, those with de novo metastatic disease had a less impressive benefit from palbociclib. This is discussed in the main CER (Efficacy Question 11, with answers in line with those in the EMA Second JRAR, Q8); a suggestion is that bone-only disease (against which addition of palbociclib was effective) was seen less in the de novo metastatic group, bringing outcomes closer across study arms.
- Investigator-assessed confirmed objective responses were reported in 42.1% (palbociclib + letrozole) versus 34.7% (placebo + letrozole). Median duration of response was 22.5 versus 16.8 months respectively. Clinical benefit (CR + PR + SD \geq 24 weeks) was observed in 89.4% versus 77.9%. There was also a large decrease in the proportion with best overall response of disease progression (7.7% versus 16.7%).
- 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.

The sponsor proposes to include an updated OS analysis in the Pre Advisory Committee Meeting (ACM) response (data cut-off 24 November 2016, that is, an additional 9 months follow-up).

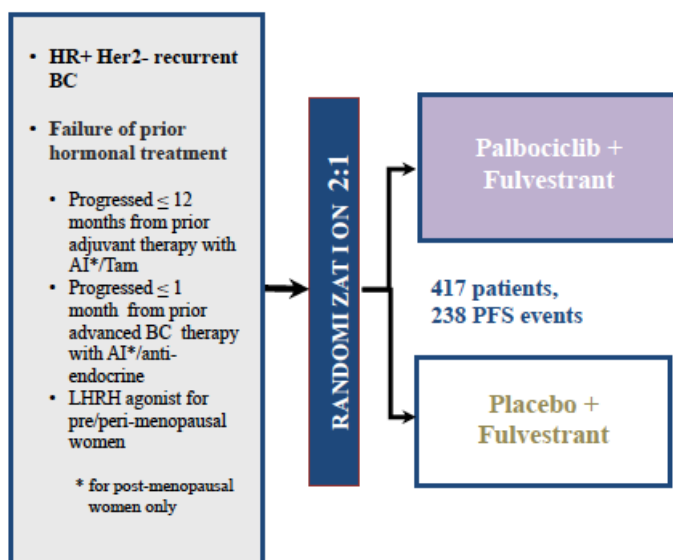
There was no clear indication that quality of life was either improved or harmed by the addition of palbociclib.

Study A5481023 ('PALOMA-3')

This study is evaluated in the main CER 58.

It was a randomised, double-blind study of palbociclib + fulvestrant (n=347) versus placebo + fulvestrant (n=174) following disease progression after prior endocrine therapy in women with HR+ HER2- advanced breast cancer. Fulvestrant (500 mg IM on Days 1 and 15 of cycle 1, every 28 days thereafter) was given with or without goserelin. Various data cut-offs were used (main CER).

Figure 4: Study schema

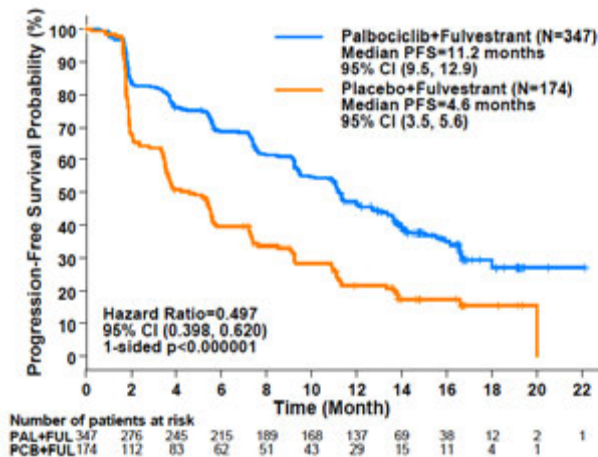


Inclusion and exclusion criteria are listed in the main CER. One previous line of chemotherapy for advanced disease was allowed in addition to prior endocrine therapy (chemotherapy could also have been used in neoadjuvant / adjuvant settings; main CER). There was local testing for HR and HER status).

Study arms were reasonably well balanced at baseline. Median age was 56-57 years across arms. 79.3% of subjects were post-menopausal. Significant minorities in each arm had 1, 2, 3 or >3 prior therapies over the course of breast cancer treatment.

The primary endpoint was PFS as assessed by the investigator. The most recent data cutoff was 23 October 2015⁴⁶; based on this, median PFS was 11.2 months in the palbociclib + fulvestrant arm versus 4.6 months in the placebo + fulvestrant arm; the PFS HR was 0.497 supporting addition of palbociclib.

⁴⁶ The formal final analysis had a cut-off of December 2014; the study was stopped at an interim analysis for efficacy reasons, so this formed the 'final analysis' (although there were two subsequent efficacy cuts, 16 March 2015 and 23 October 2015, to review maturing data). PFS outcomes are mature; OS outcomes are not.

Figure 5: PFS versus Time (month) in the two treatment arms

Subgroup analysis) was broadly supportive of efficacy in all assessed subgroups, though some variations were noted, for example, in subgroups defined by age, by disease-free interval and by prior chemotherapy use.

PFS and ORR outcomes were acceptable in those who required dose reduction.

BICR was undertaken in 40% of patients and did not suggest the investigator-assessed outcomes were inflated in any way.

Regarding OS, it is noted in the main CER:

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.

At the most recent cut-off (23 October 2015), 112 deaths had occurred (21.5% of patients). Based on 'A5481023 Progression Free Survival (PFS) Update Tables, at end of study, 20.2% of palbociclib + fulvestrant subjects versus 23.6% of placebo + fulvestrant subjects had died (70/347 versus 41/174 respectively). A detailed OS analysis is not provided but there is no indication of a deleterious impact on OS in the palbociclib-containing arm:

Table 11: Results for OS in palbociclib treated patients

Number (%) of Subjects	Palbociclib (PD-0332991) + Fulvestrant (N=347) n (%)		Placebo + Fulvestrant (N=174) n (%)	
	Ongoing	261 (75.2)	118 (67.8)	
Treated And Discontinued	84 (24.2)	54 (31.0)		
Randomized Not Treated	2 (0.6)	2 (1.1)		
Reason for Discontinuation [1]				
Lost to Follow-Up	1 (0.3)	3 (1.7)		
Medication Error without Associated Adverse Event	0	0		
No Longer Willing to Participate in Study	9 (2.6)	7 (4.0)		
Study Terminated by Sponsor	0	0		
Subject Died	70 (20.2)	41 (23.6)		
Other	6 (1.7)	5 (2.9)		

A further breakdown of deaths is provided as follows:

Table 12: Deaths in each treatment arm

	Palbociclib (PD-0332991) + Fulvestrant (N=345) n (%)	Placebo + Fulvestrant (N=172) n (%)
Number of Deaths from Start of Treatment to Last Dose Including 28 days after Last Dose	5 (1.4)	3 (1.7)
Cause of Death		
Disease Under Study	4 (1.2)	2 (1.2)
Study Treatment Toxicity	0	0
Other	1 (0.3)	1 (0.6)
Unknown	0	0
Number of Deaths during Follow-up Period Occurring after 28 Days after Last Dose	66 (19.1)	38 (22.1)
Cause of Death		
Disease Under Study	60 (17.4)	36 (20.9)
Study Treatment Toxicity	0	1 (0.6)
Other	4 (1.2)	4 (2.3)
Unknown	4 (1.2)	0

While OS data are immature, the above data are informative in that they do not generate an early signal that addition of palbociclib to fulvestrant will increase mortality (mature OS data are awaited with interest).

Objective responses were seen in 21% of the palbociclib + fulvestrant arm, versus 8.6% of the placebo + fulvestrant arm; median duration of response was similar across arms (10.4 versus 9.0 months). The 4 CRs were in the control arm. The clinical benefit rate (Complete Response (CR), Partial Response (PR) or 'stable disease \geq 24 weeks') was 66.3% versus 39.7%. Progression with no response was seen in 17% versus 33%.

Regarding patient-reported outcomes, the clinical evaluator commented on the policy of 'pro-rating'. The clinical evaluator endorsed one finding, that time to deterioration in pain was lengthened with addition of palbociclib (median time to diagnosis (TTD) 8 months versus 2.8 months; HR 0.642, 95% CI 0.487-0.846).

Clinical safety

Exposure

The most influential information about palbociclib toxicity is from Studies 1008 and 1023 (by virtue of study design, patient population, sample size and duration on treatment). Cumulatively many other studies provided additional information but the focus below is on pivotal Studies 1008 and 1023 (and to a lesser extent, Study 1003).

Exposure (including exposure to accompanying endocrine therapies) is detailed from main CER where it is noted that:

- approximately 835 study subjects have received palbociclib + letrozole, mainly in Studies 1003 and 1008 and the Expanded Access Protocol 1034 (n=238)
- 345 patients have received palbociclib + fulvestrant (\pm goserelin), in Study 1023

Table 13: Duration of exposure to palbociclib in key studies

Study (and data cut-off date)	Palbociclib-containing arm	Control arm
	Median (range) for duration of treatment, in days	
1003 Phase II (2 January 2015)	421 (7-1615)	231 (28-1241)
1008 (26 February 2016)	603 (1-1037)	413 (10-1071)

Study (and data cut-off date)	Palbociclib-containing arm	Control arm
1023 (31 July 2015)	330 (1-596)	137 (14-611)

Patients were treated for considerably longer with palbociclib than with control agents and AEs were not reported in terms of exposure-adjusted incidence rates but in terms of overall frequencies.

Toxicity profile

The focus below is on description of those events reported clearly more often in palbociclib-containing arms of Study 1008 or Study 1023, to offset the longer time on drug in the palbociclib-containing arms. This is more a picture of the additive toxicity of palbociclib than the overall AE profile of specific combination regimens.

Table 14: General indices from Studies 1008 and 1023

	Study 1008		Study 1023 ^b	
	Palbociclib + letrozole (n=444)	Placebo + letrozole (n=222)	Palbociclib + fulvestrant (n=345)	Placebo + fulvestrant (n=172)
Serious AEs	19.6%	12.6%	9.6%	14.0%
Discontinued study ^a	2.5%	1.8%	0.6%	1.2%
Discontinued palbociclib / placebo ^a	9.2%	5.4%	3.8%	4.1%
Discontinued letrozole / fulvestrant ^a	6.1%	5.0%	3.2%	2.9%
Temporarily discontinued palbociclib / placebo ^a	74.8%	15.8%	64.6%	8.1%
Temporarily discontinued letrozole / fulvestrant ^a	17.3%	9.9%	24.1%	3.5%
Palbociclib / placebo dose reduction ^a	36%	1.4%	31%	1.7%
Fulvestrant dose interruption ^a	NA	NA	0.9%	0%
a: due to AEs; b: based on data cutoff 4 April 2015				

Myelosuppression

Neutropenia

Neutropenia (including the laboratory findings of decreased neutrophils) was the most common toxicity across both Study 1023 (approximately 89% of patients) and Study 1008 (approximately 95%). Neutropenia is a generally manageable condition, so only aspects that have a greater clinical impact are tabulated below. In interpreting frequencies of events across studies, varying exposure to palbociclib itself across studies is noteworthy (median 603 days in Study 1008, median 330 days in Study 1023).

Table 15: Results for neutropaenia Studies 1008 and 1023

	Study 1008		Study 1023	
	Palbociclib + letrozole	Placebo + letrozole	Palbociclib + fulvestrant	Placebo + fulvestrant
Grade 4 neutropenia (lab findings)	51/444 (11.5%)	0/222	31/340 (9.1%)	2/171 (1.2%)
Febrile neutropenia	1.8% ⁴⁷	0%	0.9% ^b	0.6%
Temporary discontinuation ^a	64.4%	1.4%	67.8%	0%
Dose reduction ^a	29.5%	0.5%	29.6%	0.6%
Permanent discontinuation ^a	1.6%	0%	0.3%	0%
Use of G-CSF ⁴⁸	12.2%	0%	12.8%	1.2%
Infection	59.7%	42.3%	34.2% ^c	24.4% ^c
Grade 3-5 infection	6.5%	4.5%	1.7% ^d	1.7% ^d
a: due to neutropenia; b: refer to main CER: 47.2% versus 31.4% based on the later cut-off of 31 July 2015 (main CER); d: 3.2% versus 2.9% based on this later cut-off				

According to these data, while neutropenia was very common (and while Grade 4 neutropenia was seen in about 1/10 patients), relatively few patients reported febrile neutropenia or severe infections. The main clinical impacts of this toxicity would appear to be due to the need for monitoring, the very common need for temporary discontinuations or dose reductions, and the need to use G-CSF. These interventions, not insignificant in themselves, appear adequate to prevent a major imbalance in severe infection (given the differences in exposure noted above). It was also noted by the clinical evaluator (main CER):

...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 treatment⁴⁹. This would not necessarily

⁴⁷ Refer to Sponsor's Response to Q24 in the CER for PALOMA-2

⁴⁸ Frequency of use of *immunostimulants* reports (broadly equating with use of G-CSF)

⁴⁹ Refer to main CER: '...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' and to

be anticipated by medical oncologists used to managing chemotherapy-related neutropenia which is typically of a relatively short duration.

Discussion of neutropenia in the EMA Second JRAR (Q28) is noted.

Laboratory abnormalities

Thrombocytopenia

Reduced platelets were measured in 62.7% versus 13.6% (Study 1008) and 57% versus 8.2% (Study 1023), but Grade 4 reductions were seen in only 0.5% (vs 0%) in Study 1008 and 1.2% (versus 0%) in Study 1023.

Grade 3-4 bleeding was reported in <1% in both studies but there were isolated cases of severe bleeding events. For lower grade bleeding, and taking the example of epistaxis, there was a consistent imbalance across arms (Study 1008: 6.3% versus 2.7%; Study 1023: 6.7% versus 1.7%), although not one dramatically disproportionate to the imbalance in drug exposure. Multiple cases of epistaxis were temporally correlated with low platelet counts (for Study 1003, refer main CER).

Platelet counts will be monitored and treatment interrupted to allow recovery but it is plausible that rarely, life-threatening or fatal bleeding events will be due to the thrombocytopenia that palbociclib causes. However, no examples are noted across 'almost 900 patients treated in the 3 pivotal breast cancer studies'.

Anaemia

Reduced haemoglobin was measured in 78% versus 41.7% (Study 1008) and 76% versus 36.3% (Study 1023), and Grade 3-4 reductions were seen in 5.9% versus 2.3% (Study 1008) and 2.9% versus 1.8% (Study 1023). Anaemia can cause or exacerbate a range of AEs (fatigue, heart failure etc) and may require intervention, for example, transfusion.

Lymphopenia

Lymphopenia was reported as an AE in 1.2% across arms in Study 1023 and 1.4% versus 0.9% in Study 1008, but reduced lymphocyte count based on lab measures was not well characterised. There was no obvious imbalance in opportunistic infection.

Alopecia

Alopecia was reported as an AE in 32.9% versus 15.8% (Study 1008) and 18% versus 6.4% (Study 1023).

Stomatitis

This was reported as an AE in 30.4% versus 13.5% (Study 1008) and 25.2% versus 11% (Study 1023). Severe stomatitis was seen in 0.9% versus 0% (Study 1008) and 0.6% versus 0% (Study 1023).

Decreased appetite

Decreased appetite was reported as an AE in 14.9% versus 9.0% (Study 1008) and 15.9% versus 8.1% (Study 1023); the imbalance was greater in Study 1003 (20.5% versus 6.5%). There was an imbalance in dysgeusia in both studies (Study 1008: 10.1% versus 5.0%; Study 1023: 6.7% versus 2.9%) which might account, along with for example stomatitis, for the decreased appetite observed.

Cataracts / visual disturbance

Nonclinical studies revealed cataracts / irreversible lens degeneration, in rats, with no 'no observed effect level' identified.

discussion in the main CER (e.g. 'median time to recovery (ie, >1500 absolute neutrophil count) from lowest neutrophil count among patients with Grade \geq 3 neutropenia in that treatment arm was 99 days')

In Study 1008, eye disorders were observed in 21.6% (with 5/6 Grade 3 events related to cataracts) versus 13.1% (with no Grade 3-4 events). Obvious imbalances were for cataract (3.2% versus 0.5%) and increased lacrimation (5.6% versus 0.9%). In Study 1008, after protocol amendment 3, there was ophthalmic examination at baseline and Months 3, 6, 12, 24 and so on to the end of treatment.

In Study 1023, eye disorders were seen in 17.1% (no Grade 3+ events) versus 9.3% (no Grade 3+ events). More obvious imbalances were for increased lacrimation (4.3% versus 1.2%); an AE seen with some other chemotherapies⁵⁰) and blurred vision (4.9% versus 1.7%).

Other safety concerns

For the following events, there is less evidence that palbociclib causes frequent or severe toxicity.

Altered glucose metabolism

The CDK4 pathway may play a role in beta cells beyond cell cycle inhibition, for example, it may regulate glucose induced insulin secretion. Nonclinical studies revealed altered glucose metabolism, with possible non-reversibility, and no 'no observed effect level' found. The CSR for PALOMA-2 states that rats may be more sensitive to this effect than humans. A comment was made in the nonclinical evaluation regarding rats that 'there was a clear decrease in the absolute and relative number of beta cells'.

In early Study 1001, an effect was seen, as reported in the CSR for PALOMA-2:

In this study [1001], 2 treatment schedules (Schedule 3/1 [n=39]; and Schedule 2/1 [2 weeks on /1 week off; n=33]) were evaluated at escalating dosing levels (25-225mg) of single-agent palbociclib. In the 3/1 and 2/1 schedules, 16 (41.0%) and 12 (36.4%) patients experienced a worsening of serum glucose to Grade 1 from their prestudy baseline, respectively; 6 (15.4%) and 2 (6.1%) worsening to Grade 2 from their baseline, respectively; and 1 (2.6%) and 2 (6.1%) worsening to Grade 3 from their baseline, respectively. No patients experienced a worsening of serum glucose to Grade 4 from their baseline on this study. Of the 4 cases of Grade 3 serum glucose measurements observed on study (3 worsening from baseline and 1 Grade 3 at baseline), 3 occurred in patients known to be diabetic at time of study entry, and 1 case was observed in a patient being treated with short-term steroids for a gastrointestinal toxicity. Additionally, there were no reports of newly diagnosed cases of diabetes mellitus on study.

The authors speculated that this incidence of hyperglycaemia in Study 1001 '*may be explained by the characteristics of this advanced cancer patient population*'.

In Study 1008, there was less hyperglycaemia in the palbociclib + letrozole arm (2.0% versus 6.8%). Study 1008's protocol was amended on 18 September 2014 to include prospective monitoring of HbA1c. In Study 1023, there was no increase in AEs of hyperglycaemia in the palbociclib + fulvestrant arm (0.9% versus 1.2%).

Transaminitis / liver injury

A summary of laboratory assessed ALT, AST and bilirubin abnormalities follows:

Table 16: ALT, AST and bilirubin abnormalities

Study 1008		Study 1023		
	Palbociclib +	Placebo +	Palbociclib +	Placebo +

⁵⁰ Eisner and Luoh, Current Eye Research, 2011 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3205820/>

Study 1008			Study 1023					
	letrozole		letrozole		fulvestrant		fulvestrant	
	Any grade	3+	Any grade	3+	Any grade	3+	Any grade	3+
ALT	43%	2.5 %	29.9%	0%	28.9%	1.7 %	31.4%	0%
AST	51.6%	3.4 %	34.4%	0.9 %	34.7%	2.0 %	43.5%	2.4 %
Bili-rubin	6.1%	0.7 %	5.4%	0%	7%	0.6 %	5.8%	1.2 %

Increases were not greatly imbalanced (given differences in exposure). Isolated cases (in particular, one subject from Study 1023, discussed in detail from main CER), confounded by other factors that cause liver injury (for example, hepatic metastases), were not clear examples of palbociclib-induced liver injury.

QT prolongation

PK/PD evidence

The CSR for PALOMA-2 states:

...a positive correlation was observed between QTcF and palbociclib concentrations. At the mean steady-state C_{max} of palbociclib following administration of 125 mg QD on Schedule 3/1, the mean QTcF increase from baseline was 5.69 ms and the upper bound of the 1 sided 95% CI was 8.80 ms.

The CSR concludes QTc prolongation with the proposed palbociclib regimen is therefore not clinically significant.

In Study 1008, prolongation of QTc interval ≥ 60 ms was seen in 3/441 (0.7%) versus 0/220. The QT sub-study in 125 patients did not reveal a major QT liability, based on mean changes from baseline. There was no consistent imbalance in frequency of possibly related AEs (for example, tachycardia, 2.5% versus 1.4%; ventricular extrasystoles, 0.2% versus 0.5%). Some deaths were sudden and cardiac; based on further details provided by the sponsor, these seem unrelated to QT prolongation.

In Study 1023, prolongation of QT/cB/cF interval ≥ 60 ms was seen in a balanced and low percentage of subjects across arms. There was no imbalance in reports of tachycardia.

Interstitial lung disease

Reports of pneumonitis or pulmonary fibrosis or Idiopathic pulmonary fibrosis (ILD) were not prominent in Study 1023. In Study 1008, in the palbociclib-containing arm, there were three patients with these AEs, versus one in the control arm. Routine pharmacovigilance is proposed to monitor for any strengthening signal that palbociclib can cause ILD.

Peripheral neuropathy

In Study 1003, there was an imbalance in reports of peripheral neuropathy: 14.4% versus 5.2%. In larger studies, reported of peripheral neuropathy was less frequent: in Study 1023, the combined frequency of peripheral neuropathy / paraesthesia / peripheral sensory or motor or poly neuropathy was 5.0% versus 4.7%; in Study 1008, frequencies were 4.5% versus 3.2%. The similar frequencies across the larger studies (with median treatment durations 603 and 330 days respectively) do not strongly suggest cumulative toxicity.

Venous and arterial thromboembolism

In Study 1003 (Phase II), 4/83 palbociclib + letrozole patients (4.8%) versus no letrozole-only arm patients reported a pulmonary embolism (PE). However this high rate was not seen over the longer term in 1008 or 1023.

In Study 1008, 5/444 patients in the palbociclib-containing arm experienced a PE (1.1%), versus 4/222 in the control arm (1.9%), and 4 versus 1 had venous thrombosis. In Study 1023, 3/345 (0.9%) versus 0/172 had a PE, and 3 versus 0 had a venous thrombosis.

There is a detailed review of thrombosis/thromboembolism included from main CER, including updated frequencies (broadly in keeping with the above values). The higher frequency (3.5% versus 2.3%) of venous thromboembolic events in palbociclib containing arms than control arms can reasonably be accounted for by the increased duration on treatment in palbociclib containing arms.

Attribution of PE/DVT and related events solely to breast cancer (known to confer a high baseline risk of such events) is inappropriate. Medicines may increase risk of thrombosis directly or indirectly (for example, via dehydration or immobility) but in this case there is no strong evidence that palbociclib increases risk of thrombosis.

There was no strong signal of an imbalance for arterial events, which were rare.

Depression and suicide

In Study 1008, suicide was not reported and depression was reported in 7.7-9% across arms, with no imbalance in total (or higher grade) psychiatric events across arms.

In Study 1023 suicide was not reported. Depression was reported in 4.6-5.8% across arms. There were two suicide attempts in the experimental arm but this is not a strong signal given the context.

Exclusion criteria may have limited the occurrence of such events.

Summary

Addition of palbociclib to either letrozole or fulvestrant carries the clear risk of:

- Myelosuppression (neutropenia, thrombocytopenia, anaemia, lymphopenia) and its consequences (infection, bleeding and so on)
- Alopecia
- Stomatitis
- Decreased appetite
- Cataract formation (at least in combination with letrozole)

Other concerns flagged by the sponsor or evaluator (hyperglycaemia; transaminitis/liver injury; QT prolongation; interstitial lung disease; peripheral neuropathy; thromboembolism; depression / suicide) are not obviously more prominent in the palbociclib-containing arms of Study 1008 and Study 1023 than the control arms.

Many other AEs also occur with the given regimens (for example, fatigue, nausea and diarrhoea) but are not particularly more frequent with the addition of palbociclib (once the imbalance in treatment duration across arms of key studies has been factored in).

The clinical evaluator notes that:

The convenience of oral administration 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'

‘...the high proportions of temporary discontinuations, dose reductions and discontinuations suggest that palbociclib as an add-on is not particularly well tolerated by patients’

With regard to tolerability, palbociclib + letrozole appears to be less well tolerated than palbociclib + fulvestrant, in that permanent discontinuation of palbociclib in Study 1008 was more common than permanent discontinuation of placebo (9.2% versus 5.4%), whereas in Study 1023 this measure was balanced across arms.

The clinical evaluator notes some AEs may be more frequent in Asian patients. In discussion from main CER, this seems attributable to a higher frequency of neutropenia in Asian subjects. Studies 1010 and 1027 may clarify this issue. The latest RMP version has removed ‘Racial and / or Ethnic Groups’ from ‘Missing Information’ (according to the EMA Second JRAR Q24, this is because the safety concern was considered vague and unlikely to be clarified by routine pharmacovigilance). This is acceptable given that two relevant studies are being conducted and outcomes should be provided to the TGA.

Conventional cytotoxic agents are defined in the ‘*Guideline on the evaluation of anticancer medicinal products*’ as compounds inducing irreversible lethal cellular damage following short-term exposure through interference with DNA replication, mitosis and so on. Amongst non-cytotoxic compounds are cell cycle inhibitors.

Palbociclib has a toxicity profile overlapping that of some chemotherapies; for example, myelosuppression, alopecia, stomatitis and dysgeusia. The sponsor states [Clinical Overview], for neutropenia, that:

In vitro investigatory work in human bone marrow mononuclear cells suggested an improved hematologic safety profile can be anticipated for palbociclib versus that seen with traditional cytotoxic chemotherapy, based on the distinct profile for palbociclib (reversible cell cycle arrest) versus cytotoxic chemotherapy (apoptosis).

The sponsor has also suggested [PALOMA-2 CSR], based on nonclinical study data, that palbociclib may have cytoreductive as well as cytostatic effects on tumor cells.

Question for sponsor

Is it the sponsor’s current understanding that palbociclib causes reversible cell cycle arrest for haematopoietic cells, but both ‘cytoreductive’ and cytostatic effects on tumour cells? Cytoreductive effects for a medicine imply cytotoxicity. Please explain the basis for this possibly divergent mechanism of action.

Risk management plan

The RMP evaluator has summarised safety concerns and associated risk monitoring and mitigation strategies in Table 7 above.

It should be noted that an additional pharmacovigilance activity for ‘QT prolongation’ was further evaluation of this topic within the Study 1008 QT sub-study. This has been assessed within the CER for PALOMA-2.

Preclinical data and Study 1008 outcomes suggest palbociclib may, uncommonly, cause cataracts, at least in combination with letrozole. Cataracts are not amongst important identified risks in the RMP. This is acceptable if the PI includes relevant information.

Recommended condition of registration

The suggested wording is: Implement EU-RMP (version 1.3, dated 11 September 2016, dated lock point 4 March 2016) with Australian Specific Annex (version 1.3, dated 21 December 2016) and any future updates as a condition of registration.

Risk-benefit analysis

Delegate's considerations

Clinical

Second-line use in advanced breast cancer

Benefit-risk balance is positive in the second-line setting (in combination with fulvestrant in women who have received prior therapy). Study 1023 (PALOMA-3) was pivotal in this setting.

First-line use in advanced breast cancer

Benefit-risk balance is unclear in the proposed first-line setting (in combination with letrozole as initial endocrine-based therapy in postmenopausal women):

There is one pivotal study (Study 1008; PALOMA-2). Study 1003 (PALOMA-1) is not considered pivotal, because of certain design aspects and its smaller sample size (n=666 versus n=165 respectively) and it is considered a supportive study.

In PALOMA-2, a large improvement in PFS (approximately 10 months) was observed in the arm receiving palbociclib + letrozole, relative to the placebo + letrozole arm, based on final PFS analysis. There was also a large decrease in the proportion with best overall response of disease progression (7.7% versus 16.7%). There was an improvement in objective response rate (ORR) (42.1% versus 34.7%).

In PALOMA-2, a planned OS interim analysis was performed at the 26 February 2016 data cut-off at the time of the final PFS based on 133 deaths (34% of 390 events for final analysis) from 666 patients. The detailed overall survival (OS) analysis was not provided.

In the sponsor's response to Clinical questions 8-9 in the CER for PALOMA-2, received by the TGA on 28 February 2017, it was noted in part that:

An updated analysis of OS for PALOMA-2 would be submitted in March 2017, accompanying the sponsor's Pre-ACM Response to this overview.

The proportion of patients who had died on or after treatment was now 27.0% versus 28.8% respectively; but no more detailed characterisation of OS from this updated analysis (data cut-off 24 November 2016) is available at the time of writing this overview.

Palbociclib toxicity was not extreme; common events were myelosuppression (for example, neutropenia), alopecia and stomatitis. There was no clear signal that drug toxicity directly causes many patient deaths. However, toxicity was enough to cause dose delay in approximately 2/3 patients, dose reduction in approximately 1/3 and discontinuation of palbociclib in 9.2% (PALOMA-2) and 3.8% (PALOMA-3).

In PALOMA-2, there was no clear evidence that adding palbociclib to letrozole improved or detracted from quality of life, relative to the control arm.

In PALOMA-1, the validity of findings was called into question by design issues. The robustly designed Phase III PALOMA-2 did, however, confirm the magnitude of PFS benefit seen in PALOMA-1.

In PALOMA-1, OS outcomes were again immature but there was no early signal of a mortality imbalance. In the sponsor's response to Clinical questions in the CER for PALOMA-2, it is stated that an updated analysis of OS for PALOMA-1 (data cut-off 30 December 2016) will be provided in the Pre-ACM Response to this Overview.

Despite the impressive anti-tumour efficacy of palbociclib + letrozole in this setting, benefit-risk balance is unclear. While substantial improvement in PFS provides a clinical benefit viewed in isolation, there is no clear-cut net benefit to first-line patients when:

There is uncertainty about whether addition of palbociclib might be associated with lower OS (that is, the possibility that there is an OS detriment has not been sufficiently excluded⁵¹);

Delay in the need for ‘toxic chemotherapies’ is achieved by addition of an agent that confers its own chemotherapy like toxicities (albeit ones that are not typically as pronounced as those associated with traditional cytotoxic chemotherapies); and

There is no indication of improvement (relative to the control arm) in quality of life.

PALOMA-1 and PALOMA-2 examined PFS as the primary efficacy endpoint. In both studies, however, OS was an important endpoint. A general view is that ‘*irrespective of chosen primary endpoint, it is the magnitude of the treatment effect on all relevant outcome measures that forms the basis in the benefit-risk assessment*’⁵².

In an overall setting where second-line use appears to offer a clear benefit and first-line use does not offer a clear benefit, another consideration is that first-line use may deny patients the opportunity to use palbociclib in the second-line setting where, so far, clinical benefit is more incontrovertible.

HR-positive, HER2-negative advanced breast cancer

The sponsor has applied to register palbociclib for use in patients with HR+ HER2- advanced or metastatic breast cancer:

with letrozole as initial endocrine-based therapy in post-menopausal women;

with fulvestrant in women who have received prior therapy.

Metastatic breast cancer is reviewed in the main CER. The clinical evaluator writes that metastatic breast cancer is seen as incurable. Treatment is to improve progression-free *and* overall survival, to improve or maintain quality of life and to defer the need for subsequent treatments ‘*which include chemotherapy with its associated toxicities and limited clinical benefit*’. This aligns with the goals outlined by Hayes in Up-To-Date⁵³:

The primary goals of systemic treatment for metastatic breast cancer are prolongation of survival, alleviation of symptoms, and maintenance or improvement in quality of life, despite toxicity associated with treatment.

Hayes also notes that:

The optimal measure of therapeutic efficacy is debated. OS is the gold standard for comparing therapies, but it requires prolonged follow-up and may be diluted by the effects of subsequent treatment. However, no other endpoint, including progression-free survival, time to tumour progression, or objective response rate, has been shown to be a good surrogate for OS. Comparisons of objective response rates are often used to determine relative treatment efficacy, but high response rates do not necessarily translate into clinically meaningful increases in survival. In addition, symptom relief without measurable disease response and achievement of stable disease as compared with disease progression may be clinically important.

Within the framework of the TGA-adopted EU guidance on anticancer medicines, the intent of the proposed treatment is to achieve long-term disease control (that is, it is neither curative nor purely palliative).

⁵¹ It is expected that the updated OS analysis (data cut-off 24th Nov 2016) may help more precisely characterize the survival impact of palbociclib, but at the time of writing it is not possible to state whether that analysis in itself will be enough to exclude with reasonable certainty an OS detriment.

⁵² TGA-adopted EU guideline EMA/CHMP/205/95/Rev.4

⁵³ Systemic treatment for metastatic breast cancer: general principles; Topic 767 Version 30.0; 2015

Naughton and Ma⁵⁴ state that objectives of *endocrine* treatment are to maximise quality of life and reduce the relatively worse side effect profiles associated with the use of chemotherapy.

Given that a recurring aim of treatment is to avoid chemotherapy related toxicity, it is worth noting the role of chemotherapy. Chemotherapy may be used where endocrine therapy is unlikely to result in a prompt clinical response, for example, patients with rapid progression following >1 endocrine therapy, or who present with large tumour burden involving visceral organs⁵⁵. Chemotherapy can be single agent or combination and choice is tailored but includes taxanes (for example, paclitaxel), anthracyclines (for example, doxorubicin) and various other agents.

Benefit-risk for second-line setting

The benefit-risk balance is *positive* in the proposed second-line setting (in combination with fulvestrant in women who have received prior therapy). Study 1023 (PALOMA-3) was pivotal in this setting.

Benefit-risk for first-line setting

Benefit-risk balance is unclear in this proposed use (in combination with letrozole as initial endocrine-based therapy in postmenopausal women).

Key studies are PALOMA-1 (Study 1003) and PALOMA-2 (Study 1008). PALOMA-1 was exploratory; aspects of its design argue against it being considered pivotal. The two studies do not inform equally about benefit-risk; PALOMA-2 is considered the single pivotal study for the first-line indication.

A large 10.3 month improvement in PFS was seen in PALOMA-2, over the standard of care, letrozole. There was also improvement in objective response (42.1% with addition of palbociclib versus 34.7% for letrozole alone) and a large decrease in the proportion of patients with progressive disease as their best overall response. There was a suggestion that gain in PFS was less pronounced in patients with *de novo* metastatic disease (based on the supportive BICR analysis) but PFS benefit was still evident overall, in that group.

In the primary PFS analysis, the benefit seen in the palbociclib arm was due to a large decrease in the frequency of objective progression (41.2% versus 60.4%). Death without objective progression was imbalanced in the opposite direction, 2.5% versus 1.4%. Evidently this imbalance had little effect on the overall balance across arms of PFS events.

Prominent adverse events for palbociclib were neutropenia, thrombocytopenia, anaemia, alopecia and stomatitis. The frequency of serious infections was not very different across arms once the imbalance in treatment duration across arms was factored in (median duration of exposure was approximately 50% longer in the palbociclib + letrozole arm than the control arm). There was no strong signal that palbociclib's toxicities caused, in aggregate, many patient deaths on treatment. However, toxicity was enough to cause dose delay in approximately 2/3 patients, dose reduction in approximately 1/3 and discontinuation of palbociclib in 9.2%.

In PALOMA-2, a planned OS interim analysis was performed at the 26 February 2016 data cut-off at the time of the final PFS based on 133 deaths (34% of 390 events for final analysis) from 666 patients. Formal analysis of OS (for example, with accompanying hazard ratios, KM curves, etc) was not provided.

⁵⁴ Treatment approach to metastatic hormone receptor-positive breast cancer: endocrine therapy; Up-To-Date Topic 778 Version 42.0; 2016

⁵⁵ Schott, Systemic treatment of metastatic breast cancer in women: chemotherapy; Up-To-Date Topic 83848 Version 11.0, 2015

An updated OS analysis is planned for inclusion in the sponsor's Pre-ACM Response but it is not currently available. The only information relating to this updated OS analysis (data cut-off 24 November 2016, that is, 9 months after the last data cut-off) is that now, 27.0% (palbociclib + letrozole) versus 28.8% (placebo + letrozole) have died. The formal OS analysis should present OS hazard ratios, Kaplan-Meier curves for OS, and 12, 24 and 36-month survival statistics.

Updated OS outcomes are needed not for the purpose of showing palbociclib's superiority but for the purpose of helping to rule out a negative impact on OS. In the first-line setting, a large PFS benefit alongside results that sufficiently rule out a deleterious impact on OS would *likely* be acceptable evidence of positive benefit-risk balance, all other things being equal. A *precise* OS estimate is not needed⁵⁶ (the upper limit of 95% CIs around the OS HR does not need to be <1), but the point estimate of the OS HR should be <1; a trend towards OS benefit should exist. This acknowledges the well-known challenges involved in detecting a statistically significant effect on OS (for example, due to off-study cross-over, use of subsequent effective therapies, long median post-progression survival and so on).

The position of the EMA evaluators in this regard is noted (for example, Second JRAR page 7/65, '*the likelihood of an overall detrimental effect of palbociclib on OS appears low, given the large treatment effects observed on PFS*') however the same view is not held by the Delegate, given the concerns noted earlier.

While PALOMA-1's outcomes cannot be given equal weight to those of PALOMA-2, it is relevant that in PALOMA-1, a large PFS benefit was observed. OS data remain immature in PALOMA-1, as for PALOMA-2 (approximately 37% and approximately 20% of patients have died, respectively). (Of note, updated outcomes for PALOMA-1 are also expected in the sponsor's Pre-ACM Response.) In PALOMA-1, the OS HR point estimate was 0.813 favouring palbociclib + letrozole (95% CI 0.492-1.345); median OS was 37.5 months versus 33.3 months favouring palbociclib + letrozole.

Phase I/II Study 1010 also examined palbociclib + letrozole. As per PALOMA-2, the study was submitted late in the TGA evaluation phase. Study outcomes so far do not inform the discussion of discordance between PFS and OS.

In this setting it is important to consider the impact of treatments on quality of life. In PALOMA-2, there were no clear differences observed between arms in patient-reported outcomes. This can be interpreted to argue that palbociclib toxicity is not so great as to meaningfully erode quality of life or to argue that the drug's impact on the tumour is insufficient to improve cancer-related impacts on quality of life. There is no strong argument that addition of palbociclib to letrozole helps patients by preventing deterioration or improving quality of life in the first-line setting. While in PALOMA-3 there was evidence that time to deterioration in pain was lengthened by addition of palbociclib, the same benefit was not apparent in PALOMA-2.

The approach recommended in the TGA-adopted EU guideline on anticancer medicines is relevant. For confirmatory trials (see Section 7 of the guidance), in the setting of treatments given to achieve long-term disease control, the following is a paraphrase of the relevant advice:

⁵⁶ By way of example, refer to the TGA AusPAR for exemestane, August 2013, which notes that in BOLERO-2, while OS outcomes were immature, the OS HR was (a) reported, and (b) reported to be 0.77 (95% CI 0.57-1.04), with median follow-up of 17.7 months.

Table 17: Summary of approach in TGA-adopted EU guideline on anticancer medicines

Endpoints (7.1.5)	<p>Convincingly demonstrated favourable effects on survival are, from both a clinical and methodological perspective, the most persuasive outcome of a clinical trial.</p> <p>Prolonged PFS/DFS as such, however, is considered to be of benefit to the patient.</p> <p>Irrespective of chosen primary endpoint, it is the magnitude of the treatment effect on all relevant outcome measures that forms the basis in the benefit-risk assessment.</p> <p>When OS is reported as a secondary endpoint, the estimated treatment effect on OS should ensure that there are no relevant negative effects on this endpoint, in most cases by showing trends towards superiority.</p> <p>In situations where there is a large effect on PFS or if there is a long expected survival after progression, and / or a clearly favourable safety profile, precise estimates of OS may not be needed for approval.</p>
Increased toxicity expected⁵⁷ (7.3.2)	<p>Demonstrate superiority at least in terms of PFS.</p> <p>Survival data should be made available at the time of submission.</p> <p>Mature survival data cannot be expected in all cases; post-approval follow-up is then expected.</p> <p>If absence of increased treatment-related mortality is not established with reasonable certainty, mature survival data should be available for the assessment of benefit-risk prior to licensure.</p>
Major⁵⁸ increase in toxicity expected (7.3.3)	<p>The principal objective should be to demonstrate improved survival.</p> <p>This may be non-achievable due to expected good prognosis with respect to survival and availability of several active next-line regimens.</p> <p>If PFS is selected as the primary endpoint, this requires thorough justification. Even though only a major benefit in terms of PFS prolongation would be acceptable, whenever possible the number of patients included should be sufficient to obtain an estimate on overall survival where a trend in a favourable direction is expected.</p>
Follow-up and treatment after progression (Appendix 1)	<p>A large effect in terms of PFS is generally expected to be associated with an effect on OS. If this is not the case, a rational explanation should be provided.</p> <p>When comparing treatments in terms of PFS it is important to consider that treatment with an experimental agent, even if advantageous in terms of PFS, may be associated with poorer OS. This may be due, for instance, to long term toxicity, different resistance profiles to treatment used after progression, or to biological changes leading to increased metastatic potential.</p> <p>Whenever possible when PFS is the primary endpoint, complete follow-up of all patients should be available until death and there should be sufficient reassurance that there is no detrimental effect in terms of OS.</p>

PALOMA-3 demonstrates that palbociclib in combination with endocrine therapy can have a positive benefit-risk balance but the existence of two major studies in a first-line setting

⁵⁷ It is reasonable to regard addition of palbociclib to letrozole as amounting to an increase (not a major increase) in toxicity; but this is subjective; recommendations for both settings are included.

⁵⁸ 'Major' is not precisely defined (guidance page 18/33) but 'in most cases refers to a fear that the experimental regimen might be associated with an increase in treatment-related deaths, irreversible adverse events with a long-term impact on QoL, or severe impairment to patient condition'

(PALOMAs 1 and 2) means extrapolation from PALOMA-3 results to provide evidence in the first-line setting is not required or appropriate.

Efficacy by ER-positive subtype

The CSR for PALOMA-2 states:

Palbociclib was tested in vitro on molecularly characterized human BC cell lines. Results from these experiments indicate that sensitive cell lines in this panel represent mostly the luminal ER-positive subtype...

In this regard correspondence regarding the second-in-class product ribociclib, from de Gramont et al in the NEJM, 19 January 2017⁵⁹, is of note:

Hortobagyi et al. report positive outcomes associated with ribociclib combined with letrozole in first-line therapy for HR-positive advanced breast cancer. Improving the duration of progression-free survival by more than 1 year is an important achievement. However, HR-positive breast cancers are heterogeneous, and patients were not stratified according to molecular subtype. Patients with luminal B tumors have a worse prognosis than those with luminal A tumors.

In a recent study involving patients with HR-positive metastatic breast cancer who were treated with letrozole with or without lapatinib, the intrinsic luminal subtype was the strongest prognostic factor to be independently associated with progression-free and overall survival. Median progression-free survival among patients with luminal A tumors was 16.9 months, as compared with 11.0 months among patients with luminal B tumors. Furthermore, numerous studies, mostly retrospective, have suggested variations in estrogen-receptor and progesterone-receptor expression between the primary tumor and the metastases, especially among patients with luminal B tumors. Thus, we hoped that Hortobagyi and colleagues could be more precise in their assessment of the contribution of ribociclib in the different subtypes of advanced breast cancer.

The same argument can be extended to assessment of palbociclib.

Question for sponsor

Submit any subgroup analyses for Studies 1008 and 1023 according to subtype of disease (for example, luminal A versus B).

Planned or ongoing studies

The RMP Evaluation draws attention to:

- Study A5481064: a retrospective assessment of treatment patterns and outcomes associated with palbociclib in combination with letrozole in postmenopausal women with HR+/HER2–advanced breast cancer. Expected to be completed in 2019.
- Study A5481027: a multicentre, randomised, double-blind, phase 3 study of palbociclib plus letrozole versus placebo plus letrozole for the treatment of previously untreated Asian postmenopausal women with ER-positive, HER2-negative advanced breast cancer. Planned submission year: 2019
- Study A5481013: A Phase I, open-label, single dose, parallel-cohort study to evaluate the pharmacokinetics of palbociclib in subjects with impaired hepatic function. Planned submission year: 2018.

⁵⁹ Gramont A de et al Ribociclib for HR-Positive, Advanced Breast Cancer. N Engl J Med 376 (3), 288-289. 2017 Jan 19.

- Study A5481014: A Phase I, open-label, single dose, parallel-group study to evaluate the pharmacokinetics of palbociclib in subjects with impaired renal function. Planned submission year: 2017.

Question for sponsor

For Studies 1064 and 1027, are any interim CSRs planned, that may allow assessment of efficacy / safety information earlier than the dates noted above?

Proposed indication

Recognising that sponsor input and clinical expert advice are required to resolve the benefit-risk issues identified in the first-line setting, the following issues span both first and second line use.

Letrozole versus anastrozole

The proposed indication ties first-line use to combination with letrozole. It seems appropriate to allow use, alternatively, in combination with anastrozole. However this would not be driven by pivotal clinical trial evidence. The sponsor notes in its Clinical Overview that approximately 75 patients have been given palbociclib + anastrozole under clinical study conditions but that no additional efficacy data are available.

Question for sponsor

Is there any concern about indicating first-line use also in combination with anastrozole?

Hormone receptor status (ER versus PR)

In PALOMA-3, ER-positive and/or PR-positive tumours were allowed (in PALOMA-1 and -2, only ER+ disease was allowed).

In Study 1023, there were three subjects with ER-, PR+ disease by local testing and 13 subjects with ER-, PR+ disease by central testing (but no overlap between these subjects, perhaps indicative of variability between laboratory testing sites). The Main CER shows outcomes for these patients; there was no strong indication of benefit in the palbociclib + fulvestrant arm but numbers are small.

This aspect of the indication as proposed by the sponsor seems appropriate.

'Advanced' breast cancer

In PALOMA-2 and PALOMA-3, patients without metastases were allowed to enrol (according to inclusion / exclusion criteria) as follows (Table 18):

Table 18: Exclusion and inclusion criteria for PALOMA-2 and PALOMA-3

Study	Inclusions / exclusions	Numbers
PALOMA-2	<p>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.</p> <p>Measurable disease was required in the locoregionally recurrent setting, and 'tumor lesions previously irradiated or subjected to other locoregional therapy were only deemed measurable if disease</p>	<p>The large majority of patients had metastatic disease, either distant recurrence (294/444 [66.2%] palbociclib + letrozole arm, 145/222 [65.3%] placebo + letrozole) or de novo metastasis (139/444 [31.3%] and 71/222 [32.0%] respectively).</p> <p>Only 11/444 (2.5%) and 6/222 (2.7%) respectively had locoregional recurrence, local recurrence or regional recurrence.</p>

Study	Inclusions / exclusions	Numbers
	progression at the treated site after completion of therapy was clearly documented’.	<i>Source: CER for PALOMA-2</i>
PALOMA-3	<p>Evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent.</p> <p>Measurable disease was required in the locally advanced setting, and ‘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’.</p>	<p>According to CSR Table 16, the majority of patients had metastatic disease, either distant recurrence (66-69.5% across arms) or de novo metastatic disease (14.4-19.3% across arms) 49/347 (14.1%; palbociclib + fulvestrant) and 25/174 (14.4%; placebo + fulvestrant) patients had local / locoregional / regional recurrence, although in the s31 response to clinical Q15 a further patient was identified in the palbociclib + fulvestrant arm.</p>

The proposed indication refers to advanced or metastatic disease. Hayes writes:

Metastatic breast cancer may present as systemic, limited disease in the breast or chest wall (local recurrence), ipsilateral axilla (regional recurrence), or as isolated metastatic disease (eg, involving the brain, liver, or bone).

The term ‘advanced’ is already used in some PIs, for example, the indication for letrozole, while the different term ‘locally advanced’ is used in other PIs (for example, fulvestrant).

It is important to emphasise in the PI that patients with locoregional should only be considered for palbociclib if their locally advanced disease is inoperable and not amenable to neo/adjvant chemotherapy.

Use of the term ‘advanced or metastatic’ appears appropriate.

Initial endocrine-based therapy

The proposed first-line use refers to ‘initial endocrine-based therapy’. This seems open to different interpretations.

The Delegate’s view is that ‘initial’ refers to first line treatment of ‘advanced’ disease. In this case, to have palbociclib and letrozole combination treatment under the banner of ‘endocrine-based therapy’ may suggest, incorrectly, that palbociclib + letrozole is associated with the less toxic side-effect profile of endocrine therapy. The term ‘endocrine-based’ does distinguish the ‘palbociclib + letrozole’ treatment approach from pure chemotherapy-based approaches, but this is already achieved by earlier reference to ‘in combination with endocrine therapy’.

Another view is that this terminology implies that palbociclib must be started only when endocrine therapy is started (as opposed to starting palbociclib part of the way through a course of endocrine therapy). However it is noted that the wording applies only to the first-line use and if this were truly the aim, presumably it would have been applied to both indications.

Another view is that this wording allows patients to transition from chemotherapy used to treat critical visceral metastases across to ‘palbociclib + letrozole’ as this would be initial *endocrine-based* therapy (notwithstanding earlier chemotherapy for advanced disease). However, in Study 1008, no prior chemotherapy for advanced disease was allowed.

Use of goserelin in Study 1023

It is noted that in the EU Summary of Product Characteristics (SmPC), the indication includes the following statement:

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

Reference is made to use in Study 1023 of goserelin. In the proposed indication, this wording is missing.

It is considered that as long as the Clinical Trials section clarifies use of goserelin, there is no need for additional text in the indication.

Gender

The sponsor proposes use in women with breast cancer.

In the main CER, the evaluator notes that:

- breast cancer in men is seldom ER-negative or HER2+ve that is, almost always ER-positive
- no data are presented on the safety and efficacy in men and registration is not being sought
- 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

While some PK data were generated in men, this situation arises to different degrees for many NCEs. It is considered that the sponsor's overall approach has allowed reasonable characterisation of PK in the target population.

It is also considered that a large efficacy trial in men would be unlikely and there may be grounds for having an indication not specifically restricted to women.

Question for sponsor

Is there any concern about having an indication not specifically restricted to women?

Patients with critical visceral disease

The EMA Second JRAR discussed whether the indication should include a caveat around use in patients with critical / rapidly progressing / symptomatic visceral disease.

In Studies 1008 and 1023, patients with such disease were excluded.

The EMA evaluation (Q10) noted that ORR and time to response were not provided in Study 1008 sub-grouped by disease site (visceral versus non-visceral). The PALOMA-2 CSR confirms the pattern seen in PALOMA-3 for ORR: addition of palbociclib results in higher ORR in patients with visceral disease but not in patients with non-visceral (including bone-only) disease. TTR outcomes were not presented.

In the absence of a clear picture of time to response, the PI should explain that clinical trials excluded patients with critical visceral disease.

Question for the sponsor

Has an analysis of time to response, including a subgroup analysis based on site of disease, been conducted in Study 1008?

Proposed action

The Delegate had no reason to say, at this time, that the application for palbociclib should not be approved for the second-line indication as follows:

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 fulvestrant in women who have received prior therapy

The Delegate is not in a position to say, at this time, that the application for palbociclib should be approved for the first-line indication as follows:

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

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Please comment on the immature OS outcomes available in Study 1008. Please specifically consider updated OS outcomes if they are included in the sponsor's Pre-ACM Response document.
 - a. In the context of other efficacy and safety outcomes, are the reported OS outcomes and the degree of OS data maturity in PALOMA-2 considered acceptable, for approval of the first-line use?
 - b. Is there any concern that PFS benefit will not translate into an OS benefit for patients in the first-line setting?
2. Should Study 1003 be viewed as pivotal, or as supportive? (If it can be viewed as pivotal, its OS outcomes, trending towards no evidence of harm, should be given more weight. Updated outcomes for Study 1003, proposed for inclusion in the Pre-ACM Response by the sponsor, are likely to be 'mature'.)
3. Is there evidence of clinical benefit in the targeted first-line population, when efficacy and safety outcomes are taken into account? Please discuss how the major efficacy endpoints should be viewed as a whole, to inform consideration of clinical benefit (PFS; OS; ORR [DoR] / stable disease / PD; QoL).
4. Is benefit-risk balance in the proposed first-line use favourable? If so, please comment on the appropriate indication, taking into account issues raised under 'Issues Proposed Indication' in the main body of the overview.

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Questions to sponsor

1. Assuming PALOMA-2's full CSR has been submitted to the FDA for evaluation; provide an update about this process, including an indication of major issues identified to date by the FDA.
2. Discuss evidence for a clinical impact on palbociclib use of interactions with SULF inhibitors.
3. An updated OS analysis is planned for inclusion in the Pre-ACM Response. Please include a subgroup analysis of OS by PhIIP1 versus PhIIP2.

4. Is it the sponsor's current understanding that palbociclib causes reversible cell cycle arrest for haematopoietic cells, but both 'cytoreductive' and cytostatic effects on tumour cells? Cytoreductive effects for a medicine imply cytotoxicity. Explain the basis for this possibly divergent mechanism of action.
5. Submit any subgroup analyses for Studies 1008 and 1023 according to subtype of disease (luminal A versus B).
6. Is there any concern about indicating first-line use also in combination with anastrozole?
7. Is there any concern about having an indication not specifically restricted to women?
8. Has an analysis of time to response, including a subgroup analysis based on site of disease, been conducted in Study 1008?
9. For Studies 1064 and 1027, are any interim CSRs planned, that may allow assessment of efficacy / safety information earlier than the dates noted above?

Response from Sponsor

The indication sought is:

Ibrance is 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:

- *an aromatase inhibitor;*
- *fulvestrant in patients who have received priortherapy*

Pfizer agrees with the Delegate's position that the benefit risk is positive in the recurrent setting in combination with fulvestrant in women who have received prior therapy.

Pfizer does not agree with the Delegate's position that the benefit risk is unclear in the first line setting in combination with letrozole and believes the benefit risk balance is positive on the basis that palbociclib plus letrozole demonstrated:

- A magnitude of PFS benefit in the first line setting that is robust across a number of sensitivity analyses and far exceeds that of therapies with full registration in Australia for the treatment of HR-positive, HER2-negative advanced/metastatic breast cancer;
- A 10 month PFS improvement, median PFS > 2 years and 42% reduction in the risk of disease progression or death compared to letrozole alone and is supported by ORR and CBR results;
- Prolongation of PFS consistently shown in all pre-specified subgroups based on stratification factors, baseline demographics and disease characteristics;
- A well tolerated safety profile; AEs were consistent with the known safety profile and were well managed by temporary discontinuations, cycle delays and/or dose reductions;
- Favourable interim Overall Survival (OS) HR < 1 whilst maintaining quality of life.

The issues for which the Delegate is seeking advice from the ACM are discussed below. The sponsor also responded to Questions 1 – 9 submitted in response to the Delegate's Overview.

Issues

Are the OS outcomes and OS data maturity in Study A5481008 acceptable for first-line use? Is there any concern that PFS benefit will not translate into an OS benefit?

Updated OS data for Studies A5481008 and A5481003 were requested by the TGA on 14 February 2017. The analyses for the updated interim OS for Study A5481008 (cut-off date 24 November 2016) and the final OS for Study A5481003 (cut-off date 30 December 2016) were provided. Please refer to Response to Question 1.

This interim analysis (IA) of the secondary endpoint OS in Study A5481008 was performed when 28% of patients had died, and was requested by US FDA (refer to sponsor's response to Question 1). The median OS was not yet reached in the palbociclib plus letrozole arm or placebo plus letrozole arm. The primary endpoint of this study was PFS by investigator assessment. There was a statistically significant, robust, and clinically meaningful 10.3-month improvement in median PFS (42% risk reduction) compared with placebo plus letrozole (24.8 months versus 14.5 months, HR=0.576 [95% CI: 0.463, 0.718], 1 sided $p < 0.000001$). This study was a confirmatory trial of Study A5481003.

The Delegate highlights the TGA adoption of the EU guideline on anticancer medicines and Section 7 of the guidance is applicable for this study. From the results of Study A5481008, Pfizer considers Section 7.1.5 applies. The criteria for Section 7.1.5 states:

Convincingly demonstrated favourable effects on survival are, from both a clinical and methodological perspective, the most persuasive outcome of a clinical trial. Prolonged PFS/DFS as such, however, is considered to be of benefit to the patient.

When OS is reported as a secondary endpoint, the estimated treatment effect on OS should ensure that there are no relevant negative effects on this endpoint, in most cases by showing trends towards superiority.

In view of these criteria it is important to note for Study A5481008 that PFS was the primary endpoint of the study and OS was a secondary endpoint.

Section 7.1.5 further states

In situations where there is a large effect on PFS or if there is a long expected survival after progression and/or a clearly favourable safety profile, precise estimates of OS may not be needed for approval.

The results of Study A5481008 meet the criteria of Section 7.1.5 of the EU cancer guideline. There was a large effect on PFS with a greater than 10 month increase compared to standard of care first-line treatment and the secondary endpoint of OS showed the point estimate of the HR was < 1 which indicates no relevant negative effects on this endpoint.

The sponsor acknowledges the Delegate's inclusion of the Oncology Working Group (OWG) Minutes which considered that:

Despite the impressive anti-tumour efficacy of palbociclib plus letrozole in the first line setting and the absence of major toxicity that might directly account for many treatment-related deaths, the benefit-risk balance is unclear because there is a signal, based on immature OS data, of a deleterious impact on overall survival.

The demonstrated HR of < 1 should now address the OWG concern.

Should Study 1003 be viewed as pivotal or supportive?

With the readout of the much larger Phase III Study A5481008 in the first-line setting, the Phase I/II Study could now be viewed as supportive in nature. The PFS results from Study A5481003 were consistent with that of Study A5481008 with a 10.3 month improvement of PFS in the palbociclib plus letrozole arm compared with the letrozole only. The final OS analysis is now available with a median follow-up of 69.3 months in the palbociclib plus letrozole arm and 59.0 months in the letrozole alone arm. There were 116 deaths (70.3% of

all patients). The observed HR was 0.897 (95% CI: 0.623, 1.294) in favour of palbociclib plus letrozole arm. Refer also to sponsor's response to Question 3.

Evidence of clinical benefit in the first-line population-efficacy and safety outcomes; How should the major efficacy endpoints be viewed as a whole to inform consideration of clinical benefit (PFS; OS; ORR [DOR] / stable disease / PD; QoL)?

With a clinically and statistically significant median PFS of 24.8 months, a magnitude of PFS benefit that far exceeds current therapies registered in Australia and an interim OS point estimate HR <1 that favours the palbociclib plus letrozole arm while maintaining quality of life, the evidence strongly supports the clear clinical benefit of Ibrance in the first line treatment of patients with HR-positive, HER2-negative advanced breast cancer. Of note, statistically significant survival improvement in first line hormone HR-positive, HER2-negative advanced breast cancer has never been observed with the currently approved therapies, likely because results have been confounded by the subsequent therapies which make difficult to isolate the contribution of the first line treatment.

Other secondary endpoints, objective response (OR), clinical benefit response/disease control (CBR/DC) and duration of response (DOR) also favoured palbociclib. The objective response rate (ORR) for patients with measurable disease was statistically significantly higher, 55.3%, in the palbociclib plus letrozole arm compared to 44.4% in the placebo plus letrozole arm (p=0.0132). These responses were more durable in the palbociclib plus letrozole arm with duration of response of 20.1 months versus 16.7 months in the placebo plus letrozole arm. The analysis of CBR (CR+PR+SD \geq 24 weeks) demonstrated a statistically significant improvement in CBR for palbociclib plus letrozole compared with placebo plus letrozole (odds ratio of 2.451; p-value <0.0001). The CBR rates were 85.8% in the palbociclib plus letrozole arm and 71.2% in the placebo plus letrozole arm. In terms of patient reported outcomes (PRO), the addition of palbociclib to letrozole maintained breast cancer-specific health-related quality of life and general health status, with no statistically significant differences observed between the 2 treatment arms in change from baseline scores.

The results of the primary and secondary efficacy endpoints for Study A5481008 were supported by Study A5481003 and clearly demonstrate a clinical benefit of palbociclib in combination with letrozole in hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.

Safety Profile

The combination of palbociclib plus letrozole was generally well-tolerated and managed by temporary dosing discontinuation, dose reduction and/or standard medical therapy in Study A5481008, as supported by the low proportion of permanent discontinuations. No unexpected major safety findings were observed with the combination of palbociclib plus letrozole. Overall the safety profile was consistent across the 3 breast cancer studies (A5481003, A5481008 and A5481023), regardless of the combination and disease setting.

It is commented in the Delegate's Overview and Oncology Working Group (OWG) Minutes that the addition of palbociclib

confers its own chemo-like toxicities' and that 'any impact on bone marrow reserve might make it more difficult to give chemotherapy as a subsequent line of therapy.

Chemotherapy is widely associated with systemic and quality of life toxicities such as severe vomiting, nausea, alopecia, febrile neutropenia and stomatitis. Palbociclib does not appear to be associated with equivalent chemotherapy-like toxicities however is associated with reversible myelosuppression, with a median duration of neutropenia of about 1 week for Grade 4. The relatively low production rate, long maturation time and short lifespan of

neutrophils compared to the other cell types may explain the higher frequency of neutropenia observed following palbociclib treatment in the clinic.

There is a difference between palbociclib induced neutropenia and that caused by chemotherapeutic agents both in the degree and duration of the effects (see sponsor's response to Question 4). This differentiation supports the current palbociclib treatment schedule (3 weeks on, 1 week off), which provides time for bone marrow cells to recover during the 1 week treatment-free period without impacting tumour efficacy.

Unlike chemotherapeutic agents, the combination of palbociclib plus letrozole was not associated with frequent Grade 3 or 4 toxicities that are characteristic of chemotherapy, such as stomatitis severity, have limited clinical impact and are gradual in onset. These adverse events rarely required emergent intervention and oncologists are intimately familiar with their management.

The most commonly reported SAEs ($\geq 1\%$) were infections (4.3%) and febrile neutropenia (1.6%) in the palbociclib plus letrozole arm and infections (3.6%) and pulmonary embolism (1.4%) in the placebo plus letrozole arm. The frequency of serious infections was comparable between the 2 treatment arms, once the imbalance in treatment duration across arms was factored in (median duration of exposure was approximately 50% longer in the palbociclib plus letrozole arm than the placebo plus letrozole arm [603 days versus 413 days]). Overall the PRO measures for quality of life showed that quality of life is maintained while palbociclib-treated patients were on treatment.

Based on the above data, there is no evidence that palbociclib plus letrozole treatment may limit chemotherapy as a subsequent line of therapy due to myelotoxic effects impacting the bone marrow reserve.

Is benefit-risk balance in the proposed first-line use favourable?

The Delegate's Overview presents the view for palbociclib:

In the first-line setting, a large PFS benefit alongside results that sufficiently rule out a deleterious impact on OS would likely be acceptable evidence of positive benefit-risk balance, all other things being equal. A precise OS estimate is not needed (the upper limit of 95% CIs around the OS HR does not need to be <1), but the point estimate of the OS HR should <1 ; a trend toward OS benefit should exist.

In the updated interim OS analysis The OS remains very immature at approximately 28% of patient deaths.

This updated analysis noted by the OWG as 'a shift over a fairly short period of time', together with the efficacy results and a manageable well-tolerated safety profile clearly demonstrates a favourable benefit risk balance of palbociclib plus letrozole in the first line treatment of advanced breast cancer. The sponsor therefore considers the benefit risk profile to be positive.

Delaying progression of disease represents a significant medical advance in the HR-positive, HER2-negative advanced breast cancer setting that would fill a therapeutic need in this serious life threatening condition. Palbociclib, with a selective and novel mechanism of action in combination with letrozole may address this need by delivering a 42% reduction in risk of disease progression or death and a 10.3 month median PFS improvement in the Phase III setting beyond the benefit of single agent letrozole.

Prolongation of PFS in the palbociclib plus letrozole arm was consistently observed in individual patient subgroups defined by stratification factors (that is, site of disease [visceral, non-visceral], disease-free interval since the end of the [neo] adjuvant treatment to disease recurrence [de novo metastatic, ≤ 12 months, >12 months], nature of prior [neo]adjuvant anti-cancer therapies [prior hormonal therapy, no prior hormonal therapy]),

baseline demographics (age and race) and disease characteristics (prior treatment, type of disease, and ECOG performance status), supporting the robustness and internal consistency of PFS benefit findings within the study.

The PFS treatment benefit observed based on the investigator assessment was verified by the BICR analysis. The magnitude of the difference in median PFS between treatment arms in the BICR analysis was consistent with the investigator assessment analysis. Palbociclib plus letrozole was also superior to placebo plus letrozole in the secondary endpoints of OR (including the measurable disease subset), CBR/DC, and DOR.

Furthermore, patients benefited from palbociclib plus letrozole treatment regardless of the expression status of their tumour sample for the following biomarkers: ER, Rb, p16, and Ki-67. Central laboratory confirmed ER-positive patients have shown similar PFS results compared to the ITT population.

The PRO results also support the positive benefit profile of the addition of palbociclib to letrozole in the first line setting. Addition of palbociclib to letrozole maintained health-related quality of life and no statistically significant difference in overall change from baseline in total FACT-B scores was observed compared to placebo plus letrozole. The time-to-deterioration analyses also showed no statistically significant difference between the 2 treatment arms for FACT-B, FACT-G, Breast Cancer Subscale, and Trial Outcome Index. Addition of palbociclib to letrozole maintained Physical Well Being, Social/family Well Being, Functional Well Being and Emotional Well Being with no statistically significant difference compared to the placebo plus letrozole arm. Similar results were observed for general health status as assessed by the EQ-5D, with no statistically significant difference observed between the treatment arms in the Visual Analogue Scale change from baseline scores. Importantly, these PRO results suggest that the observed toxicities of palbociclib did not detract from a patients' quality of life.

Comment on the appropriate indication, taking into account 'Issues Proposed Indication'

The sponsor proposes Ibrance be indicated as follows:

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 in combination with:

an aromatase inhibitor; with letrozole as initial endocrine therapy in postmenopausal women

with fulvestrant in ~~patients women~~ who have received prior therapy'

Additions and deletions to the indication statement are marked by underline and strikethrough.

The ASCO, ABC2, and NCCN guidelines as well as extensive publications support the interchangeability of endocrine therapies anastrozole, exemestane and letrozole.⁶⁰ For these reasons, the sponsor considers that palbociclib should be indicated in combination with endocrine therapies independent of the type of endocrine therapy for the treatment of patients with hormone receptor-positive, HER2-negative advanced or metastatic breast

⁶⁰Rugo HS, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology Guideline. J Clin Oncol 2016; 34(25):3069-103.

Partridge AH, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2014; 32(29):3307-29.

Cardoso F, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Ann Oncol 2014; 25(10):1871-88.

National Comprehensive Cancer Network. Breast Cancer. In: NCCN clinical practice guidelines in oncology (NCCN guidelines). Version 2.2016. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

cancer. Beyond the sponsor sponsored studies, more than 350 patients with breast cancer have been treated with palbociclib plus anastrozole (approximately 75), exemestane (approximately 150) or tamoxifen (approximately 150) under clinical study conditions within the cooperative CRC and IIR studies. Many of these studies, including PENELOPE and PALLAS, are still blinded and thus no additional efficacy data are currently available. Available information supports a similar safety profile with these combinations compared with those of palbociclib plus letrozole or fulvestrant studied in the Phase III studies, A5481008 and A5481023, respectively. See also sponsor's response to Question 6.

In addition, since there is no impact of a patient's gender on the PK of palbociclib and generally, the patient management of male breast cancer is based on the patient management of female breast cancer, it would be reasonable to have an indication statement not restricted to female patients. Therefore, reference to women has been removed and replaced with reference to patients. See also sponsor's response to Question 7

As the Delegate indicated that the use of the terminology 'initial endocrine-based therapy' could be open to different interpretations, the sponsor proposes to remove that wording from the indication statement.

Conclusion

The favourable benefit risk profile of palbociclib in the first line treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer has been established. Palbociclib in combination with letrozole demonstrated a magnitude of PFS benefit in the first line setting that is robust across a number of sensitivity analyses, with a striking 10.3 month PFS improvement, a median PFS of more than 2 years and 42% reduction in the risk of disease progression or death compared to letrozole alone. Prolongation of PFS was consistently shown in all pre-specified subgroups based on stratification factors, baseline demographics and disease characteristics.

Observed AEs from the combination of palbociclib and letrozole were consistent with the known safety profile of palbociclib, which has been established across 3 breast cancer registration trials, one Phase II study (A5481003) and two Phase III studies (A5481008 and A5481023) and is regardless of the combination and disease setting.

The Delegate acknowledges the well-known challenges involved in detecting a statistically significant effect on OS in first line treatment space for the target population (for example, due to off-study cross-over, use of subsequent effective therapies, long median post-progression survival etc), commenting that: '*Updated OS outcomes are needed not for the purpose of showing palbociclib's superiority, but for the purpose of helping to rule out a negative impact on OS.*' The updated interim OS analysis demonstrates a trend in benefit for the palbociclib plus letrozole arm with a HR < 1 whilst maintaining quality of life.

The sponsor considers the benefit risk balance to be positive for the use of palbociclib in the first line setting for HR-positive, HER2-negative advanced or metastatic breast cancer, and the requirements of the TGA-adopted EU guidance on anticancer medicines to be met with a median PFS of over 2 years for palbociclib plus letrozole, a 10 month improvement over placebo plus letrozole, , quality of life maintained and a generally well tolerated safety profile.

QUESTION 1 Assuming PALOMA-2's full CSR has been submitted to the FDA for evaluation, provide an update about this process, including an indication of major issues identified to date by the FDA.

Sponsor response

The full CSR for Study A5481008 (PALOMA-2) was submitted to the US FDA in a supplementary New Drug Application (sNDA) on 26 October 2016 and was accepted under Priority Review on 12 December 2016. The scope of this submission is to confirm the positive benefit risk of palbociclib plus letrozole for the treatment of ER-positive, HER2-

negative advanced breast cancer in postmenopausal women observed in PALOMA-1 Study that triggered the Accelerated Approval of IBRANCE by FDA on 3 February 2015.

The main issue raised by the US FDA during review of the application was the request for an updated interim OS analysis.

On 12 January 2017 the FDA requested the sponsor conduct an updated Overall Survival (OS) analysis for Study A5481008. The sponsor performed an interim OS analysis with a cutoff date of 24 November 2016.

Following the submission of the updated OS analysis of PALOMA-2 Study the sNDA evaluation proceeded to labelling negotiations. These are now late stage and a copy of the latest version of the draft USPI under FDA evaluation is provided. The sponsor anticipates imminent FDA consent which would convert the Accelerated Approval into Regular Approval. The TGA will be informed as soon as this occurs and provided a copy of the approved USPI.

The pending indication in the US is:

Ibrance is indicated for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with:

- *an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or*
- *fulvestrant in women with disease progression following endocrine therapy*

In order to protect the study integrity the results from this interim analysis will not be publicly reported by the sponsor. Additionally, these interim OS results are still immature and the sponsor will perform the final OS analysis when the number of protocol-specified deaths have occurred.

QUESTION 2 Discuss evidence for a clinical impact on palbociclib use of interactions with SULT inhibitors.

Sponsor response

From the [¹⁴C] PD-0332991 human ADME study approximately 26% of the administered dose was recovered as the sulfamic acid conjugate of palbociclib, indicating that the fractional contribution of SULT2A1 to the overall clearance of palbociclib (f_m) is estimated to be 0.26. This relatively low f_m value suggests that inhibition of SULT2A1 likely will result in a small change in palbociclib systemic exposure.

A literature search using the University of Washington Drug Interaction Database revealed no data on in vivo inhibitors of SULT2A1. This database identified a limited number of agents as in vitro inhibitors of SULT2A1, which include the metabolites of tamoxifen. Specifically, N- desmethyltamoxifen, endoxifen, 4-hydroxytamoxifen, and tamoxifen N-oxide can inhibit SULT2A1 activity, with K_i values ranging from 2.8 to 19.4 μ M.⁶¹ In the clinical drug-drug-interaction (DDI) study of tamoxifen and palbociclib (Study A5481026), co-administration of multiple doses of tamoxifen (60 mg QD for 4 days followed by 20 mg QD for 23 days) and palbociclib (125 mg on Day 22) increased palbociclib AUC_{inf} and C_{max} by approximately 7.77% and 16.08%, respectively, relative to a single dose of palbociclib given alone. Thus, inhibition of SULT2A1 by tamoxifen and its metabolites has no clinically significant impact on the pharmacokinetics of palbociclib, which is also consistent with the relatively low SULT2A1 f_m in the clearance of palbociclib.

Another drug identified in the University of Washington Drug-Drug Interaction Database as an in vitro inhibitor of SULT2A1 was naloxone, which had an IC50 value of 156.9

M against

⁶¹Squirewill EJ, Qin X, Duffel MW. Endoxifen and other metabolites of tamoxifen inhibit human hydroxysteroid sulfotransferase 2A1 (hSULT2A1). Drug Metab Dispos. 2014;42:1843-1850.

SULT2A1.⁶² Considering such weak inhibitory effect of naloxone and pharmacokinetics of naloxone (dosed at 0.4 to 2 mg intravenously/intramuscular/subcutaneously, with C_{max} of 957 pg/mL [or $\sim 0.003 \mu\text{M}$] after 0.4 mg intramuscular injection⁶³), it is unlikely that naloxone would have significant DDI with palbociclib due to SULT2A1 inhibition.

Therefore, of the currently known in vitro SULT2A1 inhibitors, tamoxifen did not have a clinically significant impact on the pharmacokinetics of palbociclib; while naloxone is not expected to affect the elimination of palbociclib to a clinically relevant extent.

QUESTION 3 An updated OS analysis is planned for inclusion in the Pre-ACM Response. Please include a subgroup analysis of OS by Ph2P1 vs Ph2P2.

Sponsor response

The sponsor has included a subgroup analysis of Overall Survival (OS) for Study A5481003 by Ph2P1 vs Ph2P2.

This data is presented with the TGA requested updated interim OS analysis for Study A5481008 and final OS analysis for Study.

QUESTION 4 Is it the sponsor's current understanding that palbociclib causes reversible cell cycle arrest for haematopoietic cells, but both 'cytoreductive' and cytostatic effects on tumour cells? Cytoreductive effects for a medicine imply cytotoxicity. Explain the basis for this possibly divergent mechanism of action.

Sponsor response

In preclinical studies, palbociclib demonstrated in vitro and in vivo activity against neoplasms positive for retinoblastoma tumour suppressor protein RB1, acting mechanistically to inhibit CDK4/6 activity and promote G1 cell cycle arrest, halting proliferation in a RB1 dependent manner.⁶⁴ In particular, when tested in a large panel of breast cancer cell lines, palbociclib exerted considerable activity in human ER-positive breast cancer cell lines with luminal features⁶⁵. In mouse xenograft models, palbociclib also produces significant cytostatic antitumour activity in several tumour types including ER+ breast cancer xenografts^{64,66}.

Functional analysis of ER+ breast cancer cells treated with palbociclib demonstrate that the G1 cell cycle arrest is reversible once drug is removed, and apoptosis or cell death is not a significant component of tumor cell response to palbociclib, clearly differentiating it from cell death caused by cytotoxic chemotherapeutic agents. In contrast to the reversible cell cycle arrest in response to palbociclib alone, the combination of palbociclib and estrogen receptor (ER) antagonist in ER+ breast cancer cells produces a senescence-like cell cycle arrest, significantly delaying the return to proliferation following drug removal⁶⁷. This senescence like response is tumor cell selective and demonstrates a significant contrast to the effect on bone marrow hematopoietic proliferation, where palbociclib, as single agent and in combination with ER antagonist, induces only reversible cell- cycle arrest but not

⁶² Kurogi K, Chen M, Lee Y, Shi B, Yan T, Liu MY, Sakakibara Y, Suiko M, Liu MC. Sulfation of buprenorphine, pentazocine, and naloxone by human cytosolic sulfotransferases. *Drug Metab Lett.* 2012;6:109-15.

⁶³ Edwards E, Gunn R, Kelley G, Smith A, Goldwater R. Naloxone 0.4 mg bioavailability following a single injection with a novel naloxone auto-injector, EVZIO®, in healthy adults, with reference to a 1 mL standard syringe and intramuscular needle. American Association of Physicists in Medicine Annual Meeting, Jul 2015.

⁶⁴ Fry D et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Mol. Cancer Ther.* 3: 1427-1438. 2004

⁶⁵ Finn et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor positive human breast cancer cell lines in vitro. *Breast cancer Res.* 11: R77, 2009

⁶⁶ Wardell SE, Ellis MJ, Alley HM, Eisele K, VanArsdale T, Dann SG, Arndt KT, Primeau T, Griffin E, Shao J, Crowder R, Lai JP, Norris JD, McDonnell DP, Li S. Efficacy of SERD/SERM Hybrid-CDK4/6 Inhibitor Combinations in Models of Endocrine Therapy- Resistant Breast Cancer. *Clin Cancer Res.* 2015 Nov 15;21(22):5121-30

⁶⁷ Hu W et al. Mechanistic investigation of bone marrow suppression associated with palbociclib and its differentiation from cytotoxic chemotherapies. *Clin. Cancer Res.*, 2016

cellular senescence.⁶⁷ This difference in senescence induction between normal bone marrow and ER+ breast cancer cells can be explained by differential dependence of the tumor cells for ER signaling, exploiting the synergistic induction of senescence by palbociclib and ER antagonist in a tumor specific manner. In contrast to tumor xenografts responding to cytotoxic chemotherapy regimens with clear cytoreductive effects and tumor regression, tumors responding to the combination of Palbociclib and ER antagonist remain stably arrested but do not regress due to the lack of significant tumor cell death.

This dual mechanism of action supports the differentiation between palbociclib-induced neutropenia and that caused by chemotherapeutic agents, both in the degree and time of reversibility of the effects. Moreover, this data also supports the current palbociclib schedule (3 weeks on, 1 week off), which provides time for bone marrow cells to recover during the 1 week treatment-free period without impacting tumour efficacy.^{68,67}

QUESTION 5 Submit any subgroup analyses for Studies 1008 and 1023 according to subtype of disease (luminal A vs B).

Sponsor response

The sponsor would like to clarify that in both Studies A5481008 and A5481023 no pre-planned gene-expression studies were conducted on collected tumor tissues. Thus, no subgroup analyses can be performed according to Luminal A and Luminal B subtypes.

QUESTION 6 Is there any concern about indicating first-line use also in combination with anastrozole?

Sponsor response

The sponsor has no concern about indicating first-line use also in combination with anastrozole. In addition, the sponsor further proposes extrapolation from letrozole to any aromatase inhibitor (AI), that is, letrozole, anastrozole or exemestane for the following reasons:

- The pharmacodynamic mechanism of action of all 3 AIs is very similar

The mechanism of action of all 3 AIs is very similar and occurs through the inhibition of the conversion of androgens to estrogens by blocking the aromatase enzyme.

- The potential for a clinically significant effect on palbociclib PK is low

Anastrozole

The potential for a clinically significant drug-drug interaction (DDI) between palbociclib and anastrozole is considered to be low. Anastrozole inhibited CYP1A2, 2C8, 2C9 and 3A4 in vitro with K_i values ~30-fold higher than the steady state C_{max} values observed following a 1 mg daily dose. Thus, co-administration of anastrozole is unlikely to alter the PK of palbociclib, which is primarily metabolized by CYP3A and SULT2A1. In vitro and in vivo assessments of oxidative metabolism have indicated the route formation of the primary metabolite hydroxyanastrozole is predominantly through CYP3A4. Palbociclib has the potential to inhibit the primary clearance pathway of anastrozole, thereby increasing exposure to anastrozole. However, palbociclib is only a weak CYP3A4 inhibitor in vivo, as indicated by Study A5481012 where multiple doses of palbociclib increased the total exposure (AUC_{inf}) of the sensitive CYP3A substrate midazolam 61% relative to midazolam given alone. Anastrozole is not a sensitive CYP3A4 substrate and multiple enzymes are responsible for the metabolism of anastrozole therefore any impact of palbociclib on anastrozole PK is likely to be small.⁶⁹ Additionally, the therapeutic window of anastrozole is

⁶⁸ W.Hu et al. Mechanistic investigation of neutropenia associated with palbociclib. Proceedings of AACR: abs1635, 2015

⁶⁹ Kamdem LK, Liu Y, Stearns V et al In vitro and in vivo oxidative metabolism and glucuronidation of anastrozole. Br J Clin Pharmacol. 2010 70:6; 854-869

very wide and doses far in excess of the currently recommended dose (1 mg/day) are not associated with significant toxicity. Up to 60 mg of anastrozole administered as a single dose given to healthy male volunteers and up to 10 mg daily given to postmenopausal women with advanced breast cancer were welltolerated.⁷⁰

The Phase III PENELOPE study (palbociclib plus endocrine agents in the adjuvant setting) has a cohort receiving anastrozole plus palbociclib/placebo. The first 24 patients to be enrolled in the pharmacokinetic group receiving palbociclib/placebo plus anastrozole will have pharmacokinetic samples drawn to evaluate the potential DDI between palbociclib and anastrozole.

Exemestane

Similarly, the potential for a clinically significant DDI between palbociclib and exemestane is considered to be very low. Exemestane is metabolized by CYP3A4 and aldoketoreductases. It does not inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2D6, 2E1 and 3A4. Therefore, exemestane is unlikely to affect palbociclib PK. Rifampin reduced exemestane exposure by ~50%. However, in a clinical pharmacokinetic study, coadministration of ketoconazole, a strong inhibitor of CYP 3A4, had no significant effect on exemestane pharmacokinetics.⁷¹

Therefore, it is unlikely that palbociclib, which is a weak time-dependent inhibitor of CYP3A4, will have an effect on exemestane pharmacokinetics. Similar to anastrozole, the therapeutic window of exemestane is very wide and doses far in excess of the currently recommended dose (25 mg/d) are not associated with significant toxicity. At the dose levels ranging from 25 to 200 mg/d, the most commonly occurring AEs with exemestane treatment are similar including Nausea, Hot flushes, Fatigue, Increased sweating, and Dizziness. The maximum tolerated dose of exemestane has not been identified because of a lack of Grade 3 or 4 treatment-related toxicity even at daily doses up to 600 mg/d.⁷² During clinical trials a daily dose of 200 mg/d was associated with some androgenic effects in a small proportion of patients (alopecia, hypertrichosis, hoarseness, hirsutism, and acne) but was otherwise well tolerated.⁷³ Therefore, any effect of palbociclib on the PK of exemestane would likely be minor and not of any clinical significance.

One ongoing collaborative investigator initiated study, PEARL (Spanish Breast Cancer Research Group, NCT02028507), combines exemestane 25 mg PO QD (continuously) with palbociclib 125 mg PO QD for Days 1 to 21 followed by 7 days off treatment on every 28 day cycles (n=178). In this study, sparse pharmacokinetic sampling of exemestane and palbociclib is included to confirm lack of a clinically significant DDI. The palbociclib results will be compared with historical controls to assess for major differences in pharmacokinetics. Exemestane results will be compared within each patient for major differences in pharmacokinetics (due to large variability in historical reports).

Please refer the Clinical Overview supporting the submission of the Study A5481008 CSR for a more comprehensive discussion about the DDI Potential between Palbociclib and the Aromatase Inhibitors.

⁷⁰ Arimidex Product Information

⁷¹ Aromasin Product Information

⁷² Paridaens R, Thomas J, Wildiers J, Vermeiren P, Lobelle JP, di Salle E, Ornati G, Zurlo MG, Polli A, Lanzalone S, de Belder K. Safety, activity and estrogen inhibition by exemestane in postmenopausal women with advanced breast cancer: a phase I study. *Anticancer Drugs*. 1998 Sep;9(8):675-83.

⁷³ Clemett D, Lamb HM. Raloxifene: a review of its use in postmenopausal osteoporosis. *Drugs*. 2000 Aug;60(2):379-411

Thürlimann B, Paridaens R, Serin D, Bonnetterre J, Roché H, Murray R, di Salle E, Lanzalone S, Zurlo MG, Piscitelli G Third-line hormonal treatment with exemestane in postmenopausal patients with advanced breast cancer progressing on aminoglutethimide: a phase II multicentre multinational study. *Exemestane Study Group. Eur J Cancer*. 1997 Oct;33(11):1767-73.

- AIs are used interchangeably in clinical practice depending on individual patient tolerability

The European School of Oncology-European Society for Medical Oncology (ESO-ESMO) 2nd International Consensus Guidelines for Advanced Breast Cancer (ABC2), the ASCO Clinical Oncology Clinical Practice Guidelines and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology and nonclinical and pharmacology evidence supports the interchangeability of endocrine therapies. While the AIs letrozole, anastrozole and exemestane are indicated for first line treatment of postmenopausal women with HR-positive locally advanced or metastatic breast cancer, the choice of specific endocrine therapy is often driven by the individual patient's prior adjuvant endocrine therapy, time to progression on prior therapy and tolerance of the therapies' known potential side effects.

In summary, the sponsor believes the extensive Phase III trial literature and published clinical practice guidelines support the interchangeability of aromatase inhibitors (letrozole, anastrozole, and exemestane) administered as single agents within the hormone-sensitive and hormone-resistant treatment continuum of HER2-negative advanced/metastatic breast cancer. Based on the discussion above, the scientific assessment supporting minimal potential for clinically significant DDI between aromatase inhibitors and palbociclib, and the broad ongoing clinical experience with palbociclib in combination with aromatase inhibitors, the sponsor proposes to replace 'letrozole' with 'aromatase inhibitor' in the Indication section of the PI:

'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 in combination with:

- an aromatase inhibitor; with letrozole as initial endocrine therapy in postmenopausal women
- with fulvestrant in patients women who have received prior therapy'

Please also see the Response to Question 7.

QUESTION 7 Is there any concern about having an indication not specifically restricted to women?

Sponsor response

Male breast cancer is a rare disease, accounting for less than 1% of all malignancies in men and less than 1% of all incidents of BC.⁷⁴ In 2014, 2,360 new cases were diagnosed in the United States and approximately 430 men died from this disease⁷⁵. The vast majority of the male breast cancer patients are elderly, have HR-positive/HER2-luminal B disease, and more frequently present with advanced or metastatic disease. Due to the rarity of the disease, there have been no randomised, controlled trials of male breast cancer in literature as any prospective, randomised study would take years to recruit patients. Thus, the management of male breast cancer is often extrapolated from female breast cancer trials.

As summarised in the Study A5481008 Summary of Clinical Pharmacology, a population pharmacokinetic (PK) analysis for palbociclib was conducted to describe the population PK of palbociclib in patients with advanced cancer and to identify significant covariates which affect palbociclib PK. The population PK analysis for palbociclib was conducted based on 1933 PK observations from 183 patients (50 males and 133 females) with advanced cancer enrolled in 3 clinical trials; Studies A5481001, A5481002, and A5481003. The impact of a

⁷⁴ Fentiman I, Fourquet A, Hortobagyi GN. Male breast cancer. Lancet 2006; 367: 595–604.

⁷⁵ American Cancer Society Facts & Figures 2015. Accessed at: <http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2015/>.

patient's gender (male versus female) on palbociclib PK was evaluated and gender was found not to have a significant effect on the PK of palbociclib.

In summary, as there is no impact of the patient's gender on the PK of Palbociclib and generally, the patient management of male breast cancer is based on patient management of female breast cancer, it would be reasonable to have an indication statement not restricted to female patients.

QUESTION 8 Has an analysis of time to response, including a subgroup analysis based on site of disease, been conducted in Study 1008?

Sponsor response

The only analysis of time to tumour response conducted by the sponsor based on disease site was for patients with visceral disease versus patients without visceral disease. The time to tumour response was defined as time from date of randomisation to date of first objective response (Partial Response [PR] or Complete Response [CR] per RECIST v1.1). A summary of time to response for these 2 subgroups among patients who had a PR or CR (confirmed and unconfirmed) is presented in Table 19.

Table 19: Study 5481008-Time to tumour response (PR/CR, confirmed and unconfirmed)

	Palbociclib plus Letrozole [□]	Placebo plus Letrozole
Overall Population, N [□]	206 [□]	85 [□]
Median (Range) -- months [□]	3.0 (2.0, 27.8) [□]	5.3 (2.6, 22.2) [□]
Visceral ^a Subgroup, N [□]	126 [□]	50 [□]
Median (Range) -- months [□]	5.4 (2.0, 19.4) [□]	4.1 (2.6, 16.6) [□]
Non-Visceral ^b Subgroup, N [□]	80 [□]	35 [□]
Median (Range) -- months [□]	2.9 (2.1, 27.8) [□]	5.5 (2.6, 22.2) [□]

Source: Tables 1008.4021.2; 1008.4068.9[¶]

N=number of patients with a partial or complete response[¶]

^aVisceral subgroup refers to patients with any lung (including pleura) and/or liver involvement[¶]

^bNon-visceral subgroup refers to patients without lung (including pleura) and/or liver involvement[¶]

Of note, patients with critical visceral disease or visceral crisis were not eligible to enrol into Study A5481008.

QUESTION 9 For studies 1064 and 1027, are any interim CSRs planned, that may allow assessment of efficacy / safety information earlier than the dates noted above?

Sponsor response

Study A5481027 is a randomised, double-blind, placebo-controlled, parallel-group, Phase 3 clinical trial comparing the efficacy and safety of palbociclib in combination with letrozole versus placebo in combination with letrozole in postmenopausal Asian women with ER-positive/HER2-negative advanced breast cancer. Of note, the design of Study A5481027 is very similar to that of Study A5481008 (PALOMA-2).

The study is designed to have one interim analysis (IA) and the final analysis based on the primary PFS endpoint. The IA will be performed after approximately 139 patients have documented progressive disease or die (approximately 65% of the total events expected). The purposes of the interim analysis are to allow early stopping of the study for efficacy, and to assess safety of the combination regimen in Asian women.

Based on current PFS events rate projections, the IA cutoff date is estimated to be by 31-May-2017 and the IA CSR is planned to be available in the first quarter of 2018, if the study

met the primary endpoint at the time of IA. It should be noted that the actual IA data cutoff date is event-driven and thus these timelines are subject to changes.

Study A5481064 is a non-interventional, retrospective medical record review of patients with postmenopausal HR-positive/HER2-negative metastatic breast cancer who were previously enrolled in the Expanded Access Study A5481034 in the US. No interim analysis is planned.

Advisory Committee Considerations

The ACM taking into account the submitted evidence of efficacy, safety and quality, considered Ibrance capsules containing 75 mg, 100 mg and 125 mg of palbociclib to have an overall positive benefit-risk profile for the amended indication:

Ibrance is 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:

- *an aromatase inhibitor as initial endocrine-based therapy*
- *fulvestrant in patients who have received prior therapy.*

In making this recommendation the ACM:

- was of the view that the inclusion in the first-line indication of premenopausal women was acceptable; in these patients an aromatase inhibitor would be combined with ovarian function suppression.
- was of the view that inclusion of men in the first-line and second-line treatments was appropriate, given the same disease process in men and women.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine information (CMI) and specifically advised that the PI should be amended to reflect that patients will include women and men.

Specific Advice

The ACM advised the following in response to the delegate's specific questions on the submission:

1. *Please comment on the immature OS outcomes available in Study 1008. Please specifically consider updated OS outcomes if they are included in the sponsor's Pre-ACM Response document.*
 - a. *In the context of other efficacy and safety outcomes, are the reported OS outcomes and the degree of OS data maturity in PALOMA-2 considered acceptable, for approval of the first-line use?*

The ACM advised that the current data maturity from PALOMA-2 is acceptable for approval of the first-line use, given:

- the large statistically significant Progression Free Survival (PFS) benefit
- early Overall Survival (OS) data trending towards benefit (or at least not showing detriment), with the current Hazard Ratio less than 1

- although toxicities are common and require monitoring, the majority are low grade and not detrimental to Quality of Life (QoL). Level of toxicities, impact of dose delays or reductions, and impact on QoL are still less than that experienced with cytotoxics.

The ACM noted that mature data on OS will not be available until November 2020.

- b. Is there any concern that PFS benefit will not translate into an OS benefit for patients in the first-line setting?*

The ACM advised that multiple other lines of subsequent treatment and relatively long post-progression survival may impact this. The final OS data should include information on the number of subsequent lines of therapy, but this was unlikely to have a deleterious effect on OS. At this time there are no signs from toxicity data to raise concerns.

2. *Should Study 1003 be viewed as pivotal, or as supportive? (If it can be viewed as pivotal, its OS outcomes – trending towards no evidence of harm – should be given more weight. Updated outcomes for Study 1003, proposed for inclusion in the Pre-ACM Response by the sponsor, are likely to be ‘mature’.)*

The ACM advised that Study 1003 should be viewed as supportive. This study had a small number of patients (84 in the treatment group). It was also open-label and there was discordance between the Investigator Assessment and Blinded Independent Central Review of PFS (in the ITT population).

3. *Is there evidence of clinical benefit in the targeted first-line population, when efficacy and safety outcomes are taken into account? Please discuss how the major efficacy endpoints should be viewed as a whole, to inform consideration of clinical benefit (PFS; OS; ORR [DoR] / stable disease / PD; QoL).*

The ACM advised that clinical benefit was demonstrated in the median PFS of 24.8 months (versus 14.5 months) and the updated interim analysis suggest the OS hazard ratio below 1. Also, in the targeted first-line patient population with minimal symptoms, QoL was maintained (and in this patient group there is minimal scope to improve QoL).

The rate of clinical benefit response was 84.9% versus 70.3% in favour of the palbociclib group in PALOMA 2.

4. *Is benefit-risk balance in the proposed first-line use favourable? If so, please comment on the appropriate indication, taking into account issues raised under ‘Issues – Proposed Indication’ in the main body of the overview.*

The ACM advised that in view of the large PFS benefit, supported by an updated OS hazard ratio below 1, and a manageable toxicity profile, the data suggested a positive benefit-risk balance for first-line use.

The ACM advised that ‘with aromatase inhibitor as initial endocrine based therapy’ should be used to describe the first-line combination therapy. It was not necessary to limit the aromatase inhibitor to letrozole.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Ibrance (palbociclib) 75 mg, 100 mg and 125 mg capsule in bottle and blister pack, for oral administration, indicated for:

Ibrance is 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:

- *an aromatase inhibitor as initial endocrine-based therapy*

- *fulvestrant in patients who have received prior therapy.*

Specific conditions of registration applying to these goods

The Ibrance EU-RMP, version 1.3, dated 11 September 2016, data lock point 4 March 2016), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Ibrance approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the [TGA website](https://www.tga.gov.au/product-information-pi) at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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<https://www.tga.gov.au>