Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ribociclib succinate

Proprietary Product Name: Kisqali

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

June 2020

TGA Health Safety Regulation

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Contents

Common abbreviations

Abbreviation	Meaning
$5HT_3$	5-hydroxytryptamine (serotonin) 3 receptor subtype
ABCB1	ATP binding cassette subfamily B member 1
ACM	Advisory Committee on Medicines
ADR	Adverse drug reaction
AE	Adverse event
AI	Aromatase inhibitor
AIHW	Australian Institute of Health and Welfare
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific Annex
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
ATP	Adenosine triphosphate
AUC	Area under the drug concentration-time curve
$AUC_{0\text{-}24h}$	Area under the drug concentration-time curve in plasma from time zero to 24 hours
$AUC_{0\text{-}inf}$	Area under the drug concentration-time curve from dosing extrapolated to infinity
BBB	Blood brain barrier
BICR	Blinded independent central review
BRCP	Breast cancer related protein
BrdU	Bromodeoxyuridine (assay)
BSA	Body surface area
cAMP	Cyclic adenosine monophosphate
CCI284	Major ribociclib metabolite in humans

Abbreviation	Meaning
CDK	Cyclin dependant kinase
CDKi	Cyclin dependent kinase inhibitor
CHMP	Committee for Medicinal Products for Human Use (EU)
CI	Confidence interval
C_{max}	Maximum serum concentration
$C_{max,unbound}$	Maximum unbound serum concentration
CMI	Consumer Medicines Information
CNS	Central nervous system
CR	Complete response
$C_{trough,unbound}$	Minimum unbound serum concentration
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Scale
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency (EU)
EORTC QLQ C30	European Organization for Research and Treatment of Cancer Quality of Life (Core) Questionnaire
ER	Oestrogen receptor
ESMO	European Society for Medical Oncology
EU	European Union
FBE	Full blood examination
FDA	Food and Drug Administration (USA)
FMO3	Flavin containing monooxygenase 3
f_u	Fraction unbound (in plasma)
GIT	Gastrointestinal tract
GMR	Geometric mean ratio
HER2	Human epidermal growth factor receptor 2

Abbreviation	Meaning
hERG	Human Ether-à-go-go-related gene
HR	Hormone receptor
IC_{50}	Half maximal inhibitory concentration
IV	Intravenous
K-M	Kaplan-Meier
K^+	Potassium ion
K_i	Inhibitory constant
K_{inact}	Rate of inactivation
K_m	Michaelis constant
LAMP2	Liposome associated membrane protein 2
LC-MS	Liquid chromatography mass spectrometry
LEE011	Ribociclib succinate (drug development name)
LEQ803	Major ribociclib metabolite in humans
LFT	Liver function test
MCF7	Michigan Cancer Foundation 7 breast cancer cell line
MCV	Mean corpuscular volume
MDR1	Multidrug resistance protein 1
ms	Millisecond(s)
MXR	Mitoxantrone resistance protein
$Na_v1.5$	Cardiac sodium channel
NCCN	National Comprehensive Cancer Network (USA)
NCTP	Sodium/taurocholate co-transporting polypeptide
NE	Not estimable
NMT	Not more than
NSAI	Non-steroidal aromatase inhibitor
OAT	Organic anion transporter

Abbreviation	Meaning
OATP	Organic anion transporter polypeptide
OCT	Organic cation transporter
ORR	Overall response rate
OS	Overall survival
P-gp	P-glycoprotein
PBS	Pharmaceutical Benefits System
P450	Cytochrome P450 system enzyme
PD	Progressive disease
PDE	Phosphodiesterase
PDE4	Phosphodiesterase 4 subtype
PDE4D	Phosphodiesterase 4D subtype
PFS	Progression free survival
PI	Product Information
PI3K	Phosphoinositide 3-kinase
PopPK	Population pharmacokinetic(s)
PPI	Proton pump inhibitor
PR	Partial response
PSUR	Periodic safety update report
PVC	Premature ventricular contractions
QT	QT interval; 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
QTc	Corrected QT interval; QTc is the QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Frederica's formula
Rb	Retinoblastoma protein
RMP	Risk management plan
SCID	Severe combined immunodeficient

Abbreviation	Meaning
SD	Stable disease
SERD	Selective oestrogen receptor down regulator
SERM	Selective oestrogen receptor modifier
$t_{½}$	Half life
TBL	Total bilirubin
t_{last}	Time of last measured concentration
t_{max}	Time of maximum observed concentration
ULN	Upper limit of normal
US(A)	United States (of America)
UV	Ultraviolet
V_d	Volume of distribution
VMAT2	Vesicular monoamine transporter 2
V_{max}	Maximum velocity
VT	Ventricular tachycardia

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	20 October 2017
Date of entry onto ARTG	23 October 2017
Active ingredient:	Ribociclib succinate
Product name:	Kisqali
Sponsor's name and address:	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Rd Macquarie Park NSW 2113
Dose form:	Film coated tablet
Strength:	200 mg
Container:	Blister pack
Pack size:	21 tablets, 42 tablets and 63 tablets
Approved therapeutic use:	*Kisqali in combination with an aromatase inhibitor is indicated for the treatment of men and postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer, as an initial endocrine-based therapy.*
Route of administration:	Oral
Dosage:	Treatment with Kisqali should be initiated by a physician experienced in the use of anticancer therapies. Monitoring for adverse drug reactions (ADRs) is required, including complete blood counts, LFTs, serum electrolytes, and ECG; dose modification (delay, reduction) or cessation may be required. The recommended starting dose of Kisqali in the general target population is 600 mg (3 x 200 mg film coated tablets) taken orally, once daily for 21 consecutive days, followed by 7 days off treatment, resulting in a complete cycle of 28 days. An aromatase inhibitor is taken daily throughout the 28 day cycle. See the Product Information (PI) available as Attachment 1 for further details.
ARTG number:	280246

Product background

This AusPAR describes the application by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register Kisqali ribociclib succinate. The proposed indication for ribociclib is:

> *Kisqali in combination with letrozole is indicated for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy.*

The dosage form proposed is a film coated tablet containing 200 mg of ribociclib base presented in a blister pack. This is the only tablet strength proposed.

Drug class and proposed usage

Ribociclib succinate (also referred to under the drug development name LEE011 in the submitted studies) is described in the sponsor's cover letter as a '*novel cyclin dependent kinase inhibitor (CDKi)*' that is an '*orally bioavailable, highly selective, small molecule inhibitor of cyclin dependent kinases (CDK) 4 and 6*'.

Cyclin dependent kinase inhibitors (CDKi) are a new class of anti-neoplastic agent. They are postulated to target cyclin dependent kinases (CDK) involved in the regulation of the cell cycle, thereby limiting cell proliferation. There are currently 3 CDKi under investigation: palbociclib, ribociclib and abemaciclib. The first in class of these agents to receive regulatory approval was palbociclib, which received accelerated approval from the United States (US) Food and Drug Administration (FDA) in February 2015. No CDKi had received regulatory approval by the TGA as of January 2017.[1]

The sponsor proposes that it be used in combination with the non-steroidal aromatase inhibitor (NSAI), letrozole, in postmenopausal women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer as '*initial endocrine based therapy*'.

In Australia, marketing authorisations for letrozole2.5 mg tablets are held by 4 sponsors. The current TGA approved indication for letrozole is:

> *'For the treatment of postmenopausal women with hormone receptor positive breast cancer (see 'Clinical Trials').*
>
> *The safety and efficacy of neoadjuvant use of letrozole has not been established. Letrozole is not indicated in hormone receptor negative disease'.*[2]

Breast cancer in the Australian context

According to the Australian Institute of Health and Welfare (AIHW), there were an estimated 16,084 new cases of breast cancer (including 150 males, 0.9%) in 2016.[3] The incidence showed a steep age gradient, with relatively low incidence rates before the age of 45 years and peak incidence rates in the age group of between 65 to 69 years. Approximately 75% of cases occur in women approaching menopause or postmenopausal (aged 45 years or more). Australian data from 2008 to 2012 indicates an overall 5 year survival rate of 90%.

Breast cancer is the second leading cause of cancer related death in Australian women, accounting for 15.5 per cent of all cancer deaths in women. It is estimated that 3,046 Australian women will die due to breast cancer in 2016.

[1] Palbociclib was registered with the TGA in May 2017.
[2] Approved Australian PI for Letrozole; TGA, Canberra.
[3] Australian Institute of Health and Welfare Breast Cancer; 2016.

Current treatment options

The molecular subtype and menopausal state is used to guide targeted therapy. In postmenopausal women patients with metastatic HR+ breast cancer, endocrine therapy is generally recommended as first line treatment.[4,5,6] Chemotherapy is reserved for cases of rapidly progressive disease or proven endocrine resistance. Three (3) classes of endocrine therapies are available:

- selective oestrogen receptor modifiers (SERMs), such as tamoxifen, which directly bind to the oestrogen receptor (ER) and block its transcriptional activity
- selective oestrogen receptor down regulators (SERDs), such as fulvestrant, which bind to ER and induce its degradation
- aromatase inhibitors (AIs), such as letrozole, anastrozole, and exemestane, which reduce the production of oestrogen via inhibition of the aromatase enzyme in peripheral tissues and within the tumour itself

The European Society for Medical Oncology (ESMO) Breast Cancer Guidelines notes that the preferred first line endocrine therapy for postmenopausal women depends on the type and duration of adjuvant endocrine therapy and that currently available data support the use of an aromatase inhibitor, tamoxifen, or fulvestrant. Current recommended first line therapy(ies) according to guidelines are shown in Table 1, below.[4,5,6]

Table 1: Guidelines for the first-line treatment of metastatic HR positive/HER2 negative breast cancer in postmenopausal women

Guideline developer and year	Recommendations for metastatic HR+, HER2– breast cancer in postmenopausal women
ASCO 2016	Hormone therapy should be offered to patients whose tumours express any level of estrogen and/or progesterone receptors. Postmenopausal women with HR positive metastatic breast cancer (MBC) should be offered aromatase inhibitors (AIs) as part of first-line endocrine therapy. Combination hormone therapy with a nonsteroidal AI and fulvestrant may be offered for patients with MBC without prior exposure to adjuvant endocrine therapy. A nonsteroidal AI and palbociclib may be offered to postmenopausal women with treatment naive HR positive MBC, because progression free survival (PFS) but not overall survival (OS) was improved compared with letrozole alone.
ESO-ESMO 2014	The preferred first line endocrine therapy for postmenopausal patients is an aromatase inhibitor or tamoxifen, depending on the type and duration of adjuvant endocrine therapy. Fulvestrant (high dose) is also an option.

[4] ESO-ESMO Second International Consensus Guidelines for Advanced Breast Cancer (ABC2) published simultaneously in The Breast 2014, and Ann Oncol 2014; 25.
[5] National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2016 Breast Cancer
[6] Rugo H et al. Endocrine Therapy for Hormone Receptor–Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline 2016. *J Clin Oncol* 34: 3069-3103.

Guideline developer and year	Recommendations for metastatic HR+, HER2– breast cancer in postmenopausal women
NCCN 2016	First line therapy of endocrine therapy of aromatase inhibitor (non-steroidal: anastrozole or letrozole; steroidal: exemestane) or selective ER modulators (tamoxifen or toremifene) or selective ER down-regulator (fulvestrant) continued until progression or unacceptable toxicity. The combination therapy of palbociclib with letrozole may also be considered for first line therapy.

The first in class CDKi compound, palbociclib, was approved in the USA under accelerated approval in 2015, based on progression free survival (PFS) results of a Phase II trial (NDA 207103). Palbociclib was later included in the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines, both updated in 2016 (Table 1).

Treatment options in Australia

The 2008 guideline available on the Cancer Australia website, *Recommendations for use of endocrine therapy for the treatment of hormone receptor-positive advanced breast cancer*, recommends third generation aromatase inhibitors in preference to tamoxifen as first-line treatment.[7]

Of the first line endocrine therapy options described above, those available to women in Australia are limited by TGA approval and Pharmaceutical Benefits System (PBS) funding. As of November 2016, tamoxifen, toremifene, letrozole and anastrozole are all approved by the TGA for first line use in the treatment of postmenopausal women with advanced HR+ breast cancer and all 4 agents are listed on the PBS. Exemestane and fulvestrant have been approved by the TGA for second line use. Exemestane is funded by the PBS but within strict clinical criteria: patients who are not premenopausal, have HR+/HER2- metastatic breast cancer and are receiving everolimus concurrently. Palbociclib is not currently included on the Australian Register of Therapeutic Goods (ARTG).

The proposed indication is for ribociclib in combination with letrozole. As noted above, letrozole is approved by the TGA (and funded by the PBS) for the treatment of HR+ breast cancer, including first line therapy in postmenopausal women.

Endocrine therapy resistance

Endocrine therapy may provide effective disease control and induce tumour responses in a proportion of patients with metastatic HR+ breast cancer. However, this therapy is not curative and the majority of patients will progress during endocrine therapy and some patients may fail to respond to initial therapy.

The mechanism or mechanisms by which endocrine resistance develops are poorly understood and the mechanism or mechanisms by which each of the 3 classes of anti-oestrogen therapy develop resistance may differ. Current thinking is that the ER is a key player in a complex network of signalling pathways that lead to proliferation and survival of cancer cells and that combinations of endocrine therapy with other agents that target other signalling pathways may offer benefit.[8] Combinations that have been, or are

[7] Recommendations for use of endocrine therapy for the treatment of hormone receptor positive advanced breast cancer: A Clinical Practice Guideline Developed by National Breast and Ovarian Cancer Centre (NBOCC).
[8] Milani A et al. Overcoming endocrine resistance in metastatic breast cancer: Current evidence and future directions. *World Journal of Clinical Oncology*. 2014; 5: 990-1001.

currently being, explored include exemestane and the mTOR inhibitor everolimus; letrozole and lapatinib; letrozole or tamoxifen or fulvestrant and the first in class CDKI palbociclib; tamoxifen or fulvestrant and another CDKi abemaciclib; tamoxifen and the phosphoinositide 3-kinase (PI3K) inhibitor buparlisib; and the combination in this submission, letrozole and ribociclib.

Synergy between CDK4/6 selective inhibitors and ER antagonists in blocking proliferation of ER+ breast cancer tumour cells is expected. Cyclin D1 is the regulatory subunit for CDK4 and is also a transcriptional target of the ER. Overexpression of cyclin D1 may act as a driver of tumour growth and may be one mechanism for endocrine drug resistance in ER+ breast cancer.

The first in class of the CDK inhibitors to receive regulatory approval was palbociclib. This agent was given accelerated approval by the FDA in February 2015 for combination use with letrozole as initial endocrine based therapy in postmenopausal women with HR+, HER2- advanced breast cancer. An expanded indication was granted in February 2016 for palbociclib in combination with fulvestrant for the treatment of advanced breast cancer that had progressed following endocrine therapy.[9] A third CDKi, abemaciclib is currently being investigated.The FDA has designated abemaciclib as a breakthrough therapy for patients with advanced breast cancer and a Phase III trial of abemaciclib in combination with fulvestrant in women with HR+, HER2- locally advanced or metastatic breast cancer (the MONARCH-2 trial) is due for completion in 2017.[10]

Unmet need

According to the sponsor 'endocrine resistance in advanced HR+ breast cancer, and consequently progression of disease remains a critical problem in the first line treatment of these patients. Therefore, there is an unmet medical need to develop better therapeutic options to prolong endocrine sensitivity, particularly in the metastatic setting'. According to the Clinical Overview, 'Co-targeting the estrogen receptor with other key intracellular proliferation and cell survival signalling pathways reflects a viable strategy to enhance first-line endocrine responsiveness'.[11]

Regulatory status

At the time the TGA considered this application, similar applications had been submitted to the US FDA on 29 August 2016 and to the European Medicines Agency (EMA) in the European Union (EU) on 5 September 2016.

The FDA approved Kisqali on 13 March 2017 for the following indication:

> *Kisqali is a kinase inhibitor indicated in combination with an aromatase inhibitor as initial endocrine based therapy for the treatment of postmenopausal women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER) negative advanced or metastatic breast cancer.*

The EMA's Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on 22 June 2017 for the following indication:

> *Kisqali in combination with an aromatase inhibitor is indicated for the treatment of postmenopausal women with hormone receptor (HR) positive, human epidermal*

[9] Clarification: ribociclib was approved by the FDA in March 2017, based on the Phase II study MONALEESA-2. FDA granted a priority review and breakthrough therapy designation.
[10] Clarification: abemaciclib, was recently approved in September 2017 in the US
[11] Clarification: palbociclib was not approved in Australia at the time that Novartis lodged their marketing authorisation application for Kisqali (September 2016). Palbociclib was later approved in May 2017

growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer as initial endocrine based therapy.

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 23 October 2017.

Product Information

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

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR

Table 2: Registration timeline

Description	Date
Submission dossier accepted and first round evaluation commenced	31 October 2016
First round evaluation completed	21 April 2017
Sponsor provides responses on questions raised in first round evaluation	11 May 2017
Second round evaluation completed	4 July 2017
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	4 July 2017
Sponsor's pre-Advisory Committee meeting response	18 July 2017
Advisory Committee meeting	4 August 2017
Registration decision (Outcome)	20 October2017
Entry onto the ARTG	23 October 2017
Number of TGA working days from submission dossier acceptance to registration decision *	231

* Statutory timeframe for applications: 255 working days.

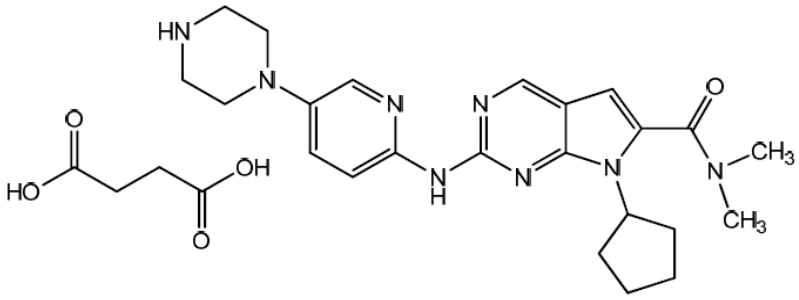
III. Quality findings

Drug substance (active ingredient)

Ribociclib succinate is a synthetic drug. It is not chiral and does not show isomerism. Ribociclib is structurally related to another CDKi, palbociclib, which was not registered in

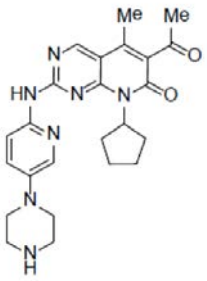
Australia at the time of the review of Ribociclib marketing authorisation application Figures 1 and 2, shown below, give the skeletal structure of ribociclib succinate, along with that of palbociclib.

Figure 1: Skeletal structure of the ribociclib succinate molecule



Ribociclib succinate: $C_{23}H_{30}N_8O.C_4H_6O_4$; Molecular weight: 552.64.

Figure 2: Skeletal structure of palbociclib



palbociclib

Ribociclib succinate is a light yellow to brown crystalline powder. It is basic (pKa value of 5.3 and 8.5). Ribociclib succinate is freely soluble in acidic solutions but solubility decreases with increasing pH and has low solubility in neutral solutions.

The particle size is adequately controlled. The impurity limits are acceptable.

Drug product

The tablets are film coated, round, unscored, light greyish violet and debossed with 'RIC' on one side and 'NVR' on the other side. They contain 200 mg ribociclib (as the succinate) with conventional excipients and coated with proprietary film coats. Blister packs of 21, 42 and 63 tablets are proposed.

The impurity profile is controlled in the tablet specifications and the proposed limit has been toxicologically qualified.

Dissolution of the tablets is controlled by an in vitro dissolution test.

There were no significant changes detected in stability trials data, which supported the proposed shelf life of 24 months when stored below 30°C.[12]

[12] Clarification; the shelf life was assessed at the time of submission; however, it may have been revised as the result of later variation applications.

Biopharmaceutics

Absolute bioavailability

An absolute bioavailability study was not provided at the time of submission. The sponsor stated that such a study was planned (Study CLEE011A2117). This has not been evaluated by the pharmaceutical chemistry evaluator. The absence of an absolute bioavailability studies is considered a clinical matter.

Formulations

Clinical studies were conducted with a capsule formulation. A 200 mg film coated tablet was developed for commercial production (as described above). The tablet was shown to be bioequivalent to the capsule formulation when administered under fasting conditions (Study A2103 Part 1: maximum serum concentration (C_{max}) geometric mean ratio (GMR) = 1.01, 90% confidence interval (CI): 0.869, 1.17; area under the drug concentration-time curve from dosing extrapolated to infinity ($AUC_{0\text{-}inf}$) GMR = 0.937, 90% CI: 0.885, 0.991). An oral solution formulation was also used in a Phase I dose escalation study.

Relative bioavailability

The extent of absorption of an oral solution and capsule formulation suggested no substantial difference in oral bioavailability between the two formulations (Study X2010, Phase I dose escalation study). This study has not been evaluated in detail.

Food effect

Study A2103 showed that, following a high fat, high calorie meal, there was no food effect on the extent and rate of ribociclib absorption for the tablet formulation (C_{max} GMR = 1.00, 90% CI: 0.898, 1.11 and AUC_{inf} GMR=1.06, 90% CI: 1.01, 1.12).). Food did however decrease metabolite LEQ803 C_{max} by 15.5% and delayed the time to maximum concentration (t_{max}) by 1 hour, but did not affect the overall exposure.

Quality summary and conclusions

There are some outstanding minor matters regarding the Product Information (PI) and labels but these are expected to be easily resolved. Registration is recommended with respect to chemistry, quality control and biopharmaceutic aspects.

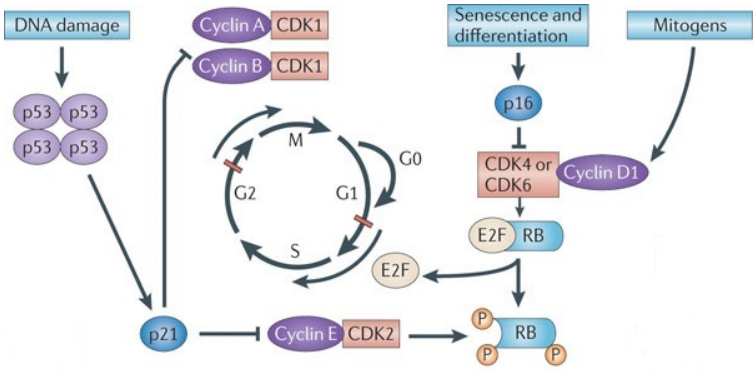
IV. Nonclinical findings

Introduction

Cell cycle progression is a tightly controlled process which is modulated by multiple checkpoints. The retinoblastoma protein (Rb) is an important checkpoint protein for G1 to S phase transition (G1 restriction point). The association between Rb and the E2F family of transcription factors prevents entry into the S phase in the absence of growth stimuli (that is, G1 restriction). For cell cycling to occur D-cyclins are synthesised which then activate CDK4/6. Once activated, CDK4/6 phosphorylate Rb inactivating it which, in turn, releases E2F which then directs the transcription of the genes needed for DNA synthesis resulting

in cell cycle progression from the M (or G_0) phase past the G1 restriction point as shown in Figure 3.[13]

Figure 3: Role of CDK4/6 in the cell cycle

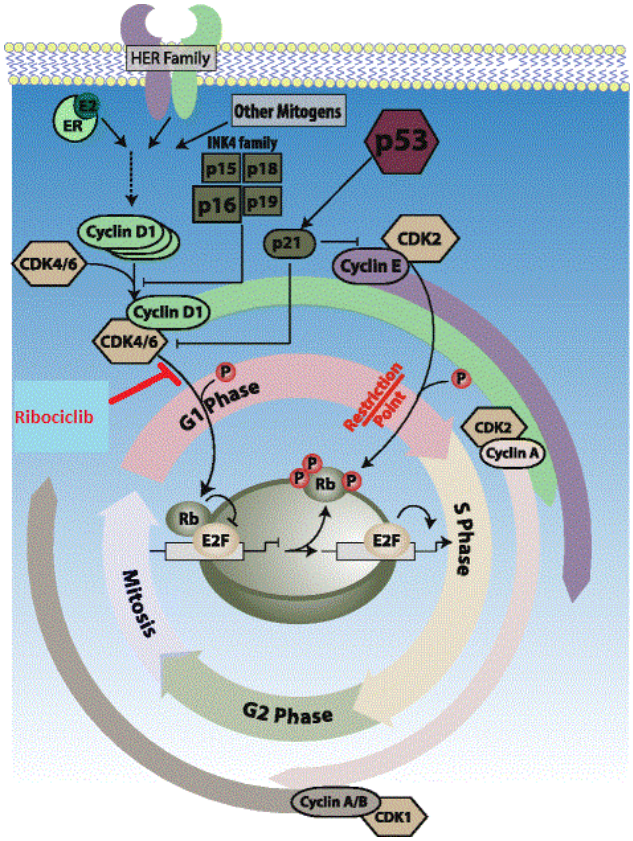


Neoplastic evasion of the G1 restriction point may occur via loss or mutation of Rb, amplification of cyclin D1 or CDK4, over activation of CDK4, or loss of endogenous CDK4 inhibitors (P16, CDKN2A). A proportion of breast cancers have dysregulated CDK4/ cyclin D1/ Rb interactions and cell lines from these cancers have overexpressed cyclin D1 or P16 alterations. Growth arrest of ER+ breast cancer cells due to anti-oestrogen therapy may act via decreased cyclin D1 and decreased Rb phosphorylation. Resistance to this therapy is associated with cyclin D1 overexpression and Rb phosphorylation. Cyclin D1 also activates the ER independently of oestrogen, creating another escape mechanism in the presence of anti-oestrogen therapy. Accordingly, treatment with selective CDK4/6 inhibitors such as ribociclib in combination with anti-oestrogen therapy may inhibit the growth of ER+ advanced or metastatic breast cancer and reduce the risk of resistance to anti-oestrogen therapy, with the mechanism shown in Figure 4.[14]

Critically, ribociclib is not selective for breast cancer cells; it will trigger cell cycle arrest at the G1 restriction point in many replicating cell types. Any dividing cell is potentially susceptible to ribociclib induced G1 restriction point inhibition of cell cycling and tissues with rapidly dividing cell subpopulations (for example, bone marrow, epithelia) will be the first affected. However, because ribociclib is largely cytostatic, rather than directly cytotoxic or directly pro-apoptotic, its adverse effects may be less than those associated with the classical radiomimetic cytotoxic anticancer drugs.

[13] Figure modified from Leemans C et al .2011 *Nature Reviews Cancer* 11**:** 9-22
[14] Figure modified from Finn R et al. 2016 *Breast Cancer Research*. 18:17

Figure 4: Proposed mechanism of action for ribociclib



Pharmacology

Primary pharmacology

The nonclinical data provides basic proof of the concept that ribociclib is a CDK4/6 inhibitor and cytostatic agent against ER+, HER2-, Rb+ neoplasia, including human breast cancer. Rb+ was an absolute prerequisite for ribociclib efficacy in vitro and cell types with direct genetic aberrations of the Rb pathway were more sensitive. In the nonclinical setting, because of ribociclib's cytostatic effects, tumour regrowth is likely during drug holidays Ribociclib is less effective;[15] (that is, less likely to induce tumour regression and more likely to only produce tumour stasis) following resumption of treatment after a drug holiday. This implies the evolution of selection pressure driven drug resistance. The possible mechanisms of drug resistance were not evaluated by the sponsor.

Enzymatic activity in vitro

In validated studies using adenosine triphosphate (ATP) concentrations at the Michaelis constant (K_m) ATP (supra-physiological) ribociclib displayed potent inhibition of and high selectivity for CDK4 and CDK6 (half maximal inhibitory concentrations (IC_{50}) of 0.008 and 0.039 µM compared with IC_{50} 113, 75.9, 43.9 and 1.52 µM against CDK1, CDK2, CDK5 and CDK9, respectively). It also displayed > 1000 x selectivity against a large panel of serine and threonine kinases.

In an in vitro kinase profiling study using 26 different tyrosine and 12 different serine kinases, ribociclib was inactive (IC_{50} > 10 µM) against 34 of the kinases tested. The ribociclib IC_{50} value against CDK4 was 0.014 µM (compared with a clinical maximum

[15] Clarification: ribociclib is less effective in the mantle cell lymphoma (MCL) Jeko-1 model tested.

unbound serum concentration ($C_{max,unbound}$) of 1.63 μM and minimum unbound serum concentration ($C_{trough,unbound}$) of 0.65 μM) implying that potent in vivo inhibition of the CDK4 is likely to occur throughout the day with the proposed clinical daily dose of 600 mg orally.

Cellular activity in vitro

In a panel of cancer cells derived from patients with acute myeloid leukaemia, breast cancer, colon cancer, liposarcoma, mantle cell lymphoma, melanoma, non-small cell lung cancer, pancreatic cancer and squamous cell oesophageal cancer, the presence of Rb function was a prerequisite for ribociclib efficacy and cell types with genetic aberrations of the Rb pathway (that is, Rb+; rather than indirect Rb dysfunction) were the most sensitive. In Rb positive breast cancer cell lines, ribociclib inhibited Rb phosphorylation (0.06 to 1.2 μM breast cancer cell lines), cell proliferation (IC_{50} 0.04 to 3.3 μM) and G1 to S phase cell cycle progression (IC_{50} by 0.07 to 0.89 μM). It had no activity against Rb negative breast cancer cells. Ribociclib's key effect was G1 arrest. Ribociclib was cytostatic, not cytotoxic and did not induce apoptosis even after prolonged treatment. Cell cycling in non-senescent cells will likely resume once ribociclib is removed.

Cellular assays using Jeko-1 mantle cell lymphoma cells demonstrated that ribociclib inhibited CDK4/6 mediated phosphorylation of Rb (IC_{50} 0.18 μM, enzyme linked immunosorbent assay (ELISA)) and inhibited cell proliferation (IC_{50} 0.08 μM, bromodeoxyuridine (BrdU) assay) by inducing G1 arrest (IC_{50} 0.11 μM, flow cytometry). Both major human metabolites also induced G1 arrest (LEQ803: IC_{50} 0.24 μM; CCI284: IC_{50} 1.14 μM, compared with an clinical $C_{max,unbound}$ of 0.05 μM and 0.11 μM, respectively). Given the low activity and plasma level relative to the parent drug, the metabolites are unlikely to make a significant contribution to the primary pharmacological effects of ribociclib *in vivo*.

Amongst human breast cancer cell lines, ER+ luminal breast cancer cell lines were the most sensitive to ribociclib (16/25 cell lines having $IC_{50} < 1$ μM).

In vivo studies

In a severe combined immunodeficient (SCID) mouse Jeko-1 (t11;14 translocation leukaemia) subcutaneous xenograft model, ribociclib dosing at ≥ 30 mg/kg/day orally for 4 days (C_{max} ≥ around 1 x the clinical value (2360 ng/mL)) dose relatedly inhibited cancer cell Rb phosphorylation by ≥ 40%, and after 21 days of treatment inhibited tumour growth by ≥ 60%. Ribociclib had no plasmatic accumulation, but accumulation occurred in tumours, possibly due to higher CDK 4/6 expression in rapidly dividing cancer cells. High doses (150 mg/kg/day; around 6 x the clinical C_{max}) resulted in tumour regression. Following a drug holiday, reinstitution of ribociclib treatment at 300 mg/kg/day resulted in slowing of tumour growth but not cessation or regression, suggesting selection pressure driven drug escape. The mechanisms of drug escape were not studied. Similar results were obtained in a nude rat Jeko-1 (t11;14 translocation leukaemia) subcutaneous xenograft model. Ribociclib dosing at ≥ 10 mg/kg/day orally for 5 days inhibited tumour xenograft Rb phosphorylation by ≥ 44% in a dose related manner. Following 28 days of 4 times daily oral dosing at ≥ 75 mg/kg/day, complete regressions occurred and dosing at 10 mg/kg/day resulted in 56% reduction in xenograft growth.

In nude mouse primary ER+ human breast cancer xenograft models, ribociclib dosing at 75 mg/kg/day orally resulted in a significant ($p < 0.05$) reduction in xenograft growth. Efficacy in this model varied depending on cell line used and dosing period. Complete regression was noted against the Michigan Cancer Foundation 7 (MCF7) breast cancer cell line after 40 days of treatment, ≥ 60% inhibition of tumour growth against KPL1, MCF7, and ZR751 cell lines after 28 days of treatment, no significant inhibition (approximately 30% inhibition) in one study and 66% inhibition in another study against the luminal breast cancer xenograft HBCx34 after 56 days of treatment. In the study which showed no

significant inhibition of tumour growth by ribociclib alone, significant tumour growth inhibition (by 73%) was observed by ribociclib (75 mg/kg/day) in combination with letrozole (2.5 mg/kg/day), associated with greater toxicity than ribociclib or letrozole alone. The efficacy of ribociclib was also enhanced by fulvestrant or a phosphoinositide 3-kinase (PI3K) inhibitor.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacodynamics

Since ribociclib displays no target cell specificity, normal cells with constitutively high mitotic rates (for example, bone marrow, immune system, enterothelial stem cells and basal keratinocytes/stem cells) will undergo G1 arrest (confirmed in the in vivo toxicology studies). However, since ribociclib is cytostatic and not cytolethal, the toxicological non-target effects are likely less severe compared with classical cytotoxic/cytolethal anticancer drugs (for example, risk of opportunistic infection due to barrier epithelia disruption and immunosuppression may be lower).

In vitro off-target secondary pharmacodynamics panel studies (144 and 147 pharmacological targets), phosphodiesterase (PDE) 4D subtype (PDE4D) inhibition (IC_{50} 0.6 μM, ≥ 15 x the IC_{50} against CDK4/6 and around 0.4 x clinical $C_{max,unbound}$)[16] was identified as a potential target. PDE4D degrades secondary messenger cyclic adenosine monophosphate (cAMP) and is expressed in a broad range of tissues with high expression in cardiovascular, neural, immune and inflammatory systems. PDE4D knockout mice have delayed growth, reduced viability, impaired ovulation and refractory to muscarinic cholinergic stimulation. Two PDE4 inhibitors, apremilast and roflumilast, have been approved in Australia for the treatment of inflammatory conditions, psoriasis and chronic obstructive pulmonary disease, respectively. Pharmaceutical PDE4 inhibitors typically trigger dose limiting central nervous system (CNS) mediated nausea and emesis due to PDE4 inhibition within the chemoreceptor trigger zone of the area prostrema.[17,18] Since the chemoreceptor trigger zone is located in one of the circumventricular organs that lacks a blood brain barrier (BBB), adverse PDE4 inhibitory effects such as nausea and emesis are possible. Peripheral skin erythema was also noted in the acute toxicology studies after IV administration of ribociclib. This effect may have been secondary to PDE4 inhibition associated vasodilation. Vomiting was observed in dogs treated with ribociclib and nausea and vomiting were reported in clinical trials with ribociclib (reported in the sponsor's Clinical Overview). PDE4D inhibition may increase cardiac pacemaker activity *in vitro*;[19] however, heart rate was unaffected in animal studies. PDE4D inhibitors induce vasculitis in primates and rodents;[20] however, these effects have also not been observed in human patients and did not occur with ribociclib dosing of rats and dogs.

Ribociclib also inhibited vesicular monoamine transporter 2 (VMAT2) with an IC_{50} 6.3 μM. However, VMAT2 is distributed in the CNS nigrostriatal and mesolimbic pathways which are protected by the BBB. Given the low BBB penetration of ribociclib, the risks of off target effects at VMAT2 are low. Clearly adverse effects attributable to the nigrostriatal and mesolimbic pathways were not observed in the nonclinical data.

[16]The TGA evaluator's calculation is based on PopPK studies for the initial application (the MONALEESA 2 trial).
[17] Giembycz MA. Can the anti-inflammatory potential of PDE4 inhibitors be realized: guarded optimism or wishful thinking? 2008. *Br J Pharmacol*.;155:288-290.
[18] Spina D. 2008. PDE4 inhibitors: current status *Br J Pharmacol*.;155:308-315
19 Perera RK et al .Atropine augments cardiac contractility by inhibiting cAMP specific phosphodiesterase type 4. *Sci Rep*. 2017;7: 15222m.
[20] Banner KH, and Press NJ. Dual PDE3/4 inhibitors as therapeutic agents for chronic obstructive pulmonary disease. *Br J Pharmacol*. 2009;157: 892-906.

The ribociclib metabolite, LEQ803 also showed inhibition of PDE4D (IC_{50} 0.6 μM, 12 x clinical $C_{max\ unbound}$ 0.05 μM), and at higher concentrations, the 5-hydroxytryptamine (serotonin) 3 receptor subtype ($5HT_3$) (IC_{50} 2.63 μM, inhibitory constant (K_i) 0.78 μM, 16 x clinical $C_{max\ unbound}$).[21] Inhibition of other targets occurred only at very high concentrations and are unlikely to be clinically relevant (ribociclib: apelin receptors IC_{50} around 10 μM, orexin-2 receptors 70% at 10 μM; LEQ803: neuronal nicotinic alpha 2 channels IC_{50} 5.7 μM/K_i 4.27 μM, cannabinoid CB_1 receptor IC_{50} 28 μM/K_i 24 μM, rat imidazoline I2 receptor 71% at 10 μM, rat brain sodium channel site II 70% at 10 μM; VMAT2 84% at 10 μM). There were no toxicology correlates with any of these effects and pharmacologically relevant exposure of receptors in the brain (that is, orexin-2 and brain sodium channel site II) to ribociclib is unlikely to occur for pharmacokinetic reasons.

Safety pharmacology

Oral dosing of rats at 200 mg/kg (C_{max} comparable to the clinical C_{max}) was not associated with adverse effects on basic neurobehaviour by functional observation or on basic respiratory parameters. No adverse effects were observed in the study, and higher doses could have been administered.

Ribociclib displayed the following channelopathic effects in vitro: a) concentration dependent inhibition of the cardiac sodium channel ($Na_v1.5$) (IC_{50} 24 μM, 15 x clinical $C_{max\ unbound}$); b) binding to the human Ether-à-go-go-Related gene (hERG) potassium (K^+) channel (50% binding at 5.5 μM 3x clinical $C_{max\ unbound}$); and c) hERG K^+ channel inhibition (IC_{50} 21 to 53 μM, 13 to 33 x clinical $C_{max\ unbound}$).[21] The major metabolite LEQ803 only bound to and inhibited hERG K^+ channels at supratherapeutic concentrations (50% binding at 6.3 μM and K^+ channel inhibition IC_{50} 4.5 μM, ≥ 90 x clinical $C_{max\ unbound}$ 0.05 μM),[21] and had no effects on hERG receptor trafficking/expression in vitro at up to 30 μM.

In vivo in telemetered dogs, dose dependent, significant ($p < 0.05$) QT interval;[22] and QTc interval;[23] prolongation occurred following a single oral dose of ribociclib at ≥ 20 mg/kg (C_{max} approximately equal to 0.5 x clinical C_{max} 2360 ng/mL)[21] and also in the 4 week repeat dose toxicity study. The effect started at approximately 1.75 hours post dose (approximately the t_{max}), and plateaued at approximately 2.5 to 4.5 hours post dose. Both the amplitude of the QT/QTc prolongation and the number of time points with statistically significant changes increased with the dose level, whereas the time of onset was similar at all dosages. The strongest increase in mean QTc was +57 milliseconds (ms) (+24.9 %) seen at 9.25 hours post dosing at 100 mg/kg (approximately 2 x clinical C_{max}) in the absence of other electrocardiographic effects. Isolated or bigeminal premature ventricular contractions (PVC) were recorded in one out of 3 dogs in another telemetered dog study after a single oral dose of 100 mg/kg, in addition to QTc prolongation (up to 31 ms, a 12% increase (range 10 to 30%)) at 3 to 20 hours post dose. The dog with PVCs had a relatively high C_{max} (9720 ng/mL compared with the clinical C_{max} 1820 ng/mL). There were no adverse effects on blood pressures or core body temperature.

One telemetry study in dogs dosed with LEQ803 at 5 mg/kg orally (C_{max} 30% of the clinical C_{max}) also showed QT prolongation (18 ms, 7%), although the study was confounded by toxicity of maleic acid, which was used in the dosing vehicle.

The nonclinical findings suggest that ribociclib may cause QT prolongation in patients.

[21] The TGA evaluator's calculation is based on PopPK studies for the initial application (the MONALEESA 2 trial /A2301).
[22] The 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.
[23] The QTc is the QT interval corrected for heart rate.

Pharmacokinetics

Absorption

Based on studies in Caco-2 cell monolayers, intestinal permeation of ribociclib is by passive perfusion limited by active efflux. Ribociclib is not a substrate of mitoxantrone resistance protein (MXR);[24] however ribociclib is a substrate of the multidrug resistance protein 1 (MDR1) efflux transporter.[25] MDR1 saturation did not occur at concentrations up to 297 μM. Intestinal secretion of ribociclib was also demonstrated in intact and bile duct cannulated rats following intravenous (IV) dosing (discussed under 'Excretion', below). An *in silico* analysis predicts that gastric pH over the range of 1.5 to 8.0 will not impact the oral bioavailability of ribociclib in humans at the proposed clinical dose of 600 mg.

Across species (mouse, rat, dog, monkey and humans) oral absorption is rapid (t_{max} 1 to 4 hours), absolute bioavailability is moderate (mouse: 65%; rat: 37 to 55%; dog: 64 to 86%; monkey: 17%) and a moderate first pass effect occurred in rats (absorption approximately equal to 1.8 x bioavailability).

Clearance

Clearance in mice, rats, dogs and monkeys was rapid (2.1 to 7.8 L/h/kg; greatly exceeding hepatic blood flow in female rats only). A sex difference occurred in rats due to higher Phase II sulfation metabolism in females (approximately 2.7 x higher clearance in females with substantially lower, > 10 x in some cases, area under the drug concentration-time curve in plasma (AUC) values in females compared with males). Plasma elimination half life ($t_{½}$) was short in rodents and monkeys (approximately equal to between 2 and 5 hours), but considerably longer in dogs (approximately 18 hours). Across species, the volume of distribution (V_d) greatly exceeded 1 L/kg (approximately 8 to 28 L/kg) implying substantial tissue sequestration. The area under the drug concentration-time curve in plasma from time zero to 24 hours ($AUC_{0\text{-}24h}$) was approximately dose proportional in rats, dogs and rabbits over the dose range used in the toxicity studies. There was no major plasmatic accumulation after repeated dosing.

Plasma protein binding and distribution in blood

Plasma protein binding was similar across species and was not concentration dependent. The mean fraction unbound in plasma (f_u) ranged from 0.20 to 0.34 in mouse, rat, dog and monkey plasma (human: 0.30). Plasma protein binding displacement effects of toxicological importance are unlikely. The blood: plasma ratio was consistent across species (0.9 to 1.30; 1.01 in humans) with no evidence of selective erythrocyte partitioning.

Tissue distribution

Drug associated radioactivity was rapidly, widely, and extra-vascularly distributed. For most non-pigmented tissues elimination $t_{½}$ was short and reflected plasma washout. Longer tissue $t_{½}$ (168 hours) occurred in lymph nodes, preputial glands, testes, Harderian glands, liver, and thyroid gland. Melanophilic sequestration (at the time of last measured concentration (t_{last}) 840 hours) occurred in the choroid, ciliary body, and meninges. Melanophilic accumulation is likely with repeated dosing, but toxicity studies showed no

[24] MXR (mitoxantrone resistance protein) is also known as BCRP (breast cancer related protein).
[25] MDR1 (multidrug restistance protein 1) is also known as P-gp (P-glycoprotein 1) and ABCB1 (ATP binding cassette subfamily B member 1)

adverse effects on these tissues. Based on quantitative whole body autoradiography and ex vivo perfusion studies ribociclib associated radioactivity does not largely cross the BBB.

In vitro human hepatocyte studies demonstrated uptake via a moderate to high passive permeation with some involvement of transporters. Transporters responsible for hepatocyte uptake have not been identified, but organic anion transporters (OAT) may be involved since co-incubation with the OAT inhibitor, p-aminohippuric acid caused a slight to moderate decrease in hepatocyte uptake. Organic anion transporter polypeptide (OATP), organic cation transporter (OCT) and sodium/taurocholate co-transporting polypeptide (NCTP) inhibitors had minimal effects on hepatocyte uptake, suggesting ribociclib is not a substrate of these transporters. *In vitro* hepatocyte uptake maximum velocity (V_{max}) and K_m is substantially higher in rats compared with dogs and humans, suggesting higher hepatic first pass clearance in rats than dogs and humans.

Metabolism

The metabolism of ribociclib is complex, with more than 50 metabolites. In rats, the predominant metabolic pathway was sulfation to metabolite M8 and N-dealkylation to M4 (LEQ803) with subsequent Phase II reactions. Higher clearance in female rats compared with males is due to higher sulfation to M8 in females, which is a minor pathway in dogs and humans. In dogs and humans, metabolism was dominated by oxidative pathways with various combinations of dealkylation, C- and N-oxygenation and oxidations, mainly by the cytochrome P450 system enzyme (CYP) 3A4. In all 3 species, the major plasma component was unchanged ribociclib. Exposure to human oxidative plasma metabolites was covered by the studies in rats, dogs and/or rabbits. Of the major human metabolites, M1 (a glucuronide metabolite by UGT2B7), LEQ803 (by CYP3A4) and M13 (CCI284, N-hydroxylation metabolite most likely by flavin containing monooxygenase 3 (FMO3)), representing approximately 7.78%, 8.6% and 9.4% of total radioactivity and17.9% , 19.8% and 21.6% of ribociclib, respectively, in human plasma, LEQ803 and CCI284 were detected in rat, rabbit and dog plasma although the levels in dogs were low. No M1 was formed in rat and dog plasma and very low level in rabbit plasma; however, since this metabolite is a phase II glucuronide, it is unlikely to be of pharmacological or toxicological significance. LEQ803 and CCI284 are pharmacologically active (discussed above under '*Primary pharmacology*'), but given the low activity and plasma level relative to the parent drug, LEQ803 and CCI284 are expected to have only a minor contribution to the overall efficacy in patients.

In vitro studies in human, canine and rat hepatocytes and recombinant human CYPs and FMO3 showed that metabolism of ribociclib by CYP3A4 and FMO3 generates reactive intermediates with subsequent formation of covalent drug-protein adducts. This may explain some of the hepatotoxicity associated with the drug. CYP3A4-mediated metabolites accounted for approximately equal to between 72 and 83% protein adduct formation. Ribociclib was a moderate to strong irreversible CYP3A4 inhibitor in pooled human liver microsomes in vitro (lowest KI 5 μM, rate of enzyme inactivation (K_{inact}) 0.02 μM); however, ribociclib CYP3A4 adducts were not conclusively identified. The metabolites LEQ803 and CCI284 are also irreversible inhibitors of CYP3A4 (KI 10 to 12 μM, K_{inact} 0.02 min^{-1} for both metabolites).

Excretion

The predominant route of excretion in rats and dogs is faecal with urinary excretion as a minor route. Around 70 to 80% drug associated radioactivity was excreted in faeces and 6 to 19% in urine following oral dosing (compared with 69.1% in faeces and 22.6% in urine in humans). The majority (≥ 65% of dose) was excreted within 24 hours of dosing. Non-metabolised ribociclib in faeces accounted for 11 to 22% of the oral dose and in urine for 3 to 13% of the oral dose. Elimination in rats, dogs and humans was mainly by

metabolism with a limited contribution of renal clearance. A study in bile duct cannulated male rats indicated that the majority of metabolites in faeces were excreted in bile, with unchanged ribociclib representing 1% of dose in bile and 8% of dose in faeces. Similar faecal excretion of unchanged ribociclib (9.5% of dose) was observed in female rats without bile cannulation following IV dosing. However, much higher faecal excretion of unchanged ribociclib (18.4%) was detected in another IV study in male rats without bile cannulation. The discrepancy was not explained by the sponsor. Nonetheless, the minimal biliary excretion and significant faecal excretion of unchanged drug following an IV dose indicate elimination of intact ribociclib by intestinal secretion.

Pharmacokinetic drug interactions

Ribociclib as a victim

Ribociclib is primarily metabolised by CYP3A4 and is a time-dependent inhibitor of CYP3A4 *in vitro*. Clinically relevant interactions are expected to occur with moderate to strong CYP3A4 inhibitors and inducers. Warning statements based on the human clinical data have been included in the PI.

Ribociclib is a substrate of P-gp (MDR1) but not BCRP (MXR).[24,25] It is actively secreted to the intestinal tract probably by P-gp and excreted in faeces in rats (9 to 18% of an IV dose recovered as unchanged ribociclib in rat faeces), suggesting intestinal secretion plays a role in ribociclib elimination. Since ribociclib has moderate passive permeability as shown in the intestinal Caco-2 cell membrane assay, oral absorption is not expected to be significantly affected by P-gp inhibitors. However, given the intestinal secretion of ribociclib is a significant route of ribociclib clearance (17.3% of dose excreted as unchanged ribociclib in human faeces), strong P-gp inhibitors might increase plasma ribociclib concentration in patients.

Ribociclib was shown to be a substrate of OAT but not OATP, OCT or NCTP. However, since it has moderate to high passive permeation into human hepatocytes in vitro, the hepatic uptake of ribociclib is not expected to be significantly affected by OAT inhibitors.

Ribociclib as a perpetrator

Ribociclib is moderate to strong irreversible (that is, time dependent) CYP3A4 inhibitor (discussed above). The major human metabolites LEQ803 and CCI284 are also time-dependent inhibitors of CYP3A4 (KI around 10 μM and K_{inact} 0.02 min^{-1}). Clinically relevant interactions with CYP3A4 substrates are highly likely). Warning statements based on the human clinical data have been included in the draft PI.

Ribociclib and the metabolite CCI284 are reversible inhibitors of CYP1A2 with K_i values 13 μM (unbound) and 14 μM (total), respectively, cf. the respective clinical $C_{max\ unbound}$ of 1.63 μM and 0.11 μM. CYP1A2 was not inhibited by LEQ803. Ribociclib is not expected to have a significant impact on the clearance of CYP1A2 substrates. Ribociclib and the 2 metabolites had no significant or only weak inhibition of CYP2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 and did not show enzyme inducing activity of CYPs tested (CYP1A2, 2B6, 2C9 and 3A4) in human hepatocytes in vitro. Ribociclib and LEQ803 did not demonstrate inhibitory activity against UGT2B7 (CCI284 not tested).

In vitro studies using mammalian cells expressing human transporters showed that ribociclib and the two major metabolites had no or only weak inhibition of P-gp, MRP2, OATP1B1, OATP1B3, OAT1, OAT3 and MATE2K. Comparisons of the IC_{50} or K_i values with the unbound clinical C_{max} (see Table 3, below) suggest that clinically relevant inhibition of transporters OCT1, OCT2, MATE1, BCRP and BSEP is possible.

Table 3: Inhibitory activity of ribociclib and metabolites against transporters

Transporter	Ribociclib		LEQ803		CCI284	
	IC_{50} or K_i[1]	IC_{50} or K_i/C_{max} ratio[2]	IC_{50} or K_i[1]	IC_{50} or K_i/C_{max} ratio[2]	IC_{50} or K_i[1]	IC_{50} or K_i/C_{max} ratio[2]
P-gp	143	88	37.2	791		
BCRP	24	15				
BSEP	4.7	3			3.93	36
OATP1B1	33.4	21			3.99	36
OCT1	17.3	11	6.39	136	3.50	32
OCT2	1.9	1.2	2.16	46	1.01	9
MATE1	1.7	1.0	0.28	6	0.58	5
MATE2K	30.7	19	2.09	44	6.2	56

1) K_i is shown where available. 2) Free fraction clinical C_{max} of 1.63 µM ribociclib, 0.047 µM LEQ803, and 0.11 µM CCI284. Note, empty cells indicate no or weak inhibition at the highest concentration tested (50 µM). Ratios in bold indicate potential for clinically relevant inhibition of the transporters.

Toxicology

Acute toxicity

Oral and IV single dose studies were performed only in dogs with only one animal per sex per dose. Dose dependent emesis was observed. The maximum tolerated oral dose was 100 mg/kg (approximately equal to 5 x the clinical dose by body surface area (BSA)) based on severe suppression of food consumption at 150 mg/kg and the maximum nonlethal oral dose was 150 mg/kg. IV dosing at 10 mg/kg resulted in immediate vomiting, trembling, and head shaking. Other clinical signs at all doses (2 to 10 mg/kg) included salivation, excessive licking, and reddened skin and oral mucosa (suggesting vasodilation). The maximum nonlethal dose by the IV route was 10 mg/kg.

Repeat dose toxicity

Repeat dose toxicity was studied in rats and dogs with dosing duration up to 27 weeks and 39 weeks, respectively. Short term studies of up to 4 weeks were performed by continual daily dosing and studies of 15 weeks and longer were by the same dosing schedule as the proposed clinical dosing, that is, 3 weeks dosing and one week off for each 28 day dosing cycle. The repeat dose studies were adequate to support the proposed clinical use, although slightly higher doses could have been administered in the cyclic dosing studies.

Relative exposure

Relatively low, generally subclinical, exposure levels of ribociclib and the major circulating metabolite LEQ803, were achieved in the repeat dose animal studies (see Tables 4 and 5, below).

Plasma CCI284 concentrations were measured in high dose males of the 26 week study in rats. The $AUC_{0\text{-}24h}$ values for CCI284 ranged from 20100 to 24400 ng.h/mL during the dosing period and were more than 3 x the steady state exposure ($AUC_{0\text{-}24h}$ 5747 ng/h/mL, Study X2101) in patients receiving 600 mg daily ribociclib. The exposures of female rats to CCI284 were much lower (> 10 fold) than those of male rats based on liquid chromatography mass spectrometry (LC-MS) peak areas of pooled plasma samples from mid dose animals in the 15 week repeat dose study. Exposure of dogs to CCI284 is expected to be negligible based on the very low circulating levels of this metabolite in a pharmacokinetic study in dogs and comparison of LC-MS peak areas of pooled plasma samples from the high dose group in the 15 week dog study and from patients receiving a 900 mg dose.

Table 4: Relative exposure to ribociclib in pivotal repeat-dose toxicity studies

Species	Study duration (ID)	Dose (mg/kg/day)	$AUC_{0\text{-}24\ h}$ (ng·h/mL)		Exposure ratio (ER)[1]	
			Male	Female	Male	Female
Rat (HanRcc: Wist)	4 weeks (0870393)	25	6180	885	0.2	0.03
		75	25900	3680	0.8	0.1
		150	47800	11000	1.5	0.3
	15 weeks[2] (1370292)	25	15300		0.5	
		50		2960		0.1
		75	55400		1.7	-
		150	104000	11100	3	0.3
		300		23400		0.7
	27 weeks[2] (1470078)	25	13200		0.4	-
		50		4610		0.1
		75	32800		1.0	-
		150	45300	9130	1.4	0.3
		300		20000		0.6
Dog (Beagle)	4 weeks (0870399)	5	5140	3490	0.2	0.1
		10	12400	9700	0.4	0.3
		20	26300	23900	0.8	0.7
	15 weeks[2] (1370291)	1	777	553	0.02	0.02
		3	3010	1910	0.1	0.06
		10	12500	12500	0.4	0.4

Species	Study duration (ID)	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (ng·h/mL)		Exposure ratio (ER)[1]	
			Male	Female	Male	Female
	39 weeks[2] (1470079)	1	635	536	0.02	0.02
		3	2340	2290	0.07	0.07
		10	9260	8180	0.3	0.3
Human (Cancer patients)	PopPK modelling[3]	600 mg qd, 12 mg/kg/d	31900			

1) animal: human plasma $AUC_{0-24\ h}$; 2) 3 weeks dosing, 1 week off; 3) Assumes a body weight of 50 kg. near the lower end of the range, to result in conservative estimates exposure ratios.

Table 5: Relative exposure to LEQ803 (M4), major metabolite of ribociclib in pivotal repeat-dose toxicity studies

Species	Study duration (Study ID)	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (ng·h/mL)		Exposure ratio[1]	
			Male	Female	Male	Female
Rat (HanRcc: Wist)	15 weeks[2] (1370292)	25	1460		0.5	
		50		78.5		0.03
		75	3360		1.2	
		150	5520	250	2	0.09
		300		402		0.2
	27 weeks[2] (1470078)	25	2360		0.9	
		50		190		0.07
		75	4480		1.7	
		150	4800	256	1.8	0.09
		300		504		0.2
Dog (Beagle)	4 weeks (0870399)	5	372	333	0.1	0.1
		10	760	855	0.3	0.3
		20	1480	2150	0.6	0.8
	15 week[2] (1370291)	1	41.2	NC	0.02	-
		3	131	109	0.05	0.04
		10	489	692	0.2	0.3

Species	Study duration (Study ID)	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (ng·h/mL)		Exposure ratio[1]	
			Male	Female	Male	Female
	39 weeks[2] (1470079)	1	NC	NC		
		3	67.7	94.2	0.03	0.04
		10	269	324	0.1	0.1
Human (Cancer patients)	Study X2107	600 mg + letrozole 2.5 mg	2690			

1) animal: human plasma $AUC_{0-24\,h}$; 2) 3 weeks dosing, 1 week off

Justification for selection of human AUC value for calculation of exposure ratios

Data for ribociclib was selected from the population pharmacokinetic analysis derived from the pooled results of studies in patients with cancer. The basis for this decision is as follows: a) the study population selected most accurately reflects the intended clinical population; b) the pooled data population pharmacokinetic analysis provides the greatest statistical power available across all the studies; and c) the proposed clinical dose and dosing regimen.

Notably, ribociclib was the major circulating component in human plasma and the focus of the population pharmacokinetic analysis in patients. Of the prominent circulating metabolites, LEQ803 and CCI284 had no significant contribution to total pharmacological activity in humans based on their *in vitro* pharmacological activities and *in vivo* exposures (each accounted for < 10% of total radioactivity). Following multiple dosing of cancer patients at 600 mg four times daily plus 2.5 mg letrozole, the mean AUC_{0-24h} for LEQ803 was and 2690 ng.h/mL (Study X2107).

Human pharmacokinetic data is based upon the use of capsule formulation and oral solution formulation. Data on the proposed film coated tablet formulation was not supplied. However, capsule formulation and coated tablet formulation were demonstrated to be bioequivalent. Thus, the values derived from the capsule formulation and oral solution formulations reasonably reflect the actual proposed clinical situation.

Major toxicities

The major toxicological effects of ribociclib were primary pharmacologically mediated, that is, by inhibition of CDK4/6. Predictably, organs and tissues with high cellular mitotic rates are more susceptible to non-target effects of ribociclib that is, bone marrow (myeloid cells, the erythron, platelet production), the immune system, spermatogenesis, basal epidermis of the skin, cartilage/bone and gastrointestinal tract (GIT). Most effects were reversible or partially reversible.

Neutropaenia and effects on the bone marrow myeloid pool

Decreased blood neutrophil counts were observed in rats and dogs. In the 4 week oral repeat dose studies the depressive effects of ribociclib on the circulating neutrophil pool were relatively small at ≥ 75 mg/kg/day in rats and at all doses in dogs (exposure ratio in male rats 1, female rats 0.3, dogs 0.1 to 0.2) and reversible following dose cessation. In both species, this effect correlated with minimally to mildly decreased myeloid to erythroid precursor ratios and percent mature myeloid cells, and bone marrow hypocellularity.

Neutrophil counts were minimally altered in the 15 and 27 week studies in rats. In the 15 and 39 week dog studies (3 weeks on, 1 week off dosing cycle), cyclical decreases in leukocyte counts (including neutrophil counts) correlated with dose cycles. In both sexes, neutrophil counts fell precipitously during the first dosing cycle but still remained within the normal biological range following dosing at ≥ 3 mg/kg/day (exposure ratio ≥ 0.06). However incomplete recovery was apparent at the end of each dose cycle resulting in an overall downward trend over the 15 or 39 week study period. Neutropaenia just below the lower limit of the normal biological range was present towards the end of the dosing period at the highest dose (10 mg/kg/day, exposure ratio 0.3 to 0.4). Full recovery occurred following dosing cessation.

In the evaluator's opinion, a severe decrease in blood neutrophil counts occurred in one of the primary pharmacology studies (Study RD-2008-50811: Jeko-1 subcutaneous xenograft model in SCID mice) following oral dosing at ≥ 75 mg/kg/day (exposure ratio 2).

These findings are also consistent with the effects of the related CDK4/6 inhibitor palbociclib and adverse effects in human clinical trials with both drugs. Neutropaenia may be associated with a higher risk of infection.

Effects on eosinophils

Dose related, mild to moderate, and reversible reductions in eosinophil counts often tracked with changes in neutrophil counts. Absolute eosinopaenia was not observed. Effects on eosinophils were most prominent in male rats, most likely due to higher plasma drug concentrations than in female rats. This finding is also consistent with the effects of the related CDK4/6 inhibitor palbociclib.

Effect on lymphocytes and the lymphoid system

Key effects in rats were dose related thymic lymphoid depletion (with lymphocytolysis in some animals) and lymphoid germinal centre depletion in lymph nodes at ≥ 75 mg/kg/day in males (exposure ratio 1) and 150 mg/kg/day in females (exposure ratio 0.3). Mesenteric lymph node sinus histiocytosis occurred following treatment for ≥ 15 weeks in males at ≥ 75 mg/kg/day and in females at 300 mg/kg/day (exposure ratio 0.6). Lymph node sinus histiocytosis was possibly a reactive inflammatory process or a sign of phospholipidosis (as observed in bile duct and lung).

Dose related cyclic (correlated with dose cycling) reductions in blood lymphocyte counts occurred in high dose male rat cohorts in the 15 and 27 week studies (exposure ratio 1.4 to 3). Cessation of dosing was associated with rapid reversal of the effect. Moderate, reversible reductions in blood lymphocyte counts were noted in the dog studies at 10 mg/kg/day (exposure ratio 0.3). These findings are also consistent with the effects of the related CDK4/6 inhibitor palbociclib.

CDK6 is essential for normal thymic Notch/AKT dependent T cell development in mice.[26,27] While thymic development is not relevant to the proposed ribociclib patient population, the use of the drug may produce specific types of immunotoxicity associated with effects on T cell development.

Effects on the erythron

Dose related reductions in the mature circulating erythrocyte count (normochromic to hyperchromic with small increases in mean corpuscular volume (MCV) and distribution width) and decreased reticulocyte count occurred in rats and dogs. In rats, the effects were more prominent in males than in females due to the higher exposure in male rats. Notably, cyclic doses (3 weeks on and 1 week off) at the highest dose (exposure ratio 1.4) for up to

[26] Hu M et al. A Requirement for Cyclin-Dependent Kinase 6 in Thymocyte Development and Tumorigenesis. *Cancer Res* 2009; 69: 810-818.
[27] Hu M et al. CDK6 kinase activity is required for thymocyte development. *Blood* 2011; 117: 6120-6131.

27 weeks did not produce overt adverse anaemia. Splenic haematopoiesis (a normal compensatory response to anaemia) was noted in the high dose groups (exposure ratio 3 for males, 0.7 for females) in the 15 week study, correlating with bone marrow hypocellularity in males.

Mild dose-related reductions in circulating erythron in dogs correlated with bone marrow hypocellularity following dosing at ≥ 10 mg/kg/day (exposure ratio 0.3 to 0.4). In the 15 and 39 week studies with cyclic dosing (3 weeks, 1 week off), dose-related cyclic reductions in circulating erythron mass (with mild macrocytosis) occurred at ≥ 3 mg/kg/day (exposure ratio 0.1). There was partial recovery by the end of each dose cycle, but an overall downward trend in circulating erythron mass was apparent in the long term studies. Notably, increased MCV above the normal biological range also occurred in the high dose group. Reticulocyte counts also tended to be lower.

The effects on erythron were likely due to primary pharmacologically mediated suppression of cell division during haematopoiesis. These findings are also consistent with the effects of the related CDK4/6 inhibitor palbociclib and the known effects of CDK6 knockout in mice. The effects are likely due to a combination of suppression of replication of erythropoietic cells, shortened erythrocyte life-span and increased sensitivity of erythroctyes to mechanical stress. Erythrocytes in CDK6-/- mice also have a shortened lifespan and greater sensitivity to mechanical stress due to impaired F-actin formation.[28]

Effects on platelets

Thrombocytopaenia (just below the lower limit of normal) was associated with dosing at 10 mg/kg/day (exposure ratio 0.4) in the 15 week canine study. Dose related, cyclical (correlated with dose cycling) reductions in platelet count occurred in both sexes with partial recovery after cessation of dosing. The effect was more apparent in males than in females. Coagulopathies did not occur in the study. Surprisingly, fewer effects on platelet were observed in the 39 week study with the same dosing regimen, although reductions in platelet count occurred in males at 10 mg/kg/day. The effect is consistent with the mode of action of ribociclib. These findings are also consistent with the effects of the related CDK4/6 inhibitor palbociclib and decreased platelet count in clinical trials with ribociclib and palbociclib.

Hepatobiliary toxicity

Hepatobiliary effects in animals were comparatively mild and generally only present in the high dose groups. In the rat studies, minimal bile duct epithelial vacuolation and/or hypertrophy were noted in males dosed at ≥ 75 mg/kg/day (exposure ratio 1) and in females at 300 mg/kg/day (exposure ratio 0.6) with incidence generally increasing with dosing duration. These findings imply mild biliary epithelial toxicity and are consistent with the demonstration of minimal to moderate intrahepatic bile duct hyperplasia, periductular fibrosis, mild cholecystitis, cholestasis and inspissated bile with calculi in gallbladder detected dogs at 20 mg/kg/day for 4 weeks (exposure ratio around 0.7) and/or 25 mg/kg/day for 2 weeks (exposure ratio 1.6). In rats, the biliary effect correlated with increased serum total bilirubin levels. Liposome associated membrane protein 2 (LAMP2) immunohistochemistry in rats demonstrated increased lysosomes in the biliary epithelium, likely due to drug associated phospholipidosis (consistent with the presence of foamy macrophages in lymphoid tissues and lung of dogs), a common effect of cationic amphiphilic agents.

The hepatobiliary effects correlated with increased serum alanine transaminase (ALT) and alkaline phosphatase (ALP) (≥ 27 x increase compared with pre-exposure values in 2 dogs) in the 4 week dog study, although the magnitude of increase in serum ALT and

[28] Uras I et al. Cdk6 contributes to cytoskeletal stability in erythroid cells *Haematologica*. 2017 Mar 2. pii: haematol.2016.159947.

ALP did not correlate with the severity of the histological biliary findings. Hepatocyte lesions (periportal hepatocyte necrosis) were observed only in one high dose (20 mg/kg/day) dog in the 4 week study and in dogs at 25 mg/kg/day in a 2 week preliminary study. The same dog in the 4 week study and dogs in the 2 week study at 25 mg/kg/day also had fibrinoid necrosis of small to medium-sized portal arteries, arteriopathy (focal wall degeneration, medial disorganization, haemorrhage) in the hilar region.

Hepatobiliary adverse events were common in human patients (as reported in the draft PI Table 2).

Renal toxicity

In the 15 and 27 week rat studies dosing at ≥ 75 mg/kg/day in male rats (exposure ratio ≥ 1) was associated with minimal degeneration and regeneration of renal tubular epithelia. The effect included the development of basophilic foci due to piling up of epithelial cells and an increased nuclear to cytoplasmic volume ratio. These changes are probably attributable to primary pharmacologically mediated disruption of normal epithelia cell turnover. The histological lesions were not associated with increased plasma creatinine or urea nitrogen, suggesting decompensated renal failure did not occur. No renal effects were observed in dogs.

Effects on the skin

In the 4 week dog study reversible, minimal multifocal thinning/atrophy of the epidermis (palmar and plantar pads) was observed in 2/6 animals dosed at 10 mg/kg/day (exposure ratio 0.3 to 0.4) and in 6/6 animals dosed at 20 mg/kg/day (exposure ratio 0.7 to 0.8). Labelling indices using Ki67 immunohistochemistry (marker of basal keratinocyte proliferation) detected significantly lower basal keratinocyte proliferation rates in footpad skin in dogs. These effects are likely primary pharmacologically mediated. Skin effects were not detected in longer term studies at 10 mg/kg/day or in any rat study.

Effects on bone and cartilage

Reversible, minimal decreases in proliferating and hypertrophic chondrocytes, and in the height and number of the columns of chondrocytes at the costochondral junction (zone of bone growth) of ribs was accompanied by minimal reduction of the primary bone spongiosa in dogs dosed at 20 mg/kg/day (exposure ratio 0.7 to 0.8) in the 4 week dog study. This is again consistent with the non-tissue specific cytostatic actions of ribociclib. Effects on bone and cartilage were not detected in longer term studies in dogs at up to 10 mg/kg/day or in rats. Decreased trabeculae of the femur was reported in rats (but not in dogs) dosed with the related drug, palbociclib. The effects on bone and cartilage may be pharmacologically mediated. However, it is of low certainty in adult patients except perhaps in the context of fracture healing.

Effects on GIT

GIT was not a major target organ of ribociclib. The only intestinal findings were atrophy, villus thinning and glandular dilatation with hyaline plugs in the intestines of dogs in the 2 week dose range-finding study at doses ≥ 15 mg/kg/day for 2 weeks (exposure ratio 0.6 to 1.6) and raised foci of the non-glandular mucosa of the stomach and watery and mucoid content in the small intestine (histopathology not performed) in high dose pregnant rats at the lethal dose 1000 mg/kg/day. GI effects (erosions and ulcerations, enlarged nuclei and basophilic cytoplasm in intestinal glands/crypts) were prominent findings in rats and dogs treated with palbociclib.

Suspected but undetected risks associated with CDK 4/6 inhibition

Diabetes mellitus and effects on pancreatic beta cells

CDK4$^{-/-}$ mice develop insulin-deficient diabetes mellitus due to a reduced number of pancreatic beta cells.[29,30] Functional CDK4 is essential for postnatal pancreatic beta cell proliferation. Insulin deficiency was not demonstrated in any of the *in vivo* studies with ribociclib, likely because of the low relative drug exposures employed. Insulin deficient diabetes mellitus was a noted finding with the related CDK4/6 inhibitor palbociclib.

Effects on the adenohypophysis

Due to cell proliferative defects in the adenohypophysis CDK4-/- mice have infertile females and partially fertile males due to low levels of circulating progesterone and prolactin secondary to a reduced number of pituitary prolactin-producing lactotrophs, pituitary hypoplasia and disruption of the hypothalamic pituitary gonadal axis.[30,31] This is consistent with reproductive toxicity of ribociclib (discussed below).

CDK4-/- mice also develop pituitary dwarfism/growth retardation due to inhibition of production of growth hormone associated with pituitary hypoplasia.[32]

Ribociclib may result in endocrine disorders associated with hypoprolactinaemia, reduced progesterone production, and reduced growth hormone production. However, in the overall context of the use of ribociclib in patients with advanced or metastatic breast cancer these risks are inconsequential in relation to the objective of drug treatment.

Genotoxicity

An ICH S2(R1) compliant screening package was supplied.[33] Ribociclib had no mutagenic potential in *in silico* analyses, in *in vitro* bacterial reverse mutation assays, in an *in vitro* chromosome aberration assay in human lymphocytes, in an *in vitro* mammalian cell micronucleus test in mouse lymphoma cells and in an *in vivo* rat bone marrow micronucleus test. All tests were validated by the use of appropriate controls. Notably, the cytostatic mode of action of ribociclib is likely a confounding factor in the *in vivo* rat bone marrow micronucleus test because of its potential to disturb erythropoiesis. Palbociclib induced bone marrow micronuclei in rats probably through an aneugenic mechanism.

Carcinogenicity

As per ICH S9, carcinogenicity studies were neither required nor supplied.[34]

[29] Rane SG, et al. Loss of Cdk4 expression causes insulin-deficient diabetes and Cdk4 activation results in β-islet cell hyperplasia. *Nat. Genet* 1999; 22: 44–52

[30] Tsutsui T, *et al*. Targeted Disruption of CDK4 Delays Cell Cycle Entry with Enhanced p27^{Kip1} Activity. *Mol. Cell. Biol.* 1999; 19: 7011–7019.

[31] Moons DS, *et al.* Intact Follicular Maturation and Defective Luteal Function in Mice Deficient for Cyclin-Dependent Kinase-4. *Endocrinology* 2002; 143: 647–654.

[32] Jirawatnotai S, *et al.* Cdk4 Is Indispensable for Postnatal Proliferation of the Anterior Pituitary *J Biol Chem*. 2004; 279: 51100-51106.

[33] ICH S2(R1): International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH Harmonised Tripartite Guideline: Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use. Current Step 4 version dated 9 November 2011.

[34] ICH S9: International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Nonclinical evaluation for anticancer pharmaceuticals. Current Step 4 version dated 29 October 2009.

Reproductive toxicity

Consistent with ICH S9, only embryofetal development studies (in rats and rabbits) were supplied. Galactogenic and placental transfer was evaluated in rats.[34]

Relative exposure

The relative exposure of ribociclib in reproductive toxicity studies is shown below in Table 6.

Table 6: Ribociclib relative exposure in reproductive toxicity studies

Species	Study (Study ID)	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio[1]
Rat (Crl:WI (Han))	Embryofetal development (1470245)	50	2090	0.07
		300	13800	0.4
		1000	92300	3
Rabbit (Hra(NZW)SPF)	Embryofetal development (1470801)	10	8510	0.3
		30	36700	1
		60	93000	3
Human (Cancer patients)	PopPK modelling for 50 kg patients	600 mg	31900	–

1) animal:human plasma $AUC_{0-24\,h}$

Effects on fertility

No fertility studies were conducted for ribociclib. As discussed above, CDK4-/- mice have infertile females and partially fertile males due to low levels of circulating progesterone and prolactin secondary to a reduced numbers of pituitary prolactin-producing lactotrophs, pituitary hypoplasia and disruption of the hypothalamic pituitary gondadal axis. Consistent with the findings in CDK4-/- mice, ribociclib treatment of rats at ≥ 75 mg/kg/day (exposure ratio 1) was associated with disruption of spermatogenesis, germ cell depletion, seminiferous tubule atrophy/disorganisation, and Sertoli cell vacuolation and epididymal oligospermia. In dogs, similar disruption of spermatogenesis was noted at 1 mg/kg/day (exposure ratio 0.02). Palbociclib induced similar effects.

Overall, while specific fertility studies were not performed, there is strong direct and mechanistic evidence to suspect adverse effects on male (and likely female) fertility. Given the proposed patient population, such effects are likely inconsequential in relation to the objective of drug treatment.

Placental transfer

In pregnant rats, the percentage of ribociclib concentration in fetal plasma relative to maternal plasma at 3 hours on gestation Day 17 following maternal dosing increased with increasing maternal dose; however the percentage in fetal plasma remained relatively low (approximately equal to 29% following maternal dosing at 1000 mg/kg/day and approximately 13% following maternal dosing at 300 mg/kg/day).

Galactogenic transfer

In rats ribociclib associated radioactivity concentrated in milk (milk: plasma ratio of total radioactivity 5 and of ribociclib 4) and a different metabolite profile compared with plasma was present (dominated by oxidation metabolites).

Maternal effects

Evidence of local gastrointestinal drug intolerance (damage to the gastrointestinal mucosa), which was associated with mortality, was present in rats dosed at 1000 mg/kg/day (exposure ratio 3). Salivation and decreased body weight gain were observed in rats at ≥ 300 mg/kg/day (exposure ratio 0.4). Mortality (2/20) was also noted in rabbits dosed at 60 mg/kg/day (exposure ratio 3), but for one animal, the death was considered likely unrelated to ribociclib and for the other one, it was not certain whether the death was ribociclib related. There were no other signs of materno-toxicity in rabbits.

Effects on embryofetal development

Maternotoxic dosing (1000 mg/kg/day) of rats was associated with total fetal resorptions in 7/24 dams. This effect did not occur in rats or rabbits at non-lethal doses. Fetal weights were decreased at 300 mg/kg/day in rats. The incidence of fetuses and litters with ossification centres on the seventh cervical vertebra and rib(s) on the seventh cervical vertebra was significantly increased at 300 mg/kg/day and incidences of the former were slightly increased at 50 mg/kg/day (exposure ratio 0.07). The incidences for both findings at 300 mg/kg/day were above the historical control range of the test facility. The incidence of litters and fetuses with unossified/incomplete/irregular/semi-bipartite/bipartite sternebrae and xiphisternum was significantly increased.

In rabbits, sub-maternotoxic dosing at ≥ 30 mg/kg/day (exposure ratio 1) was associated with a significant ($p < 0.05$) increase in the incidence of fetal malformations. Key effects included reduced/small lung lobes, absent accessory lobe, fused lung lobes, an additional vessel on the aortic arch, diaphragmatic hernias, extra/rudimentary thirteenth ribs and misshapen hyoid bone and reduced number of phalanges in the pollex. Effects observed only at 60 mg/kg/day (exposure ratio 3) included micropthalmia, exencephaly, premature eyelid opening with cataract formation and malpositioning of digits. Fetal weights were decreased at 60 mg/kg/day.

There is strong mechanistic data (based on observations in CDK4 knockout mice) to suspect developmental effects including adenohypophyseal hypoplasia, maldevelopment of the immune system, pancreatic beta cells and pituitary dwarfism (discussed above).

Pregnancy classification

Malformations observed in animal studies and observations in CDK4 knockout mice indicate that Pregnancy Category D is appropriate for ribociclib.[35] Pregnancy Category D is also recommended for palbociclib.

Local tolerance

Based on the results of a rabbit semi-occlusive primary skin irritation/corrosion study and a mouse local lymph node assay study ribociclib is not a skin irritant or sensitiser.

Effects on the GIT are discussed above under 'Repeat dose toxicity'.

[35] Australian Pregnancy 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.

Phototoxicity

While ribociclib absorbs ultraviolet (UV) B and UV A light, an in vitro phototoxicity assay indicated that ribociclib is not phototoxic.

Paediatric use

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

Nonclinical summary and conclusions

Comments on the nonclinical safety specification of the risk management plan

The information contained in the nonclinical sections of the risk management plan (RMP) and the conclusions of the RMP are in general agreement with the findings of the nonclinical evaluation except for the following:

- *Lung and mesenteric lymph node:* Accumulation of alveolar macrophages/foam cells was unlikely due to inhalation of small droplets of the formulation. The finding was most likely a sign of phospholipidosis, which is a systemic effect of ribociclib and common finding in toxicity studies with cationic amphiphilic agents.
- *Effect of ribociclib on transporters:* Ribociclib showed inhibitory activity against OCT1 with a K_i value of 17.3 μM, which is only 11 fold higher than the clinical steady state unbound C_{max}. Thus clinical interactions with OCT1 substrates may occur.

Nonclinical summary

- The submitted nonclinical dossier was ICH S9 compliant and was of acceptable quality.[34]
- Ribociclib selectively inhibited CDK 4/6 *in vitro* and indirectly inhibited Rb phosphorylation in neoplastic cells producing G1 restriction point, cytostasis, cell cycle arrest. Amongst human breast cancer cell lines, ER+ luminal breast cancer cells were the most sensitive *in vitro*. Ribociclib had no inhibitory activity against pRb negative breast cancer cell lines. In immune deficient mice xenograft models, ribociclib inhibited tumour growth in most cases and induced regressions in some tumour types. In ER+ tumours efficacy was increased by concurrent anti-oestrogen treatment (letrozole or fulvestrant) or PI3K inhibition. Post drug holiday resumption of treatment was less efficacious (slowed growth, no regressions). The primary pharmacological actions of ribociclib are not target cell specific that is, cytostatic effects occur in many replicating cell populations. Rapidly dividing populations are more susceptible to its effects (nonclinical and human clinical correlates detected). Off target inhibition of PDE4D may occur (nausea and emesis are possible due to actions on PDE4). Two major human metabolites, LEQ803 and CCI284 have lower CDK4/6 inhibitory activity than ribociclib, and are unlikely to have a significant contribution to the primary pharmacological effects of ribociclib.
- Safety pharmacology studies assessed effects on the cardiovascular, respiratory (no adverse effects) and central nervous systems (no adverse effects). Ribociclib was channelopathic at hERG and Nav1.5, and induced QTc prolongation and, more rarely, PVCs *in vivo* in dogs.
- GI absorption was by rapid, moderate passive perfusion. *In silico* modelling predicts gastric pH (pH 1.5 to 8.0) will not affect oral bioavailability. Oral bioavailability (lower

in rats compared with dogs and humans) was moderate (first pass effect). Clearance was rapid (lowest in dogs, highest in rodents/monkeys) and greatly exceeded hepatic blood flow. High phase II sulfation in female rats resulted in higher clearance and lower AUC (> 10 x in some cases) than in male rats. V_d was high (in part due to melanophilic sequestration). Plasma protein binding was moderate (f_u 0.2 to 0.34 in all species including human). Drug associated radioactivity was rapidly, widely and extra-vascularly distributed (except CNS). Tissue elimination $t_{½}$ was short except in pigmented tissues, lymph nodes, preputial glands, lacrimal glands, Harderian glands, pituitary and testis. Hepatic uptake was mainly by passive permeation. In rats metabolism was by sulfation to metabolite M8 and N-dealkylation to LEQ803 with subsequent phase II reactions. In dogs and humans, metabolism was by oxidation. The major plasma form was ribociclib with two major metabolites (LEQ803 and CCI284), both of which were formed in animal species used in the toxicity studies. Ribociclib metabolism is mainly by CYP3A4 with minor contribution by FM03. CYP3A4 metabolism generated reactive intermediates and covalent drug-protein adducts (which might be responsible for hepatobiliary injury). The major route of excretion was faecal with some active P-gp mediated intestinal excretion.

- Drug-drug interactions are likely at CYP3A4 (ribociclib is predominantly metabolised by CYP3A4 and is an inhibitor of this enzyme). Ribociclib is an inhibitor of several transporters. Clinically relevant inhibition of OCT2 (renal uptake), MATE1 (renal and biliary efflux), BSEP (biliary efflux), BCRP (biliary and intestinal efflux), MATE2K (renal efflux, low risk), and OCT1 (hepatic uptake) may occur. Ribociclib is a P-gp substrate. However, due to its moderate to high passive permeability, the rate and extent of ribociclib absorption in humans are unlikely to be significantly impacted by co-administered P-gp inhibitors or inducers. Strong P-gp inhibitors might have some effects on active P-gp mediated intestinal secretion.
- Ribociclib had a low order of acute oral toxicity in dogs (key effect after an oral dose: emesis; possibly PDE4 inhibition related).
- Oral repeat dose toxicity studies were conducted in rats (≤ 27 weeks) and dogs (≤ 39 weeks) at relatively low exposure levels. Major targets were bone marrow and haematolymphopoietic system (bone marrow hypocellularity, anaemia, neutropaenia, thrombocytopenia, lymphoid germinal centre depletion), hepatobiliary system (mild), renal tubular epithelia (mild, no decompensated renal failure), skin (epidermal atrophy), bone and cartilage (decreased chondrogenesis and osteogenesis), and spermatogenesis. The effects (except hepatobiliary) were likely primary pharmacologically mediated. The skeletal effects may result in poor fracture healing/malunions. Findings in CKD4 knockout mice suggest that the following effects not observed in the toxicology studies may occur in patients: a) insulin deficient diabetes mellitus and decreased pancreatic beta cells; b) adenohypophyseal hypoplasia due to decreased lactotrophs; c) defects in thymic T cell development; d) GI tract erosions and ulceration; and e) decreased erythrocyte lifespan and increased fragility.
- Ribociclib was not mutagenic in bacterial mutation assays or clastogenic *in vitro* (in human lymphocytes and mouse lymphoma cells) or *in vivo* (rat bone marrow micronucleus test).
- Subclinical doses of ribociclib disrupted spermatogenesis. Ribociclib or its metabolites cross the placenta and galactogenic transfer is high in rats. Sub-maternotoxic dosing of rabbits was associated with adverse effects on the development of the lungs, aortic arch, diaphragm, ribs, hyoid bones, manus and pes, skull and eyes in the fetus. CDK4 knockout mouse data suggest that ribociclib may inhibit pancreatic beta cell, adenohypophysis and T cell development.

- Ribociclib has low phototoxic risk. Ribociclib is not irritating or corrosive to the skin; however, there are strong mechanistic reasons (based on CDK4/6 knockout mouse data) to suspect that ribociclib will cause GI erosion and ulceration.

Conclusions

- The nonclinical primary pharmacology studies support the proposed indication of ribociclib, although ribociclib had no inhibitory activity against pRb negative breast cancer cell lines *in vitro*.
- Ribociclib will likely induce selection pressure associated drug escape and resumption of ribociclib treatment after a drug holiday will likely be associated with reduced efficacy. The mechanisms of ribociclib resistance have not been studied.
- The animal toxicity studies revealed the following clinically relevant findings: a) cardiac channelopathies and QT prolongation; b) adverse effects on bone marrow and lymphoid systems resulting in anaemia, neutropaenia, thrombocytopenia and lymphoid depletion (potentially increased risk of infection); c) skin atrophy; d) defective chondrogenesis/osteogenesis; and e) disruption of spermatogenesis (risk of male infertility).
- Based on CDK4/6 knockout mouse data, there are strong mechanistic reasons to suspect that ribociclib treatment may be associated with: a) increased risk of diabetes mellitus (including adverse developmental effects); b) increased risk of adverse effects on the adenohypophysis (including adverse developmental effects), hypoprolactinaemia and other disruptions of the hypothalamic pituitary gonadal axis; and c) gastrointestinal disturbances.
- Clinically relevant drug interactions may occur at CYP3A4, OCT2 (renal uptake), MATE1 (renal and biliary efflux), BSEP (biliary efflux), BCRP (biliary and intestinal efflux), MATE2K (renal efflux, low risk), and OCT1 (hepatic uptake). Strong P-gp inhibitors might increase plasma ribociclib concentration.

Nonclinical evaluator's recommendation

There are no nonclinical objections to the approval of ribociclib. The toxicity of combination treatment with letrozole has not been evaluated in nonclinical studies. The absence of toxicity studies for new combination therapy is not uncommon for anticancer drugs.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Clinical rationale

The sponsor's Clinical Overview provided a product development rationale. This included a brief description of the epidemiology of breast cancer worldwide and current treatment options for the target indication. The treatment options described include agents that are available outside of Australia, such as palbociclib in combination with letrozole.

As summarised below, the Clinical Overview also described:

- The unmet need in the first line setting for postmenopausal women with HR positive, HER2 negative advanced breast cancer due to endocrine resistance, as described in the *Introduction to product submission* and the *Product background*, (see above).
- The purported mechanism of action and development of CDKi.

Contents of the clinical dossier

- Biopharmaceutic/pharmacokinetic studies:
  - Study A2103, bioequivalence of the capsule formulation film coated tablet; food effect on the pharmacokinetics of the 600 mg film coated tablet formulation (single dose).
  - Study A2111, food effect on the pharmacokinetics of the 600 mg drug in capsule formulation (single dose).
  - Study X2101, relative bioavailability of the capsule formulation to an oral solution.
- Pharmacokinetic studies in healthy subjects:
  - Studies A2102, A2102b, A2102c and A2102d; initial tolerability studies.
  - Study A2109 in patients with impaired hepatic function.
  - Studies A2101 and A2106; drug interaction studies.
  - A population pharmacokinetics (PopPK) study and exposure response study (absolute neutrophil count).
- Key clinical studies included with the initial submitted data were:
  - Study A2301, the pivotal Phase III study (also known as the MONALEESA-2 trial).
  - Study X2107, a supportive Phase I/II supportive study.
  - Studies X2101, X1101 and XUS03; additional early phase, open label, single arm studies.
- Analyses across more than one study:
  - LEE011 QT/QTc safety analysis report.
  - LEE011 hepatic safety report.
- Other documents of clinical relevance included:
  - A Nonclinical Overview and Nonclinical summaries; Quality Overall Summary and Drug Product Summary; a Clinical Overview Clinical Summaries for Biopharmaceutic Studies and Associated Analytical Methods; Summaries of Clinical Pharmacology, Clinical Efficacy, and Clinical Safety.
  - Synopses or summaries of individual studies; study reports for in vitro and animal studies.
- Following the first round evaluation, the sponsor provided data the following ongoing studies:
  - Study F2301 (also known as the MONALEESA-3 trial).
  - Study E2301 (also known as the MONALEESA-7 trial).
  - Study XDE01 (also known as the RIBECCA trial).
  - Study A2404 (also known as the CompLEEment-1 trial).

Paediatric data

No paediatric data is provided. The sponsor's EU Safety RMP version 1.0 provides the following rationale: '*Breast cancer occurs almost entirely in adults (extremely rare in children), and is covered by EMA's class waiver (CW/1/2011) and the applicability of this class waiver for the proposed ribociclib indication was confirmed by EMA on 12 September 2014 (EMEA-521229-2014). In the US [the sponsor] has received a full waiver of the requirement to conduct paediatric studies with ribociclib at the time of the initial NDA submission for the HR+ positive metastatic breast cancer patient population'.* A copy of the EMA's class waiver and the EMA's confirmation of applicability of this to ribociclib for the proposed indication is provided in the dossier.

Good clinical practice

The sponsor's cover letter states that '*The nonclinical and clinical program for ribociclib was conducted in accordance with the available guidelines, and was discussed with health authorities in the USA and Europe over the course of the development program'*.

Pharmacokinetics

Studies providing pharmacokinetic data

Studies A2101, A2102, A2103, A2106, A2109, A2111, X1101, X1201, X2107 and A2301 provided pharmacokinetic and biopharmaceutic data.

Evaluator's conclusions on pharmacokinetics

The sponsor has provided a number of studies that investigate the pharmacokinetics of ribociclib in healthy subjects and in patients with advanced cancer, including postmenopausal women with advanced ER+/HER- breast cancer. The pharmacokinetics of ribociclib in humans were not fully described by these studies. Animal and *in vitro* studies provided some additional information.

In the evaluator's opinion, high inter-individual variability appears to be inherent with ribociclib. This variability limited the capacity to compare ribociclib pharmacokinetics in different populations and in different circumstances; the ranges reported across individuals and variables were so wide that considerable overlap was inevitable. This effect was more marked with smaller groups.

Within this limitation, the pharmacokinetics of ribociclib appeared similar in healthy subjects and in patients with advanced cancer. The ribociclib pharmacokinetics also appeared similar between patients with advanced cancer and postmenopausal women with advanced ER+/HER- breast cancer.

Ribociclib appears to be rapidly absorbed and widely distributed. The extent of absorption and degree of first-pass effect in humans is not known. An estimate of absorption of 58.8% of an orally administered dose has been made. In animal studies, ribociclib does not appear to cross the blood brain barrier but does cross the placental barrier and does appear in breast milk. In rats, ribociclib was highly concentrated in melanin containing structures in the eye and meninges.

Clearance appears to be largely by hepatic metabolism (predominately by CYP3A4), with excretion of the metabolites in the bile. The extent of clearance of unchanged ribociclib by biliary or GIT secretion is not known but would represent less than 17% of an administered dose on the basis of the absorption, distribution, metabolism and excretion

study. Renal clearance (of unchanged ribociclib and metabolites) accounts for 22% of the administered dose but may account for approximately 40% of the absorbed dose.

Accumulation occurs with multiple daily dosing, with steady state reached within 8 days.[36] Trough levels at Day 15 of the first 6 cycles do not show any accumulation across cycles. Dose dependency was not demonstrated, with single or multiple doses.

Body weight was found to have a significant impact on ribociclib pharmacokinetics in a PopPK analysis. This was assessed as not clinically important due to the estimated effect with body weight being much less than the inherent inter-individual variability.

The effect of renal impairment on ribociclib has not been adequately demonstrated.

Moderate and severe hepatic impairment appears to increase ribociclib exposure.

The effect of Asian race, or other races, on ribociclib pharmacokinetics has not been adequately demonstrated.

Drug-drug interaction studies found that:

- Ribociclib pharmacokinetic clearance was reduced and exposure increased by a strong CYP3A4 inhibitor.
- Ribociclib pharmacokinetic clearance was increased and exposure decreased by a strong CYP3A4 inducer.
- Ribociclib reduces the clearance and increases exposure to a sensitive CYP3A4 substrate.
- Ribociclib has a clinically unimportant effect on the pharmacokinetics of a sensitive CYP1A2 substrate.

In the evaluator's opinion, potential drug-drug interactions with agents that raise gastric pH, with letrozole, and with moderate or weak CYP3A4 inhibitors have not been adequately described.[37]

A PopPK analysis was provided. This analysis was limited due to the small numbers of patients included in many of the covariates that were investigated and the high inter-individual variability that was found. Conclusions should, therefore, be drawn with care with respect to the covariate factors of CYP3A4 inhibitors, proton pump inhibitors (PPI), age, renal impairment, hepatic impairment and ECOG PS.[38] However, the findings that the effect of body weight on ribociclib is unlikely to have clinical significance as the effect is less than that of the remaining inter-individual variability and that the effect of gender is negligible, are reasonable.

[36] Clarification: The evaluator attributed accumulation to auto-inhibition of CYP3A4.
[37] Clarification: Potential drug-drug interactions with agents that raise gastric pH, with letrozole, and with moderate or weak CYP3A4 inhibitors have been evaluated based on clinical data, popPK and PDPK modelling and drug-drug interaction is not expected. No dose adjustments are required for mild and moderate CYP3A4 inhibitors, however, if treatment with a moderate CYP3A4 inhibitor is initiated, close monitoring for ribociclib-related AEs is recommended.
[38] ECOG PS: Eastern Cooperative Oncology Group Performance Scale; a validated 6 point scale of standardised criteria with 0 signifying full activity, able to carry out all pre-disease activity without restriction and 6 signifying death. Oken M et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

Pharmacodynamics

Studies providing pharmacodynamic data

Studies A2301, X2101, X2107, X1101, a QT/QTc safety analysis report and an exposure-response analysis provided pharmacodynamic data.

Evaluator's conclusions on pharmacodynamics

The nonclinical and clinical studies have demonstrated that ribociclib may have an inhibitory effect on tumour growth. However, the limited results from the clinical studies do not confirm the proposed mechanism of action.

According to the proposed mechanism of action, and as shown in the in vitro and in vivo studies, phosphorylated Rb is expected to increase with ribociclib treatment and the percentage of tumour cells expressing Ki67 is expected to decrease. According to the preclinical studies, inhibition of tumour growth would be limited to those patients whose tumours were pRB positive.

Interpretation of the results with regard to effects of ribociclib on phosphorylated pRB and Ki67 in patients is limited due to a number of factors:

- the large number of missing results (paired tumour specimens for only 10 to 15 of 134 patients and paired skin specimens for 48/134 patients in Study 2101; paired tumour specimens for only 4 to 6/47 patients in Study X2107 and no paired specimens for Studies X1101 or A2301).
- the small number of samples overall.
- the limited time frame with the on-treatment specimens collected after the first 15 to 21 days of treatment
- the wide range of results with overlapping of the ranges for baseline and steady state for those studies in which baseline and on-treatment specimens were available.

It is notable that, for the small number of individual patients for whom there are paired specimens available, the results show no consistent pattern of change in either phosphorylated pRb or Ki67. An effect of ribociclib on the downstream effects of inhibition of CDK4/6 has not been satisfactorily demonstrated in any of the clinical studies presented by the sponsor. This may be due to the limitations of the investigations listed above.

The effect of the intact expression of the biomarker pRB on the efficacy of ribociclib in patients has not been adequately explored. The limited information that is available does not appear to support the mechanism of action. According to the proposed mechanism of action of ribociclib, patients with no or low pRB would be expected to obtain no benefit from ribociclib treatment and the outcome in the 2 treatment arms of Study A2301 for these patients should reflect the effect of letrozole alone. However, a similar benefit per investigator was reported with ribociclib for patients with low or high total pRB. The efficacy analysis according to biomarker status did not include an analysis of efficacy performed within the ribociclib + letrozole arm. The sponsor was asked and provided this for patients with high versus low total pRB by H-score.[39]

[39] The H-score is a commonly used method of assessing the extent of nuclear immunoreactivity, applicable to steroid receptors. McCarty K et al. Estrogen receptor analyses. Correlation of biochemical and immunohistochemical methods using monoclonal antireceptor antibodies. *Arch Pathol Lab Med*. 1985;109: 716–721.

The secondary pharmacodynamics effects of ribociclib seen in the clinical studies are consistent with the target organs of toxicity identified in the nonclinical studies. The effects on bone marrow, lymphoid system, testes, intestinal mucosa and skin are considered to be due to the pharmacological effect of ribociclib on rapidly dividing cells. The mechanism of injury to the liver is unknown. The effect on QT prolongation was predicted from the effect of ribociclib (and LEQ803) on the hERG channel in *in vitro* and nonclinical studies. Exposure-response analyses have been performed for hepatotoxicity, neutropaenia and QT prolongation. Neutropaenia and QT prolongation were found to be dose dependent and to show some recovery to baseline during the week off in the dosing regimen. Hepatotoxicity was not found to be dose dependent, but data was limited.

An investigation of the pharmacodynamic effect of letrozole during co-administration with ribociclib found that reduction in plasma oestradiol levels from baseline were unaffected by ribociclib. Other drug-drug interactions may be predicted from the pharmacokinetic interactions described above, in particular, the increased risk of concentration-dependent secondary pharmacokinetic effects of ribociclib with co-administration of a CYP3A4 inhibitor. An additive effect, and therefore increased risk, is expected if ribociclib is co-administered with other agents that also increase the QT interval.

Dosage selection for the pivotal studies

Studies providing dose selection data

Studies X1101, X2101 and X2107 provided dose selection data.

Evaluator's conclusions on dose selection for the pivotal studies

On the basis of the studies provided, and in the absence of any investigations of alternative dosing schedules, the dose of 600 mg using a 3 weeks on/1 week off dosing regimen is appropriate for the pivotal study. The choice of control arm is consistent with current recommendations.

Efficacy

Studies providing efficacy data

Study A2301 was provided as the pivotal Phase III study for the proposed indication, with Study X2107 considered as supportive. In addition, a number of early phase studies were provided in the dossier; these included Studies X2101, X1101 and XUS203.

Evaluator's conclusions on efficacy

The sponsor has provided a pivotal Phase III double blind, randomised, multicentre study of ribociclib + letrozole versus placebo + letrozole in 668 postmenopausal women with ER+/HER2- advanced breast cancer who had previously received no prior therapy for their advanced breast cancer. Randomisation was 1:1 and stratified according to the presence of visceral disease (lung and/or liver metastases). The primary endpoint was progression free survival (PFS) according to investigator assessments of tumour response; an analysis according to the assessments of tumour response by an independent radiology group (blinded independent central review; BICR) was provided as supportive evidence.

Secondary endpoints included overall survival, overall response rate, duration of response;[40] and clinical benefit rate.

An interim analysis of efficacy was performed after 80% of expected PFS events had occurred. The median duration of follow-up for PFS at this time was 11.1 months and there had been 243 progression events, 93 in the ribociclib/letrozole arm and 150 in the placebo/letrozole arm. There were 425 patients censored from the analysis: 241 (72.2%) in the ribociclib + letrozole arm and 184 (55.1%) in the placebo + letrozole arm. The Kaplan-Meier (K-M) estimate of median PFS was not reached in the ribociclib + letrozole arm (95% CI: 19.3, upper bound not estimable (NE)) and was 14.7 months in the placebo + letrozole arm (95% CI: 13.0 to 16.5) with hazard ratio 0.556 (95% CI: 0.429 to 0.720; stratified log rank $p = 3.29 \times 10^{-6}$). This met the pre-specified criteria for interim analysis of PFS to conclude superior efficacy of ribociclib plus letrozole over placebo plus letrozole. Results were similar for the stratification groups of visceral disease and no visceral disease. The K-M analysis of PFS per BICR assessments also favoured the ribociclib + letrozole arm with HR = 0.592 (95% CI: 0.412, 0.852; p = 0.002). The analysis was based on 122 progression events (compared to 243 events per local investigator) with 50 in the ribociclib/letrozole arm and 72 in the placebo/letrozole arm. There were 546 (82%) patients censored from the analysis: 284 (85.0%) in the ribociclib + letrozole arm and 262 (78.4%) in the placebo + letrozole arm. In contrast to the primary analysis per investigator, the K-M estimate of median PFS was 22.9 months in the ribociclib + letrozole arm and was not reached in the placebo + letrozole arm. In the evaluators' opinion, this supportive analysis did not meet the prespecified criteria for interim analysis of PFS to conclude superior efficacy of ribociclib plus letrozole over placebo plus letrozole.[41]

The results for overall survival, time to response and duration of response were immature, with no conclusions able to be drawn.

The overall response rate according to investigator assessments of tumour response was 40.7% (with 9 patients achieving complete response (CR) and 127 achieving PR) for the ribociclib + letrozole arm and 27. 5% (with 7 patients achieving CR and 85 achieving PR) for the placebo + letrozole arm ($p = 1.55 \times 10^{-4}$). The clinical benefit rate (defined as CR + PR + SD or non-CR/non-progressive disease (PD) for 24 weeks or more) was similar in each arm with 79.6% in the ribociclib + letrozole arm versus 72.8% in the placebo + letrozole arm (p = 0.018).

The result of the primary analysis in the pivotal study shows a potentially clinically meaningful improvement in PFS in patients treated with ribociclib in combination with letrozole. An estimate of the potential increase in PFS cannot be made as the median duration of PFS has not been reached in the ribociclib + placebo arm. [In the evaluator's opinion], the supportive analysis of the PFS endpoint according to BICR assessments did not meet the pre-specified criteria for interim analysis of PFS to conclude superior efficacy of ribociclib + letrozole. There were considerable discrepancies between the investigator and BICR assessments of tumour response, with 243 progression events per investigator compared to 122 progression events per BICR. The reliability and reproducibility of the method used to determine progression in this analysis is questionable, given this lack of agreement between the investigators and the BICR despite using the same tool (the sponsor's version 3.1 Guideline to the RECIST 1.1 Criteria) and the same radiological images for their assessments.

[40] Clarification: duration of response was an exploratory objective of Study A2301.

[41] The study was designed as a 2-look group sequential design with Haybittle-Peto boundary; in order to conclude superior efficacy the observed p-value had to be less than p = 1.29×10-5 (or Z = 4.2077, HR = 0.56) for PFS analysis based local investigator assessment.
BICR analysis was a supportive analysis without any plan to compare with efficacy stopping boundaries.

The interim analysis was performed later than originally planned (after 80 of expected PFS events instead of the 70% specified in the original protocol).[42] This analysis has resulted in a number of important results being immature, with these including the median PFS, overall survival (OS) and duration of response. At the September Pre-submission meeting, the sponsor was requested by the TGA to provide a justification for the timing of this analysis and the application, given that another analysis is planned by the sponsor in early 2017 and that more meaningful results for OS may be available at that time. This justification was provided in the sponsor's response to action items from the Pre-submission meeting. According to this response, the sponsor considered the results for PFS to be mature and robust at the time of the interim analysis and that this analysis was actually performed with 243 PFS events (per investigator) instead of the planned 211. The sponsor confirmed that the scheduled analysis for OS is to take place after 120 OS events and this is expected in the first half of 2017.

The evaluator does not agree that the results for the PFS are mature or robust. There were 425/664 (64%) patients censored from the analysis per investigator and 546 (82%) patients censored from the analysis per BICR. This resulted in the median PFS in the analysis per investigator being not evaluable for the ribociclib arm while the median PFS in the analysis per BICR was not evaluable for the placebo arm. The sponsor's argument that the median PFS per BICR of 22.9 months for the ribociclib arm was driven by one PFS event goes against these being 'robust' results. The results for PFS may be statistically significant but such a high proportion of censored patients and the differing results between the analyses per investigator and per BICR, creates uncertainty around the result. The results for the other important endpoints of OS and duration of response are too immature to be meaningful.

The interim results for Arm 1 of the open label, single arm, Phase Ib/II study, Study X2107, provides additional information regarding the use of ribociclib + letrozole in postmenopausal women with ER+/HER2- advanced breast cancer in the first-line and subsequent setting. In the 28 women who had not received prior treatment for advanced breast cancer, and after a median duration of treatment of 8.3 months of ribociclib + letrozole, the overall response rate (ORR) was 39.3% (one patient achieved CR, 10 patients achieved PR) and the K-M estimate of median PFS was not reached. In the 19 women who had received prior treatments for advanced breast cancer and after a median of 3.6 months of treatment, the ORR was 5.3% (one patient achieved PR) and the K-M estimate of median PFS was 5.2 months (95% CI: 2.3, 8.0). This study shows dramatically different results in the 2 small groups analysed. This may be due to poor efficacy of ribociclib + letrozole in pre-treated or it may be due to the effect of small numbers or there may be other factors affecting the results .Whatever the reason, these results raise further uncertainties regarding the efficacy of ribociclib.

The limited efficacy information available from the early phase studies suggest that ribociclib has little biological activity as a single agent, even in malignancies that are pRb positive. This is counter to the proposed mechanism of action which suggests that biological activity should be observed in these tumours and is not consistent with the results of the nonclinical studies as described by the sponsor.

The evaluator is of the opinion that the efficacy of ribociclib + letrozole for the proposed indication has not been adequately established. The immaturity of the interim analysis performed in the pivotal study, together with the discordance between the investigator's and the BICR assessments for tumour response, raise too much uncertainty. The difference in results between the 2 groups in the supportive study raises further uncertainty.

[42] The interim analysis was planned after 70% (211/302) of the 302 targeted PFS events and actually performed after 80% (243/302) of the 302 targeted PFS events.

Safety

Studies providing safety data

The pivotal Study A2301 and supportive Study X2107, along with monotherapy based Studies X2101, XUS03 and X1101 provided safety data.

In addition, 2 documents that address specific safety concerns were provided: a hepatic safety report and a QT/QTc safety assessment report. An exposure-response analysis of neutropaenia in cancer patients was also provided.

Patient exposure

The sponsor's overall safety evaluation is based on data from 568 patients: 381 patients from ribociclib 600 mg/letrozole 2.5 mg combination therapy Studies A2301 and X2107, and 187 patients on ribociclib 600 mg monotherapy from Studies X2101, XUS03 and X1101.

Safety issues with the potential for major regulatory impact

There are 3 toxicities reported that have possible major regulatory impact: neutropaenia, hepatotoxicity and QT prolongation. The latter 2 of these were each examined in a specific safety report provided by the sponsor. Neutropaenia was investigated in an exposure response analysis.

Postmarketing data

Not applicable. At the time of submission, ribociclib was under evaluation and not approved in any country or region.

Evaluator's conclusions on safety

There is limited experience with ribociclib to date with the safety analysis based on 568 patients overall and 381 patients for the combination of ribociclib + letrozole. There is virtually no experience with long-term use, with only 201 patients treated with ribociclib 12 months or longer and 44 for 18 months or longer. These numbers will not allow identification of rare adverse events, full characterisation of identified serious adverse effects, adverse effects associated with long-term use, and characterisation of safety in subgroups.

Study A2301 has shown that the addition of ribociclib to letrozole is associated with an overall substantial increase in toxicity. AEs from Study A2301 are summarised in Table 7.

Table 7: Summary of AEs, Study A2301

	Study A2301; Median duration of follow-up 15.3 months	
	ribociclib + letrozole N = 334 n(%)	placebo + letrozole N = 330 n(%)
Relative dose intensity	87.5%	100%
On-treatment deaths	3 (0.9)	1 (0.3)
Grade 3 or 4 AEs	271 (81.1)	108 (32.7)

	Study A2301; Median duration of follow-up 15.3 months	
	ribociclib + letrozole N = 334 n(%)	placebo + letrozole N = 330 n(%)
AEs leading to discontinuation	50 (15.0)	10 (3.0)
Dose reduction and/or interruption due to AE	244 (73.1)	52 (15.8)
AE Neutropaenia, Grade 3/4	161 (48.2)	2 (0.6)
QTcF increase > 60 ms	9/329 (2.7)	0
Hy's law cases	4/327 (1.2)	0

This resulted in a relatively high proportion of patients who discontinued ribociclib treatment due to adverse events (AE) and a very high proportion that needed dose modification due to AEs. Despite this, acceptable levels of exposure of ribociclib were achieved. There were a low number of non-disease related deaths.

Common AEs that were reported in a greater proportion of patients receiving ribociclib were in keeping with the pharmacological effects of ribociclib: neutropaenia (+56%), nausea (+23%), alopecia (+18%) vomiting (+14%), anaemia (+14%), and AST/ALT increase (+12%).

There are 3 identified toxicities that have been identified and that have possible regulatory impact: neutropaenia, hepatotoxicity and QT prolongation. Of these, neutropaenia appeared to be adequately managed by monitoring and dose modification in accordance with the guidelines provided. There was a low rate of febrile neutropaenia reported.

Hepatotoxicity was common in patients receiving ribociclib although the mechanism of injury is not understood. In Study A2301, hepatotoxicity events of any grade were reported in 24% of the patients receiving ribociclib compared to 14% of patients receiving placebo. In the patients receiving ribociclib, 11% of patients had Grade 3/4 hepatotoxicity events and 7.6% of patients required dose modification. Of greatest concern is that there were 4 confirmed Hy's law cases identified in patients receiving ribociclib in the pivotal study and a further 3 cases identified in non-dossier studies.[43] None of these cases had fatal outcome. Early detection of ribociclib and cessation of treatment resulted in return to baseline in most patients, although this could be prolonged.

QT prolongation appears to be due to a dose related effect of ribociclib on the hERG channel. This adverse effect and its management is still being characterised.[44] Although electrocardiogram (ECG) monitoring has been included in all clinical studies, there were 2 safety related protocol amendments in Study A2301 that enhanced the recommendations regarding the management and monitoring for QT prolongation. These

[43] Hy's law criteria: Evidence of hepatocellular injury with The drug causes hepatocellular injury, an elevated ALT or AST > 3 x the upper limit of normal and bilirubin of greater than 2× the upper limit of normal with no other reason to explain the rise in aminotransferases and bilirubin.
[44] Guidelines for dose modifications and monitoring are captured in the PI for this adverse effect and its management, with additional characterisations ongoing

included the recommendation that ECGs be performed on Day 1 of every cycle to Cycle 9 and that if a patient had any QTcF values ≥ 481 ms at any time, then continued ECG monitoring was indicated for all subsequent cycles.[45] Potential complications related to QT prolongation include ventricular arrhythmias, unexplained sudden death or cardiac arrest and syncope. Each of these, except for ventricular arrhythmias, has been reported with ribociclib. The lack of ECGs that were performed prior to or at the reported syncopal events precludes the exclusion of QT prolongation by ribociclib as a contributor. The event of sudden death occurred during ribociclib treatment in a patient with hypokalaemia and who had previously had QTcF of 481 ms.

Additional serious toxicities may be identified with greater ribociclib experience. These may include pulmonary toxicity.

Close monitoring and proactive dose modifications were used in the clinical studies to manage these adverse events. The use of ribociclib will add unfamiliar monitoring and complexity in the choice of co-administered treatments for oncologists managing these patients. It is important that clear and rigorous monitoring recommendations, together with appropriate management advice, is provided in the post-approval setting if the safety reported in the clinical trials is to be replicated in the wider setting.

The TGA adopted EMA 'Guideline on the evaluation of anticancer medicinal products in man' (EMA/CHMP/205/95/Rev.4) recommends that, treatments that are administered with the intent to achieve long-term disease control, if there is a major increase in toxicity, then the principal object should be to demonstrate improved survival. In the evaluator's opinion, the addition of ribociclib to letrozole treatment has resulted in a major increase in toxicity.

First round recommendation regarding authorisation

Authorisation of ribociclib for the proposed indication is not recommended. This recommendation may be changed if a subsequent application provides evidence of a favourable effect on overall survival and a better characterisation of serious toxicities.

Clinical questions

Discussion of the clinical questions posed to the sponsor and requests for further clinical data are beyond the scope of this AusPAR.

Second round evaluation of clinical data submitted in response to questions

Discussion of the sponsor's responses to clinical questions and requests for further clinical data are beyond the scope of this AusPAR.

Second round benefit-risk assessment

The sponsor has provided more mature efficacy results that confirm a clinically meaningful improvement in median PFS of 9 months over treatment with letrozole alone. This improved PFS may result in a beneficial delay in disease progression and the use of chemotherapy (in patients where this may be considered appropriate). Results for OS remain immature but are encouraging.

[45] QTcF is the QT interval corrected for heart rate using Fredericia's formula.

As noted above, the PFS benefit comes at the cost of a substantial increase in toxicity over letrozole alone. In the pivotal study, these toxicities appear to be manageable, within the confines of a monitoring structure that continued throughout treatment combined with detailed dose modification recommendations for toxicities detected through this monitoring. However, it is important to note that there was one event of sudden death in a patient with QT prolongation and hypokalaemia.

On the basis of the updated efficacy results and according to the safety reported in the pivotal study, the evaluator considers the benefit-risk assessment to be in favour of ribociclib for the proposed patient population.

The evaluator does not consider the safety of ribociclib to have been fully characterised, given the relatively small number of patients exposed and the even smaller number of patients treated long term. It is possible that the use of ribociclib in the wider population will result in a better understanding of the critical toxicities of hepatotoxicity, QT prolongation and myelosuppression and future information (from routine pharmacovigilance or from ongoing or future clinical studies) may alter the benefit-risk assessment.

The benefit-risk assessment may also be altered if, for other reasons, the safety as reported in the pivotal study is not reflected in the wider population. The evaluator is concerned that the draft PI recommends a considerable reduction in the duration of monitoring for toxicities, compared to that used in the pivotal study (first 6 months of treatment compared to throughout treatment), and that this may limit the ability for early detection of toxicities and result in worsened outcomes. The evaluator is particularly concerned that the toxicity of QT prolongation is infrequently managed by oncologists and its importance may be under-appreciated. These concerns should be addressed by ensuring that monitoring and dose modification advice provided in the PI is the same as that used in the pivotal study and by increasing the prominence of the warnings and advice provided in the PI regarding QT prolongation.

Second round recommendation regarding authorisation

The evaluator recommends that ribociclib be approved for the indication of:

> *Kisqali in combination with a non-steroidal aromatase inhibitor is indicated for the treatment of postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer, as an initial endocrine-based therapy.*
>
> *Note to indication: this approval is based on an improvement in PFS. An improvement in overall survival has not been demonstrated.*

This is provided there are adequate safeguards in the product documentation and the target population is appropriately informed of the risks of treatment.

VI. Pharmacovigilance findings

- The sponsor has applied to register a new chemical entity, ribociclib (Kisqali). Kisqali, in combination with letrozole, is proposed to be used for the treatment of postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer, as an initial endocrine-based therapy. Ribociclib is a reversible inhibitor of cyclin-dependent kinase 4 and 6.

- At the second round of evaluation, the sponsor revised the proposed indication to state *'in combination use with an aromatase inhibitor'* instead of *'in combination with letrozole'*.
- The proposed dosing regimen involves oral administration of three 200 mg tablets (600 mg) once daily for 21 consecutive days, followed by 7 days off treatment, resulting in a complete cycle of 28 days. Kisqali is co-administered with one letrozole 2.5 mg tablet taken once daily throughout the 28 day cycle.
- The sponsor has submitted EU-risk management plan (EU-RMP) version 1.0 (dated 24 August 2016; data lock point (DLP) 29 January 2016) and Australian specific Annex (ASA) version 1.0 (dated 19 September 2016) in support of this application. In its response to issues in the first round evaluation the sponsor has submitted EU-RMP version 1.1 (dated 13 February 2017, DLP 29 January 2016) and ASA version 2.0 (dated 28 April 2017) in support of this application.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below including changes agreed to by the sponsor in the response to issues raised in the first round evaluation (Table 8).[46]

Table 8. Summary of safety concerns with risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Myelosupression*	✓	–	✓	–
	Hepatobiliary toxicity	✓	–	✓	–
	QT interval prolongation	✓	–	✓	–
	Reproductive toxicity	✓	–	✓	–
Important potential risks	Renal impairment [To be changed to renal toxicity in the next RMP update]	✓	–	✓	–
Missing information	Safety in Japanese patients	✓	–	–	–
	Safety in patients with moderate or severe hepatic impairment*^	✓	–	✓	–
	Safety in patients with severe renal impairment*^	✓	✓	✓	–
	Safety in male patients with breast cancer*	✓	–	–	–

[46] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Long term use*^	✓	–	–	–
	Pulmonary toxicity**				

*Recommended by the RMP – The following recommendation was not agreed to by the sponsor: Hyperglycaemia (Important Potential Risk) and has been removed from the table.
** Recommended addition to Missing Information by the clinical evaluator at the second round of evaluation. Following Post-second round/Reconciliation: the clinical evaluator agreed to not include 'pulmonary toxicity' in the RMP.
^Recommended by the clinical evaluator – The following recommendations were not agreed to by the sponsor: Pulmonary toxicity/pneumonitis (Important Potential Risk) and Drug-drug interactions with moderate CYP3A4/5 inhibitors; agents that alter gastric pH; letrozole (Missing Information) and have been removed from table.

- No additional pharmacovigilance or risk minimisation activities were proposed in the first round. In its response, the sponsor agreed to add 'Safety in patients with severe renal impairment' as Missing Information, which has additional pharmacovigilance (Study CLEE011A2116). Also added under Missing Information are: Long term use and Safety in male patients with breast cancer.
- Routine risk minimisation is proposed for all important identified and potential risk, as well as for missing information in patients with hepatic and/or renal impairment.

New and outstanding recommendations – second round

The sponsor has adequately addressed the recommendations made in the first round report. There are two new recommendations following the second round evaluation:

- Recommendation 7: Pulmonary toxicity should be included as 'Missing Information' in the ASA as per the Clinical Evaluator's recommendation. Pharmacovigilance and risk minimisation activities should be assigned.[47]*
- Recommendation 8: The sponsor should provide an update to the TGA if an additional pharmacovigilance activity for the Missing Information 'long-term use' is implemented.

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 1.1 (Dated 13 February 2017, DLP 29 January 2016) with ASA version 2.0 (Dated 28 April 2017) to be revised to the satisfaction of the TGA, must be implemented (see outstanding issues above).

[47] ** Regarding safety specifications, the clinical evaluator recommended that the ASA to the RMP introduce 'pulmonary toxicity' as missing information. It is considered that Study A2301 and other presented studies were in total of sufficient size to detect a major signal for pulmonary AEs if one existed. There was no striking evidence in the controlled Study A2301 of such a signal. Overall, there has been a reasonable opportunity to examine whether ribociclib causes pulmonary toxicity. Therefore, it is not necessary to include 'pulmonary toxicity' as missing information, although the sponsor should present updated analyses of this issue in upcoming PSURs*

VII. Overall conclusion and risk/benefit assessment

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

Overview

HR+/HER2- advanced breast cancer

The evaluator writes*: 'There are no curative options currently available for advanced breast cancer and the aim of current therapy(ies) is to achieve long-term disease control.'*

In the Delegate's view, treatment of advanced breast cancer 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 list aligns with the goals outlined by Hayes et al. in UpToDate:

> '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'.[48]

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'.[48]

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).

Naughton and Ma state objectives of endocrine treatment are 'to maximise quality of life and to reduce the relatively worse side effect profiles associated with the use of chemotherapy'.[49]

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 organs.[50] Chemotherapy can be single agent or various combinations; choice is tailored but includes taxanes (for example, paclitaxel) and anthracyclines (such as doxorubicin).

[48] Hayes D et al., Systemic treatment for metastatic breast cancer: general principles; UpToDate,Topic 767 Version 30.0; 2015.
[49] Naughton M, and Ma C., Treatment approach to metastatic hormone receptor positive breast cancer: endocrine therapy; UpToDate Topic 778 Version 42.0; 2016.
[50] Schott A, Systemic treatment of metastatic breast cancer in women: chemotherapy; UpToDate Topic 83848 Version 11.0, 2015.

Therapeutic landscape

CDK4/6 inhibitors are new within the breast cancer therapeutic landscape.

Palbociclib was registered on the ARTG on 3 May 2017 with the following 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.*

At the time of ribociclib submission to the TGA (October 2016), palbociclib was not yet approved. Abemaciclib is not registered on the ARTG.

Mechanism of action

Ribociclib is a selective inhibitor of CDK4 and 6. More information about the mechanisms of CDK inhibitors can be found under the nonclinical findings section of this document. It is considered cytostatic rather than cytotoxic or pro-apoptotic.

Regulation (Australia)

Regulatory guidelines

The TGA has adopted the EU Guideline on the evaluation of anticancer medicines, EMA/CHMP/205/95/Rev.4 (and relevant appendices). Some other EU guidelines are relevant, for example 'Points to consider on application with 1) meta-analysis; 2) single pivotal study' (CPMP/EWP/2330/99). Variation from recommendations in such guidelines may suggest a need for examination of particular quality, efficacy and/or safety issues.

Regulation (Overseas status)

United States Food and Drug Administration

For the purposes of the Delegate's Overview, the status was last checked on 13 June 2017. Ribociclib was approved by the US FDA on 13 March 2017 with the following indication:

> *Kisqali is a kinase inhibitor indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.*

Post-marketing requirements

Post-marketing requirements were as follows in Table 9, with post marketing commitments listed in Table 10.

Table 9: Post-marketing requirements following Kisqali ribociclib approval (US FDA)

Number	Detail	Timeline
3168-1	Conduct a clinical trial to assess the efficacy and safety of an alternative dosing regimen for ribociclib after evaluation of ECG, pharmacokinetics and efficacy data from the ongoing MONALEESA-3 trial (Study CLEE011F2301) and MONALEESA-7 trial (Study CLEE011E2301) studies. The objective of studying an alternative dosing regimen is to mitigate the risks for QT prolongation without compromising efficacy. The primary safety assessments should include QT prolongation, hepatobiliary toxicities, and neutropaenia. The primary efficacy endpoint should be objective response rate (ORR).	Draft Protocol Submission: 06/2018 Final Protocol Submission: 12/2018 Trial Completion: 04/2022 Final Report Submission: 10/2022
3168-2	Complete ongoing clinical pharmacokinetic Study CLEE011A2116 (part 1) to determine an appropriate dose of ribociclib in patients with severe renal impairment.	Trial Completion: 10/2017 Final Report Submission: 04/2018

Table 10: Post-marketing commitments (US FDA)

Number	Detail	Timeline
3168-3	Submit the third overall survival (OS) interim data and analysis, and the final overall survival (OS) data and analysis from a clinical trial entitled 'MONALEESA-2' CLEE011A2301.	Interim Report Submission (Third OS Interim Data and Analysis): 12/2019 Final Report Submission (OS Data and Analysis): 06/2022
3168-4	Conduct additional in vitro studies to evaluate discriminating ability of dissolution acceptance criterion - using approved dissolution method with a validated HPLC analytical method for drug quantification in combination with collecting in vivo pharmacokinetic data using film coated tablet batches .	Final Report Submission: 09/2018

A co-pack (Kisqali and Femara) is also available in the US.

Review documents for the FDA evaluation are publically available online.[51]

European Medicines Agency (European Union)

For the purposes of the Delegate's Overview, the status was last checked on 27 June 2017.

The CHMP adopted a positive opinion on 22 June 2017. The full indication is:

> *Kisqali in combination with an aromatase inhibitor is indicated for the treatment of postmenopausal women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer as initial endocrine based therapy.*

Formal EMA approval normally follows without change to the indication.

The sponsor has shared with the TGA various EMA evaluation documents for ribociclib.

Quality

A summary of quality issues noted there are some outstanding minor matters regarding the PI and labels but these are expected to be easily resolved. Registration is recommended with respect to chemistry, quality control and biopharmaceutic aspects.

Nonclinical

The nonclinical evaluator had no objection to registration.

PDE4D inhibition was identified as a potential off-target effect that might contribute to nausea and vomiting (presumably a targeted effect on CDK4/6 would also contribute to GI effects via local mechanisms, but PDE4 inhibitors have dose limiting CNS mediated nausea and vomiting 'due to PDE4 inhibition within the chemoreceptor trigger zone of the area postrema'; this part of the brain lacks a BBB).

Pregnancy Category D was recommended by the evaluator and this was accepted by the sponsor.[35]

Clinical

Clinical evaluator's view

In the clinical evaluation report, the clinical evaluator outlines benefit/risk balance for ribociclib in the proposed indication, concluding: *'On the basis of the updated efficacy results and according to the safety reported in the pivotal study, the evaluator considers the benefit/risk assessment to be in favour of ribociclib for the proposed patient population'.*

The evaluator emphasises that monitoring and dose modification advice in the PI should be strengthened to help maintain this benefit/risk balance with real world use. The evaluator also recommends the following indication:

> *Kisqali in combination with a non-steroidal aromatase inhibitor is indicated for the treatment of postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer, as an initial endocrine-based therapy.*

[51] Accessed via www.accessdata.fda.gov; Kisqali (ribociclib) tablets; Novartis Pharmaceuticals Corporation Application No. 209092 Approval Date: 03/13/2017.

Note to indication: this approval is based on an improvement in PFS. An improvement in overall survival has not been demonstrated.

Overview of submitted data

The clinical evaluator describes the scope of clinical data in the submission. Key studies included in the initial submitted data were:

- Study A2301 (also known as theMONALEESA-2 trial, the pivotal study)
- Study X2107 (a Phase I/II supportive study)

Important studies introduced following the first round evaluation and evaluated in the second round evaluation included:

- Study E2301 (ribociclib + anastrozole pharmacokinetics from the MONALEESA-7 trial; see below)
- Study X2106 (ribociclib + exemestane).

Other important studies

The clinical evaluator reports on some ongoing studies:

- The MONALEESA-3 trial (Study F2301) is evaluating ribociclib in combination with fulvestrant compared to fulvestrant alone in men and post-menopausal women with HR+/HER2- advanced breast cancer who have received no or a maximum of one prior endocrine therapy.
- The MONALEESA-7 trial (Study E2301) is investigating ribociclib in combination with endocrine therapy (tamoxifen or letrozole or anastrozole) and goserelin compared to endocrine therapy and goserelin alone in premenopausal women with HR+/HER2- advanced breast cancer who have not previously received endocrine therapy. Primary analysis of PFS is expected in December 2017, with a TGA submission possible by the third quarter of 2018.
- The RIBECCA trial (Study XDE01) is investigating ribociclib + letrozole in women and men with HR+/HER2- advanced breast cancer.
- The CompLEEment-1 trial (Study A2404) is a single arm study of ribociclib + letrozole in men and postmenopausal women with HR+ / HER2- advanced breast cancer who have not received prior hormonal treatment.

Formulation

A film coated tablet is proposed for commercialisation; a capsule was used in clinical studies. The capsule versus tablet bioequivalence Study A2103 did not use the tablet proposed for commercialisation, but differences appear to relate to the film coating.

Pharmacology

The scope of the pharmacokinetic studies is indicated in the clinical evaluation report [inclusion is beyond the scope of this AusPAR], although it is noted on that: *'The pharmacokinetics of ribociclib are not completely described by the clinical studies presented. Additional information from in vitro studies, animal studies and from the sponsor's Simcyp prediction module is used to supplement the information available from clinical studies'.*

Ribociclib accumulation was attributed to a *'combined effect of drug accumulation and auto-inhibition of CYP3A4'.* Steady state was reached by Day 8. Accumulation does not occur across cycles (21 dosing days then a 7 day break). The attribution to auto-inhibition was considered speculative by a TGA PopPK Working Group.

In a human absorption, distribution, metabolism and excretion study, 23% of the administered dose was excreted in urine, and 69% in faeces; of the latter, most was 'changed'. From the evaluation report: *'...oral absorption was estimated to be 58.8%, with this calculated from the sum of radioactivity recovered in urine and radiolabelled metabolites in faeces. This calculation assumes that all unchanged ribociclib in the faeces represents ribociclib that was not absorbed and that none of the metabolites resulted from gut metabolism'.*

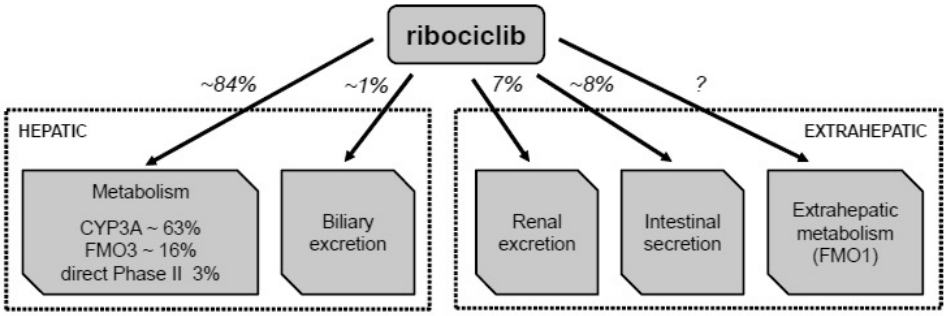
No absolute bioavailability study was performed.

Administering ribociclib with high fat, high calorie food delayed t_{max} and modestly lowered C_{max} but did not affect AUC.

Volume of distribution is estimated to be high, that is, distribution is wide. Nonclinical studies suggest absence of brain penetration (but high exposure in certain tissues such as the eye ciliary body and choroid); furthermore, ribociclib was found to be concentrated in milk of lactating rats.

Clearance is mainly via CYP3A4 mediated metabolism, with a minor contribution by flavin containing monooxygenase 3 (FMO3). A prominent metabolite is LEQ803; based on pharmacodynamic tests this was thought to contribute little to activity. Disposition was described as shown in Figure 5, below.

Figure 5: Schematic description of ribociclib disposition pathways



?: unknown contribution; CYP: cytochrome P450; FMO: flavin-containing monooxygenase.

Anticipated human clearance pathway contributions based on results of the human ADME (renal excretion, [Study A2102]), rat ADME (biliary excretion, intestinal secretion, [DMPK R0800526]) and in vitro enzyme phenotyping [DMPK R0800536]

Consistent with this, co-administration with ritonavir increased AUC by > 3 fold, and co-administration with rifampicin decreased exposure by 90%. The sponsor: *'...had recommended a dose reduction to 200 mg daily if co-administration with a strong CYP3A4 inhibitor could not be avoided but that no dose reduction was required for moderate or weak CYP3A4 inhibitors...'.*

The conservative choice of 200 mg was recommended the sponsor due to concerns regarding exposure related QT prolongation.

The FDA label endorses a reduction to 400 mg only. [Information redacted]

No particularly conservative approach is adopted by the sponsor regarding concomitant use of moderate CYP3A4 inhibitors, although close monitoring for AEs is suggested. [Information redacted]

The clinical evaluator notes that with 23% of the administered dose excreted in urine, but oral absorption of around 59%, influence of renal clearance should not be downplayed. Half of radioactivity in urine was from unchanged ribociclib.

Ribociclib is a P-gp substrate. Ribociclib may also inhibit BSEP, BCRP, MATE1 and OCT2. Ribociclib inhibits CYP3A4 (for example, increases exposure to concomitant midazolam about 4 fold). Letrozole is cleared via CYP3A4 (and CYP2A6, which may have a greater

role). There was only indirect evidence that ribociclib does not significantly influence the PK of letrozole, and the evaluator was concerned that in the pivotal Study A2301, in the combination arm, more patients had letrozole interruptions due to AEs.

Body weight was found to influence PK; the effect was considered small relative to the quite substantial overall interpatient variability that was seen.

The evaluator notes that few data about ribociclib PK were gathered in patients < 40 years of age (n = 10).

The evaluator was not convinced that the sponsor's PopPK approach adequately characterised the influence of race on ribociclib pharmacokinetics; and the sponsor described as 'inconclusive' the data relating to influence of race. Given that some AEs (for example, neutropaenia) might well be more pronounced with increasing exposure, this is a deficiency of the submission.

In a hepatic impairment study, moderate or severe impairment increased exposure by approximately 30%. The evaluator had concerns about safe use in hepatic impairment. The sponsor has suggested a dose reduction to 400 mg for patients with moderate or severe hepatic impairment, explaining 'exposure at the 400 mg dose in patients with moderate and severe hepatic impairment is expected to provide similar exposure from 600 mg in patients with normal hepatic function'.

There has been no dedicated study of patients with renal impairment. The PopPK based analysis (without data from patients with severe impairment) found no effect of mild or moderate renal dysfunction on pharmacokinetics. The evaluator raised some concerns about use in patients with moderate or severe renal impairment. A protocol for a dedicated renal impairment Study A2116 in otherwise healthy volunteers was supplied; an FDA post-marketing obligation has been noted earlier.

The evaluator was not convinced that interactions with PPIs, CYP3A4/5 inhibitors and letrozole were sufficiently excluded via a PopPK approach. There was also little evidence about pharmacokinetic interactions with other agents that raise gastric pH. On this point, further discussion is presented in the second round evaluation (inclusion is beyond the scope of this AusPAR). The evaluator noted that a clinically relevant interaction between ribociclib and PPIs was unlikely.

Scope of PD studies is shown in an introductory table of the *Pharmacodynamics* section. Biomarker analysis in Study A2301 is discussed. While nonclinical studies suggested ribociclib sensitivity *'is absolutely dependent on intact pRb expression by the tumour cells'* in Study A2301, efficacy was not related to pRb status (for example, patients deemed to have low total pRb by H score still appeared to benefit from addition of ribociclib, consistent with what was seen with palbociclib). Further discussion is presented following the first round evaluation (inclusion is beyond the scope of this AusPAR). The sponsor's conclusion *that 'pRb as a singular molecular event is insufficient to be the sole negative predictive biomarker for CDK4/6 inhibitors'* seems reasonable. The sponsor is following up on some other biomarkers [Information redacted].

In a sample of n = 158 patients from Study A2301, oestradiol levels were monitored. A decrease from Baseline was observed median 94.9% in the combination arm, median 92.9% in the letrozole arm.

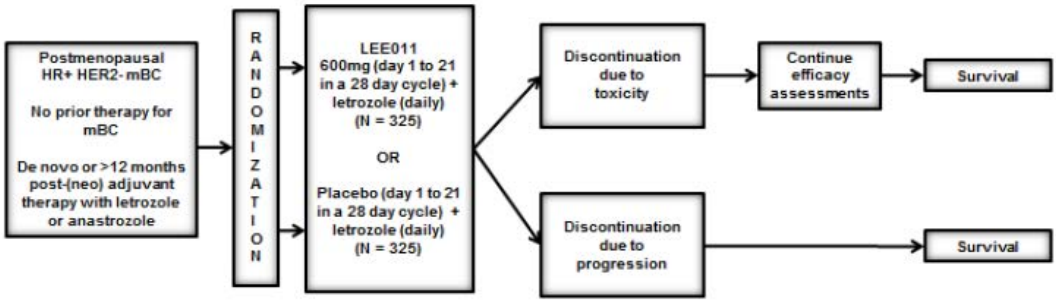
Efficacy

Dosage selection for the pivotal study is discussed under the relevant subsection of section: *Clinical findings*, above.

Study A2301

This was the pivotal study, and it has been published.[52] Design is summarised below in Figure 6.

Figure 6: Study A2301 design



Crossover from the placebo arm to ribociclib was not permitted at progression.

Key inclusions/exclusions are noted. The population consisted of postmenopausal women with HR+, HER2-, advanced breast cancer, who had previously received no prior therapy for their advanced breast cancer. Exclusions included inflammatory breast cancer; CNS metastases; and active cardiac disease or a history of cardiac dysfunction that would increase risk of QT prolongation. Reasons for screening failure are outlined on in the clinical questions (inclusion of these questions and responses are beyond the scope of this AusPAR); cardiac history was a prominent reason for exclusion.

Patients were randomly assigned to one of the below treatment arms:

- Letrozole (2.5 mg once daily) + ribociclib 600 mg (Days 1 to 21 in a 28 day cycle); or
- Letrozole (2.5 mg once daily) + placebo (Days 1 to 21 in a 28 day cycle).

Ribociclib could be taken 'without regard to meals', with evening doses strongly not recommended.

668 patients were randomised (334 per arm). Baseline data: median age was 62 years (range 23 to 91); 82% were Caucasian; 61% had ECOG PS = 0, others had PS = 1. De novo metastatic disease was seen in a third of patients. Of others, approximately 10% had a disease free interval of < 24 months (a shorter disease free interval suggests greater resistance to endocrine therapy in patients who received it as adjuvant treatment). Almost all patients were ER+ and approximately 82% were PR+. About 22% had bone only disease. About 34% had 3+ metastatic sites. Prior therapy is tabulated in the clinical evaluation report (inclusion of this is beyond the scope of this AusPAR).

The study is ongoing pending final analysis of OS. Analyses are summarised in Table 11.

[52] Hortobagyi et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med* 2016; 375: 1738-1748).

Table 11: Summary of analyses

Cut-off date	Description	Comment
29 January 2016	Preplanned interim PFS analysis. Timed for 70% of expected 302 PFS events. Accompanied by first planned OS interim analysis.	This analysis was presented in the initial dossier and was evaluated in the first round clinical evaluation report. mPFS: NE versus 14.7 months. OS hazard ratio: 1.128.
22 June 2016	PFS analysis (planned with FDA).	Presented in the sponsor's post-first round report response stage, evaluated in the second round clinical evaluation report.
2 January 2017	Second planned OS interim analysis as per protocol version 05. Accompanied by unplanned PFS analysis (investigator, not BICR).	Presented in the sponsor's post-first round report response stage, evaluated in the second round clinical evaluation report. Median PFS: 25.3 versus 16.0 months. OS hazard ratio: 0.746.
Future	Third planned OS analysis. After 300 OS events	
Future	Fourth planned OS analysis. After 400 OS events.	

The primary efficacy variable was PFS derived from the investigator's assessment of radiology data using RECIST 1.1. PFS by BICR was supportive. Discrepancies between local and BICR assessment were noted so a quality control audit was made by a third party independent radiologist leading to process changes for the BICR. There is little agreement between local, BICR and auditor conclusions, but all approaches show similar differences across arms.

PFS analyses using three different data cut offs were presented.

Pre-planned interim PFS

Based on the interim PFS analysis (data cut off 29 January 2016), median PFS was not reached in the ribociclib + letrozole arm versus 14.7 months in the placebo + letrozole arm, with a hazard ratio of 0.56 (95% CI 0.43 to 0.72) (per investigator).

Based on BICR data, median PFS was 22.9 months (ribociclib + letrozole) versus not reported (placebo + letrozole), with a HR of 0.59 (95% CI 0.41 to 0.85) favouring ribociclib.

Poor concordance between the 2 approaches is discussed in the clinical evaluation report (not included in this AusPAR).

PFS subgroup analyses did not reveal anomalous outcomes.

Unplanned (June 2016) PFS analysis

This is summarised in the clinical evaluation report. The median PFS was 22.4 versus 15.3 months; PFS hazard ratio was 0.559 (95% CI 0.443 to 0.706) (investigator assessed). By BICR, median PFS was not reported versus not reported (hazard ratio 0.597, 95% CI 0.430 to 0.830). Poor concordance persisted.

Unplanned (January 2017) PFS analysis

Median PFS was 25.3 versus 16.0 months; PFS hazard ratio was 0.568 (95% CI 0.457 to 0.704) (investigator assessed). BICR outcomes were not reported.

OS outcomes are described as immature but encouraging. OS analyses were provided for two time points, shown below in Table 12, taken from the clinical evaluation report.

Table 12: Overall survival outcome results

	Interim OS Results (29 January 2016 cut off)		**Second Interim OS Results (2 January 2017 cut off)**	
	Ribociclib plus letrozole N = 334	**Placebo plus letrozole N = 334**	**Ribociclib plus letrozole N = 334**	**Placebo plus letrozole N = 334**
Death events, n (%)	23 (6.9)	20 (6.0)	50 (15.0)	68 (19.8)
Censored	311 (93.1)	314 (94.0)	284 (85.0)	268 (80.2)
Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	33.0 (33.0, NE)
Hazard ratio, estimate (95% CI)	1.128 (0.619, 2.055)		0.746 (0.51, 1.08)	
p-value	0.653		0.09*	
NE = not estimable				

Source: CDER multidisciplinary review document; note: * the p-value in the EMA documents and in the report provided to the TGA is shown as 0.059 and not 0.09.

Time to deterioration of ECOG performance score was similar across arms. Analysis of global health status using the EORTC QLQ-C30 did not reveal differences.[53] Resource utilisation outcomes are noted; reasons for hospital stay aligned with known additive toxicities (infection; hepatotoxicity; myelosuppression). Other endpoints are discussed from in the clinical evaluation report (inclusion is beyond the scope of this AusPAR).

[53] EORTC QLQ-C30: Aaronson N et al., The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. *Journal of the National Cancer Institute* 1993; 85: 365–376

Study E2301

The sponsor provided a pharmacokinetic summary report of this study in the post-first round response (not included in this AusPAR).There was no control arm without ribociclib, so there was reference to historical pharmacokinetic outcomes. Only limited review was undertaken.

Study X2106

The sponsor provided 'first interpretable results' from Study X2106 in the post-first round response. Only limited review was undertaken. Results supplied were related to double (ribociclib + exemestane) treatment (n = 14, patients with pharmacokinetic results at Cycle 1). The evaluator wrote:

> 'There was no control arm of patients receiving exemestane without ribociclib. The CSR did not include a comparison of exemestane and ribociclib to historical controls, nor did it include a discussion of drug-drug interactions between ribociclib and exemestane.
>
> The evaluator concludes that the information presented in the CSR is inadequate to exclude drug-drug interactions between exemestane and ribociclib'.

Other studies

These are discussed in the clinical evaluation report but were not considered particularly influential.

Safety

Exposure

The sponsor's overall safety evaluation is based on data from 568 patients: 381 patients from ribociclib 600 mg/letrozole 2.5 mg combination therapy Studies A2301 and X2107, and 187 patients on ribociclib 600 mg monotherapy from Studies X2101, XUS03, and X1101.

In Study A2301, as of the data cut off of 29 January 2016, the median duration of exposure to the study treatment was 13.0 months in the ribociclib + letrozole group (range: 0 to 23 months) and 12.4 months (range: 0 to 22 months) in the placebo + letrozole group. 76 to 78% of patients received study treatment for ≥ 6 months. There is little experience with 'long term' use.

Safety updates were provided at the post-first round response stage of the TGA evaluation, with approximately 5 months of additional safety observations in Study A2301 (median follow up was increased from 15.3 months to 20.1 months). The emphasis below is on initial safety data.

Adverse events

General indices

Addition of ribociclib was associated with significant toxicity, as shown in Table 13 based on a data cut-off of 29 January 2016.

Table 13: Adverse events across Studies A2301, X2107 and monotherapy studies (data cut-off: 29 January 2016)

Category	Studies A2301 + X2107 Ribociclib + Letrozole N = 381 n (%)	Study A2301 Placebo + Letrozole N = 330 n (%)	Monotherapy Studies Ribociclib N = 187 n (%)
All AEs	376 (98.7)	320 (97.0)	186 (99.5)
Grade 3/4 AEs	305 (80.1)	108 (32.7)	135 (72.2)
Grade 3/4 SAEs	63 (16.6)	29 (8.8)	60 (32.1)
AEs leading to discontinuation	53 (13.9)	10 (3.0)	16 (8.6)
AEs needing dose modification (delay, reduction)	262 (68.8)	52 (15.8)	104 (55.6)
All deaths	23 (6.0)	19 (5.8)	49 (26.2)
On treatment deaths	3 (0.8)	1 (0.3)	20 (10.7)

In the evaluator's opinion, addition of ribociclib to letrozole treatment has resulted in a major increase in toxicity.

Dose interruptions, delays and reductions in Study A2301 are tabulated in the clinical evaluation report (inclusion of this is beyond the scope of this AusPAR). Use of ribociclib resulted in considerable ribociclib dose interruption, delay and/or reduction. For example, 33.2% of ribociclib patients required one dose reduction, and a further 20.7% required 2+ dose reductions. Interruptions and reductions were generally due to AEs, with neutropaenia prominent.

Dose interruptions for letrozole were slightly more common in the ribociclib + letrozole arm (for example, 3+ interruptions: 13.2% versus 8.2%).

Dose discontinuations were frequent, and commonly due to elevated liver function tests (LFT). Other AEs causing discontinuation were vomiting; neutropaenia; hepatotoxicity; and respiratory AEs.

Common adverse events

These are reported in the clinical evaluation report (full inclusion is beyond the scope of this AusPAR). Neutropaenia, nausea, diarrhoea, alopecia, vomiting, anaemia, rash, LFT elevations, stomatitis and thrombocytopenia were all substantially more frequent with addition of ribociclib. The profile resembles that of cytotoxic chemotherapy in qualitative terms (myelosuppression; gastrointestinal toxicity; alopecia).

QT prolongation

This risk is described under Clinical Findings: *Safety,* (see above). The evaluator has summarised clinical data as follows in Table 14, based on a data cut-off of 29 January 2016.

Table 14: Summary of ECG (QT interval) changes and relevant clinical outcomes (data cut-off: 29 January 2016)

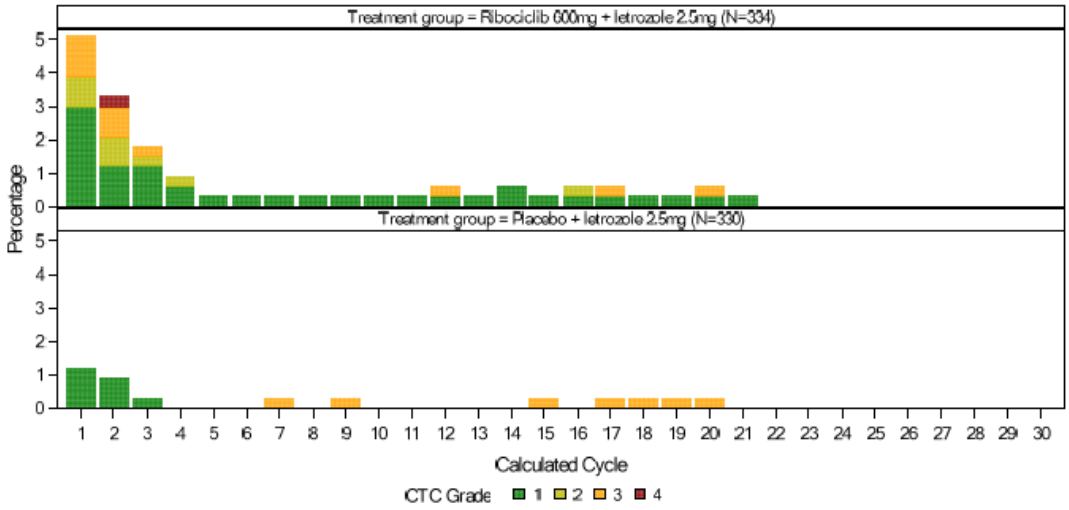
	Studies A2301 + X2107 ribociclib + letrozole N = 381 n (%)	Study A2301 Placebo + letrozole N = 330 n (%)	Monotherapy Studies Ribociclib N = 187 n (%)
QTcF (ms)			
New > 480	15/376[$] (4.0)	1 (0.3)	16 (8.6)
New > 500	1/376[$] (0.3)	0	6 (3.2)
Increase from Baseline > 60 ms	12/376[$] (3.2)	0	20 (10.7)
AE ECG QT prolonged			
All grades	17 (4.5)	4 (2.1)	29 (15.5)
Grade 3/4	1 (0.3)	0	4 (2.1)
All AEs			
Syncope	9 (2.4)	3 (0.9)	5 (2.7)
Loss of consciousness	1 (0.3)	0	0
Sudden death	1 (0.3)	0	1*(0.5)
Ventricular tachycardia	1 (0.3)	0	0
Cardiorespiratory arrest	0	0	1 (0.5)
SAEs			
Syncope	3 (0.8)	0	0
Sudden death	1 (0.3)	0	0
Cardiorespiratory arrest	1*(0.3)	0	1 (0.5)
AES leading to discontinuation	1 (0.3)	0	1 (0.5)
AEs needing dose adjustment or interruption	3 (0.8)	0	7 (3.7)
QT prolonged	2 (0.5)	0	6 (3.2)
Syncope	1 (0.3)	0	1 (0.5)

* event of cardiac arrest in Study A2301 and sudden death in Study X2101 were not included in the sponsor's Safety Report and have been added from the Study CSRs by the evaluator.

$: As assessed by number of patients at risk for a specific category

Another method of summary is given via a histogram of QTc prolongation events by treatment and cycle, shown in Figure 7.

Figure 7: Histogram of events of QTc prolongation by treatment and cycle data cut-off 22 June 2016



A dose dependent and concentration dependent increase in change from Baseline for the QTcF was reported in patients treated with ribociclib from 400 mg to 900 mg (400/600/750/900 mg).

This clearly indicates drug induced QT prolongation. Some arrhythmias/sequelae are likely to be related to this effect. Use of ribociclib is also associated with vomiting and diarrhoea, and with greater need for medicines such as certain antibiotics that can either increase exposure to ribociclib, or increase the risk of QT prolongation themselves.

Of note regarding studies of ribociclib + letrozole, '*a Kaplan-Meier analysis of the time to first occurrence of Grade 2 or worse QT prolongation found that 13/15 events in the patients receiving ribociclib + letrozole occurred within 4 weeks of commencement with a median time to first occurrence of 15 days*' (as reported in the clinical evaluation report)).

In Study A2301, exclusions included:

- Patients who had active cardiac disease or a history of cardiac dysfunction that would increase the risk of QT prolongation
- Patients that were currently receiving the following medications if these could not be discontinued seven days prior to the start of the treatment: any known strong inducers or inhibitors of CYP3A4/5 OR medications with a known risk to prolong the QT interval or induce Torsades de Pointes or medications with a narrow therapeutic window and are predominantly metabolised through CYP3A4/5.

The dose interruption advice regarding QT prolongation was strengthened in protocol amendments 3 and 4.

- *QT prolongation ≥ 481 ms* was to be managed by a blood sample to check for electrolyte abnormalities; review of any new concomitant medications; and review of technical aspects of the ECG. In the absence of other contributors, the ECG was to be repeated one hour later. If QTcF remained ≥ 481 ms, the dose was to be delayed. If QT prolongation subsequently recurred the dose was to be reduced. Repeat ECGs were to be performed 7 days and 14 days after dose resumption.
- *QT prolongation ≥ 501 ms* (confirmed on repeat ECG) was managed by repeat ECG after one hour. If < 481 ms, then dose reduction and repeat ECGs as above. If QTcF ≥ 501 ms

persisted, or recurred, then treatment should be discontinued and cardiology consultation obtained.

- *If there was any event of arrhythmias* such as Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia together with QT/QTc ≥ 501 or > 60 ms change from Baseline, treatment should be discontinued and cardiology consultation obtained.

Prohibited concomitant medications included those causing QT prolongation.

The evaluator writes in the clinical evaluation report that after review of 'narratives of deaths' across studies including Study A2301, '*there are 3 deaths in which a contribution of QT prolongation induced malignant arrhythmias cannot be excluded'.*[54]

Hepatotoxicity

In Study A2301, 4 cases conformed to Hy's law, and additional laboratory testing and strict management guidelines were implemented. The evaluator has summarised clinical data, as shown in Table 15.

Table 15: Hepatotoxicity related events

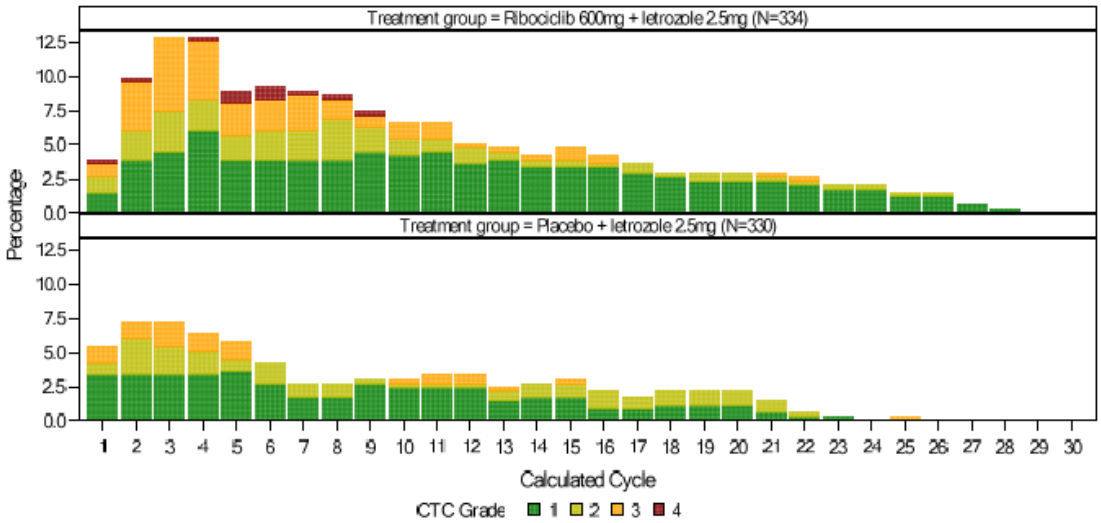
Finding n (%)	Studies A2301 + X2107 Ribociclib + Letrozole N = 381 n (%)	Study A2301 Placebo + Letrozole , N = 330 n (%)	Monotherapy Studies Ribociclib (N = 187) n (%)
Hepatotoxicity event of any grade	91 (23.9)	45 (13.6)	59 (31.6)
Hepatotoxicity event, Grade 3/4	42 (11.0)	12 (3.6)	16 (8.6)
Grade 3/4 ALT elevation	33 (8.7)	4 (1.2)	5 (2.7)
Grade 3/4 AST elevation	20 (5.2)	4 (1.2)	4 (2.1)
Grade 3/4 bilirubin elevation	4 (1.0)	1 (0.3)	5 (2.7)
AST or ALT elevation >10 x ULN	22/374 (5.9)	0	1/181 (0.6)
AST or ALT > 10 x ULN + TBL > ULN	11/374 (2.9)	0	0
Confirmed Hy's Law Case	4/374 (1.1)	0	0
Hepatotoxicity SAE	8 (2.1)	0	5 (2.7)

[54] Clarification: of these 3 cases, two reported a sudden death. A third case, was assessed as not related to ribociclib by the investigator.

Finding n (%)	Studies A2301 + X2107 Ribociclib + Letrozole N = 381 n (%)	Study A2301 Placebo + Letrozole , N = 330 n (%)	Monotherapy Studies Ribociclib (N = 187) n (%)
Discontinuation due to hepatotoxicity	22 (5.8)	3 (0.9)	2 (1.1)
Dose modification due to hepatotoxicity	29 (7.6)	9 (2.7)	7 (3.7)
Hy's Law: ALT or AST > 3 x upper limit of normal (ULN) and total bilirubin > 2 x ULN and ALP < 2 x ULN with other clinical causes excluded.			

This clearly indicates drug-induced liver dysfunction extended in some cases to significant liver injury. Another method of summary as a histogram is shown in Figure 8.

Figure 8: Histogram of hepatobiliary toxicity events by treatment and cycle data cut off 22 June 2016



Of the 4 patients with confirmed Hy's law AEs, there were no fatalities. However, some significant LFT elevations in other patients did not fully resolve. The Delegate reviewed the comments from the sponsor's own Advisory Board for hepatotoxicity.).

The evaluator's opinion about this toxicity is outlined in the first round clinical evaluation, but was updated in the second round evaluation.

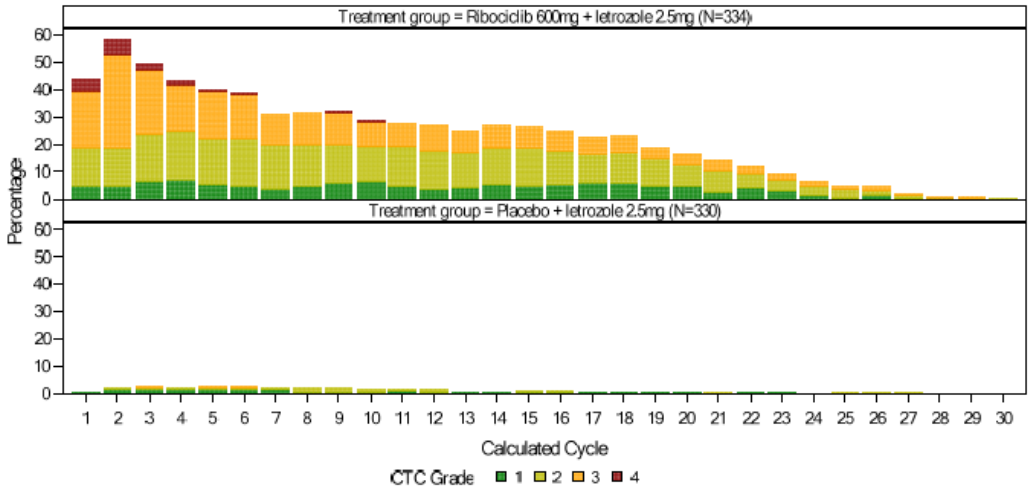
Myelosuppression

Bone marrow suppression with accompanying neutropaenia, leukopenia, anaemia, and/or thrombocytopenia is associated with ribociclib.

Neutropaenia

Neutropaenia is a very common occurrence; it is described in the clinical evaluation report and is summarised in Figure 9.

Figure 9: Histogram of neutropaenia events by treatment and cycle, data cut off 22 June 2016

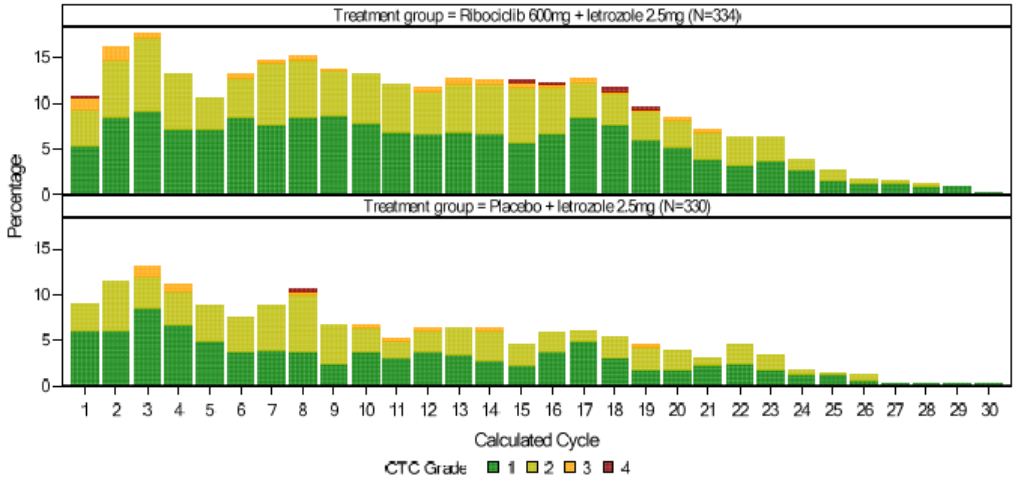


In Study A2301, 7.5% of patients required granulocyte colony stimulating factor G-CSF in the ribociclib + letrozole arm (versus 0.3% in the placebo + letrozole arm). However, there were only 4 events of febrile neutropaenia.

Infectious events

Infections are discussed in the clinical evaluation report and summarised in Figure 10. There was a modest increase in reports of severe infection or infection requiring hospitalisation. One concern is that *'17.8% of patients in the ribociclib plus letrozole arm received antibiotics as concomitant medications with known risks of QT prolongation (for example, azithromycin, clarithromycin, and moxifloxacin)'.*

Figure 10: Histogram of infectious events by treatment and cycle, data cut off 22 June 2016



Anaemia

In Study A2301, 3.6% versus 1.5% respectively required packed red blood cell transfusion for anaemia.

Thrombocytopaenia

Thrombocytopenia was an AE in 9% (ribociclib + letrozole) versus 0.6% (placebo + letrozole) in A2301 (the laboratory abnormality of platelet count decreased was seen in 29% versus 6.4%). While there was no particular evidence of an increase in significant bleeding, there was an increase in epistaxis (4.5% versus 1.8%).

Renal impairment

The kidneys were identified as a target organ of toxicity in multiple dose animal studies. Analysis of clinical chemistry changes found that in Study A2301, increased creatinine was found in 18.9% of the ribociclib + letrozole group compared to 5.5% of the placebo + letrozole group. Of potential relevance from the clinical evaluation report:

The clinical study report for Study A2109 speculates that the increase in creatinine may be due to an effect on renal transporters rather than renal toxicity given that *in vitro* studies have found that ribociclib inhibited renal transporters OCT2 and MATE1 which are involved in the active secretion of creatinine from the proximal tubules and given that cystatin C, which is freely filtered, was not affected.

On the other hand, in Study A2301, four patients in the ribociclib + letrozole group and 1 patient in the placebo + letrozole group experienced renal failure.

Thromboembolism

Thromboembolic events occurred in 9 patients (2.7%) in the ribociclib + letrozole arm, versus 3 patients (0.9%) in the placebo + letrozole group. Of these, 4 patients (1.2%) experienced pulmonary embolism in the ribociclib + letrozole group versus 1 patient (0.3%) in the placebo + letrozole group.

Pulmonary toxicity

The evaluator notes 2 fatal cases of pulmonary toxicity that may have been ribociclib-related, but concludes there is insufficient information to categorise this toxicity as an 'Important potential risk' in the ASA to the RMP.

Risk Management Plan evaluation

There was no objection to registration.

It was noted that Australian packaging contains a dosing tracker, to help address the risk that patients inadvertently take ribociclib without a 7 day break per cycle.

Regarding safety specifications, the clinical evaluator recommended that the ASA to the RMP introduce 'pulmonary toxicity' as missing information. It is considered that Study A2301 and other presented studies were in total of sufficient size to detect a major signal for pulmonary AEs if one existed. There was no striking evidence in the controlled Study A2301 of such a signal. Overall, there has been a reasonable opportunity to examine whether ribociclib causes pulmonary toxicity. Therefore, it is not necessary to include 'pulmonary toxicity' as missing information, although the sponsor should present updated analyses of this issue in upcoming periodic safety update reports (PSURs).

Proposed conditions of registration

The following condition of registration is proposed: Implement EU-RMP version 1.1 (Dated 13 February 2017, DLP 29 January 2016) with ASA version 2.0 (Dated 28 April 2017) or as revised to the satisfaction of the TGA.

Risk-benefit analysis

Issues

Efficacy

Adding ribociclib to letrozole in HR+/HER2- postmenopausal women with no prior treatment for advanced breast cancer results in substantial lengthening of PFS; immature OS data suggest no OS detriment. There is no improvement in quality of life at the time of the interim analysis, but other than via inference from the AE profile, there is no sign of a decline.

There is limited evidence that addition of ribociclib to anastrozole would not result in problematic pharmacokinetic interactions. Drug-drug interactions with exemestane have not been excluded with any degree of rigor. The Delegate's view is that it is reasonable to expect similar efficacy and safety outcomes in these setting too.

Correspondence regarding ribociclib, from de Gramont et al., in the New England Journal of Medicine (NEJM) 19 January 2017; 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 tumours have a worse prognosis than those with luminal A tumours [55]
>
> 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 tumours was 16.9 months, as compared with 11.0 months among patients with luminal B tumours. Furthermore, numerous studies, mostly retrospective, have suggested variations in estrogen-receptor and progesterone-receptor expression between the primary tumour and the metastases, especially among patients with luminal B tumours'.

Safety

QT prolongation

Ribociclib causes QT prolongation that has apparently translated in some patients to ventricular arrhythmias.[56]

Issues are summarised from the clinical evaluation report. The evaluator recommends inclusion of a boxed warning in the PI/Consumer Medicines Information (CMI) documentation, and other measures, also supported in large part by the Delegate.

Hepatotoxicity

Issues are summarised from the clinical evaluation report. The evaluator writes in the report: *'The evaluator acknowledges that, with early recognition and appropriate dose*

[55] De Gramont A et al., Correspondence to the Editor. *N Engl J Med* 2017; 376: 288-289.
[56] Clarification: One case of ventricular tachycardia NOT suspected to be related to the study drug was reported in one patient (CSR listing 16.2.7-1.1). The ECG submitted to the cardiology vendor was showing sinus tachycardia. A query was raised in the eCRF in July 2016. The AE term was consequently updated by the site staff to 'sinus tachycardia'. Therefore, no cases of ventricular tachycardia or ventricular fibrillations have been reported to date in Study CLEE011A2301, regardless of relationship to study drug. Novartis requests the deletion of the statement saying that QT prolongation has apparently translated in some patients to ventricular arrhythmias.

modification, ribociclib hepatotoxicity in the clinical trial setting has been manageable and reversible. For this to be reproduced in the wider setting, the evaluator considers it essential that a similarly rigorous monitoring approach to that used in the clinical trials is recommended in the PI.

The evaluator recommends more frequent LFT monitoring than is proposed by the sponsor'.

Monitoring for adverse events

Issues are summarised from the clinical evaluation report. Of note:

> 'Treatment with ribociclib was associated with a substantial increase in toxicity over letrozole alone in the pivotal study. Close monitoring throughout the study enabled early detection of toxicities and appropriate management by ribociclib dose modifications. Given the substantial increase in toxicity and the absence of a demonstrated improvement in overall survival, it is particularly important that these toxicities be as well managed in the wider world as they were in the clinical study.'

As noted above, the evaluator does not accept the sponsor's arguments regarding the duration of monitoring for myelosuppression, hepatotoxicity and QT prolongation and recommends that this monitoring occur with every cycle throughout treatment and that this should include laboratory testing of full blood examination (FBE), serum chemistry (including electrolytes potassium, magnesium and calcium), liver function tests and ECG. The evaluator does not consider that monthly monitoring of these routinely available tests would be too onerous for the proposed patient population and that as noted by the sponsor for complete blood counts, these tests are '*universally accepted, readily available, and accessible at local clinics/hospitals or laboratory centres near patients' homes*' and that '*results can be communicated directly to the treating physician/oncologist who can adjust the patient's dose of ribociclib'.*

With regards the dose modification tables, the evaluator accepts the sponsor's arguments regarding the haematology toxicity table, hepatotoxicity table and other toxicity table (provided the haematology toxicity table is re-titled 'Neutropaenia and Febrile Neutropaenia' and haematological toxicities of anaemia and thrombocytopenia are not excluded from the 'Other Toxicities' table).

However, as noted above, the evaluator does not accept the sponsor's arguments regarding the dose modification advice for QT prolongation and considers it particularly important that additional advice is provided regarding this life-threatening complication, with which oncologists will have little familiarity.

The current PI includes recommendations for monitoring however; presentation of this is beyond the scope of the AusPAR.

The evaluator suggests that 'ongoing' monitoring be specified as monthly, rather than left as 'as clinically indicated'.

Summary of issues

There were no manufacturing, quality control, nor nonclinical issues precluding registration.

Clinical

Efficacy

Adding ribociclib to letrozole in HR+ HER2- postmenopausal women with no prior treatment for advanced breast cancer results in substantial lengthening of PFS; immature

overall survival data suggest no OS detriment. There is no improvement in quality of life, but other than via inference from the AE profile, there is no sign of a decline.

Safety

QT prolongation

Ribociclib causes QT prolongation that has apparently translated in some patients to ventricular arrhythmias.

Issues are summarised from the clinical evaluation report. The evaluator recommends inclusion of a boxed warning in the PI/CMI documentation, and other measures, also supported in large part by the Delegate.

Hepatotoxicity

Issues are summarised from the clinical evaluation report. The evaluator writes:

> 'The evaluator acknowledges that, with early recognition and appropriate dose modification, ribociclib hepatotoxicity in the clinical trial setting has been manageable and reversible. For this to be reproduced in the wider setting, the evaluator considers it essential that a similarly rigorous monitoring approach to that used in the clinical trials is recommended in the PI.
>
> The evaluator recommends more frequent LFT monitoring than is now proposed'.

Monitoring for adverse events

Issues are summarised from the clinical evaluation report. Of most note:

> '…the evaluator does not accept the sponsor's arguments regarding the duration of monitoring for myelosuppression, hepatotoxicity and QT prolongation and recommends that this monitoring occur with every cycle throughout treatment...'

The current PI includes recommendations for monitoring, which are beyond the scope of this AusPAR.

The evaluator suggests that 'ongoing' monitoring be specified, rather than left as 'as clinically indicated'.

Use with aromatase inhibitors other than letrozole

There is limited evidence that addition of ribociclib to anastrozole would not result in problematic PK interactions. Drug-drug interactions with exemestane have not been excluded with any degree of rigor. The Delegate's view is that it is reasonable to expect similar efficacy and safety outcomes in these setting too.

Risk management plan

A risk management plan (RMP) has been proposed, outlining routine risk minimisation and pharmacovigilance measures to be implemented upon marketing. There were no objections to registration from the RMP evaluator.

Delegate's considerations

Overall risk-benefit, and indication

The sponsor's most recently proposed indication is as follows:

> *Kisqali in combination with an aromatase inhibitor is indicated for the treatment of postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer, as an initial endocrine-based therapy.*

This is considered from the clinical evaluation report. The evaluator recommends the indication be revised to include non-steroidal AIs (that is, letrozole, anastrozole). In the decision making process for palbociclib, advice was accepted that a broader indication would be appropriate. In the absence of specific issues raised by Studies E2301, X2106 and mechanistic considerations, this approach seems reasonable for ribociclib.

The evaluator proposes a note to the indication, stating:

> *This approval is based on an improvement in PFS. An improvement in overall survival has not been demonstrated.*

With updated OS outcomes, approval is not solely on the basis of PFS. Important to the Delegate's understanding of benefit/risk was updated data showing no sign of detriment to OS (it is acknowledged that improvement in OS has not been shown, and that OS outcomes remain immature). This updated OS data must be reported in the PI, as it reflects part of the basis for approval. Conversely, there is no need for a note to the indication.

The Delegate's pre-Advisory Committee on Medicines (ACM) view is that the following indication is reasonable:

> *Kisqali in combination with an aromatase inhibitor is indicated for the treatment of postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer, as an initial endocrine-based therapy.*

The indication accepted for palbociclib is noted below:

> *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.*

Attention is drawn to ACM's recommendation that the palbociclib indication need not be limited to postmenopausal women, but should apply to all men and women with HR+ HER2- advanced or metastatic breast cancer. The ACM has been asked whether a similar approach should be adopted for ribociclib.

Conditions of registration may be imposed regarding provision of clinical data, as per the clinical evaluator's recommendation:

- Subsequent analyses for Study A2301 according to the timeline proposed in the FDA approval letter.
- The final report for the study exploring the efficacy and safety of an alternative dosing regimen for ribociclib to mitigate the risk of QT prolongation.
- The final report for Study A2116 be provided to the TGA to assist in determination of the appropriate dose of ribociclib in patients with severe renal impairment.
- The final reports (and any interim analyses) from the Studies CLEE011E2301 and CLEE011F2301 regardless of whether the efficacy data is sufficient to support an indication submission.
- The final reports (and any interim analyses) from the Studies CLEE011XDE01 and CLEE011A2404.

Questions for sponsor

Regarding other ongoing studies:

1. Given the FDA request for analysis of different dosing regimens, do dose regimens in major studies vary from that proposed for use in Australia, that is, a starting dose of 600 mg daily for 21 consecutive days per 28 day cycle?
2. Please provide additional detail about the alternative dosing regimen(s) being examined to fulfil the FDA post marketing requirements and commitments.

Regarding pharmacology:

3. Has a conclusion about absolute bioavailability been drawn from Study [information redacted]?
4. Clarify the optimal recommended dose reduction for patients on concomitant strong CYP3A4 inhibitors.
5. Is there sufficient evidence to include a warning in the PI that patients from certain ethnic backgrounds may be at higher risk of AEs such as neutropaenia due to likely higher exposure to ribociclib?
6. Comment on variation between the proposed text about interactions with transporters and the position outlined in the EU Day 180 List of outstanding issues.

Regarding safety:

7. Regarding the Study A2301 patient receiving ribociclib + letrozole where ventricular tachycardia (VT) was reported (and where ECGs transmitted to the central radiology vendor showed sinus tachycardia), please clarify whether the ECGs transmitted to the central vendor were exactly those used locally to arrive at the diagnosis of VT, or whether they were taken separately (for example, before or after the ECG used locally to diagnose VT). This is considered important since VT may be transient. Please also clarify whether the central 'radiology' vendor applied specialist cardiology expertise to arrive at the ECG diagnosis of sinus tachycardia.

Regarding benefit/risk:

8. Comment on any subgroup analyses for Study A2301 according to subtype of disease (for example luminal A versus B).
9. Does the sponsor have any view about the evidence base or clinical implications of expansion of the indication to include men?
10. Does the sponsor have any view about the evidence base or clinical implications of expansion of the indication to include all women (as opposed to postmenopausal women)?
11. Will all pack sizes be marketed? If the 21 tablet pack is not marketed, what extra steps will the sponsor take to minimise medication error in patients who are dose reduced to 200 mg per day on Days 1 to 21 per cycle?

Request for ACM advice

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

1. Should the indication allow use with:
    a. letrozole (supported by Study A2301);
    b. with non-steroidal aromatase inhibitors (the clinical evaluator's preference); or
    c. with aromatase inhibitors (proposed by the sponsor, endorsed by the FDA's approved indication, supported by the EMA's Committee for Medicinal Products

for Human Use (CHMP), and corresponding to indication wording for palbociclib)?

2. Does the ACM support a boxed warning for QT interval prolongation? If so, does it have any suggestions about the content of this warning?
3. Given the clinical evaluator's reservations about the sponsor's proposed monitoring approach, does the ACM have any suggestions about a preferable approach to be included in the PI?
4. Given:
   a. the apparently different safety profile of ribociclib versus palbociclib;
   b. the different evidence base for the two products; and
   c. the expectation of new data informing use in pre-menopausal women (Study E2301; TGA submission possible by Q3 2018);

   does the ACM recommend that the ribociclib indication be limited to *'post-menopausal women*', to '*men and post-menopausal women'*, or to '*men and women as per palbociclib*'?

Please also take into account the sponsor's Pre-ACM response to questions in this regard.

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.

Response from sponsor

[Information redacted]

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, supported the registration of Kisqali film-coated tablet, containing 200 mg of ribociclib for the following indication:

> *Kisqali in combination with an aromatase inhibitor is indicated for the treatment of men and postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer, as an initial endocrine-based therapy.*

The ACM noted that ribociclib is approved by the US FDA; a decision by the EMA has not yet been made (but CHMP adopted a positive opinion on 22 June 2017).

General comments

ACM considered the following issues with regards to the black box warning and administration instructions:

- The proposed monitoring, being less than that provided in the pivotal trial, was unacceptable.
- ECG and electrolyte monitoring needs to occur more intensively than is proposed by the sponsor, and there should be ongoing monitoring with ECG for QTc prolongation and ongoing electrolyte monitoring, given that QTc prolongation was seen throughout the entire treatment duration.
- Alongside documentation (and physician estimation of QTc), electrolytes and all concomitant medications should be reviewed, at a minimum prior to each cycle but

more intensively in initial cycles, recognising that QTc prolongation is often the result of multiple medications, electrolyte abnormalities and patient specific factors.

- The ACM suggested that the ECG and blood tests (FBE, electrolytes, LFTs) be monitored weekly for Cycle 1 and every other week for Cycles 2 and thereafter before Day 1 (D1) for each cycle.
- A QTc of > 500 ms was an absolute contraindication to drug administration. Furthermore, documentation of QTc prolongation of > 60 ms after exposure to drug was a contraindication to further use,
- The instructions to physicians need to be re written in order to clearly incorporate the above concerns.
- The instructions for a physician need to state that Torsade de pointes, ventricular tachycardia and syncope (unless reviewed by a cardiologist or physician with identification of another aetiology) also constituted a contraindication to further use,
- The PI and CMI both needed significant alterations regarding the risk of QTc prolongation and information provided.

Specific advice

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

1. *Should the indication allow use with: letrozole (supported by Study A2301); with nonsteroidal aromatase inhibitors (the clinical evaluator's preference); or with aromatase inhibitors (proposed by the sponsor, endorsed by the FDA's approved indication, supported by the CHMP, and corresponding to indication wording for palbociclib)?*

The ACM agreed that a broad indication in the PI should be considered. The ACM suggested that the indication include aromatase inhibitors rather than letrozole alone or restriction to nonsteroidal aromatase inhibitors.

2. *Does the ACM support a boxed warning for QT interval prolongation? If so, does it have any suggestions about the content of this warning?*

The ACM supported the evaluator's recommendation for a boxed warning in PI and CMI.

The ACM agreed that a boxed warning for QT interval prolongation was beneficial. ACM suggested that the following be included in the content of the black box warning:

- Dose dependent increase in QT prolongation (400 to 900 mg).
- Concomitant medications which cause QT prolongation need to be listed.
- Add the following additional statement in the black box content '*Acquired QT interval prolongation may result from the combined effects of medication(s) and electrolyte abnormalities. Vigilance is required for possible adverse interactions*'.

3. *Given the evaluator's reservations about the sponsor's proposed monitoring approach, does the ACM have any suggestions about a preferable approach to be included in the PI?*

The ACM agreed that given the high incidence of significant neutropaenia, other cytopaenias, raised LFTs and serious AEs of prolonged QT interval, the proposed monitoring does seem inadequate.

The ACM noted that given the possibility of electrolyte abnormalities leading to QT prolongation electrolyte be monitored weekly. ACM also noted that neutropaenia and ECG changes are most likely to happen in the first 4 weeks.

The ACM suggested that the ECG and blood tests (FBE, Electrolytes, LFT) be monitored weekly for Cycle 1 and every 2 weeks for Cycle 2 and thereafter before Day 1 for each cycle.

4. *Given (a) the apparently different safety profile of ribociclib versus palbociclib, (b) the different evidence base for the two products, and (c) the expectation of new data informing use in pre-menopausal women (Study E2301; TGA submission possible by Q3 2018), does the ACM recommend that the ribociclib indication be limited to post-menopausal women, to men and post-menopausal women, or to men and women as per palbociclib?*

The ACM agreed that ribociclib should be limited to postmenopausal women and all male population but not pre-menopausal women. ACM noted that the opportunity of having a trial for male breast cancer would be unlikely. ACM agreed that there is existing evidence for efficacy of combination of AIs with ovarian suppression (either oophorectomy or goserelin) in premenopausal women. ACM noted that there were no biological reason to expect different efficacy or toxicity in males and that prior TGA approval of palbociclib in these populations was supported.

Other comments

The ACM also noted that:

1. Treatment should be initiated by a medical oncologist.
2. Recommended dosing regimen refers specifically to letrozole and recommends that dosing schedule be for the individual aromatase inhibitor to be used.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Kisqali ribociclib 200 mg (as succinate) film coated tablet blister pack.

The approved indication for this therapeutic good is:

> *Kisqali in combination with an aromatase inhibitor is indicated for the treatment of men and postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer, as an initial endocrine-based therapy.*

Specific conditions of registration applying to these goods

- The ribociclib EU Risk Management Plan (RMP), version 1.4 (Dated 22 June 2017, DLP 29 January 2016) with ASA version3.0 (Dated 12 October 2017) and any subsequent revisions, as agreed with the TGA will be implemented in Australia as a condition of registration.
- Supply as part of a Category 1 application, promptly after they become available, Clinical Study Reports reflecting updated analyses of Study A2301.
- Supply as part of a Category 1 application, promptly after they become available, the final report (and any interim analysis) for any study exploring the efficacy and safety of an alternative dosing regimen for ribociclib to mitigate the risk of QT prolongation.

- Supply as part of a Category 1 application, promptly after it becomes available, the final report for Study A2116 to assist in determination of the appropriate dose of ribociclib in patients with severe renal impairment.
- Supply as part of a Category 1 application, promptly after they become available, the final reports (and any interim analyses) from the Studies CLEE011E2301 and CLEE011F2301 regardless of whether the efficacy data is sufficient to support an indication submission.
- Supply as part of a Category 1 application, promptly after they become available, the final reports (and any interim analyses) from the Studies CLEE011XDE01 and CLEE011A2404.

Attachment 1. Product Information

The PI for Kisqali 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 at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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