22 June 2017
EMA/CHMP/506968/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kisqali

International non-proprietary name: ribociclib

Procedure No. EMEA/H/C/004213/0000

Note

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

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Table of contents

List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AI	aromatase inhibitor
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics classification system
BIRC	Blinded Independent Review Committee
BR23	breast cancer specific module of the EORTC QLQ-C30
BSEP	bile salt export pump
BU	Blend uniformity
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
CFU	Colony forming units
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmax	maximum (peak) plasma drug concentration
CTCAE	Common Terminology Criteria for Adverse Events
CU	Content uniformity
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
EC	European Commission
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-5L	EuroQol five-dimension five-level questionnaire
ER	estrogen receptor
EU	European Union
FAS	Full Analysis Set
FCT	film-coated tablet
FDA	Food and Drug Administration
GC	Gas chromatography
HER2	human epidermal growth factor receptor 2
HPLC	High performance liquid chromatography
HR	hazard ratio or hormone receptor
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry

IDMC	Independent Data Monitoring Committee
IR	Infrared
IRT	Interactive Response Technology
JP	Japanese pharmacopoeia
KF	Karl Fischer titration
LFT	liver function test
MATE1	multidrug and toxin extrusion protein 1
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	non-evaluable
NF	National formulary
NSAI	non-steroidal aromatase inhibitor
OCT2	organic cation transporter 2
ORR	objective response rate
OS	overall survival
PA	Polyamide
PCTFE	Polychlorotrifluoroethylene
PDE	Permitted daily exposure
PE	polyethylene
PET	polyethylene terephthalate
PFS	progression-free survival
Ph. Eur.	European pharmacopoeia
PK	parts per million
PPS	Per-protocol Set
pRb	retinoblastoma protein
PVA	Polyvinyl acetate
PVC	Polyvinyl chloride
QoL	quality of life
QTc/QTcF	corrected QT interval/QT interval corrected for heart rate using Fridericia's formula
Rb	retinoblastoma
RECIST	Response Evaluation Criteria In Solid Tumors
RH	Relative humidity
rpm	revolutions per minute
SAE	serious adverse event
SmPC	Summary of product characteristics
SMQ	standard MedDRA query
Tmax	time taken to reach maximum concentration
TTP	time to progression
TTR	time to response
T1/2	terminal half-life
ULN	upper limit of the normal range
USP	United States pharmacopoeia
UV	Ultraviolet
WBC	white blood cell
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd submitted on 5 September 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Kisqali, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 April 2015.

The applicant applied for the following indication:

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 initial endocrine-based therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Applicant's requests for consideration

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 20 November and 18 December 2014. The

Scientific Advice pertained to quality, and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Aranzazu Sancho-Lopez

- The application was received by the EMA on 5 September 2016.
- The procedure started on 29 September 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 20 December 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 30 December 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 03 January 2017.
- During the meeting on 26 January 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 January 2017.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 February 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 March 2017.
- During the CHMP meeting on 21 April 2017, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 May 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 9 June 2017.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 16 June 2017.
- During the meeting on 22 June 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kisqali on 22 June 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Kisqali is proposed for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer.

2.1.2. Epidemiology

Breast cancer is the second most common cancer in the world and the most frequent among women. An estimated 1.67 million women were diagnosed with breast cancer worldwide in 2012 (representing around 25% of all cancers in women) and approximately 522,000 deaths were recorded[1]. In EU there were 3.7 million new cases, and 1.9 million cancer deaths and 9.7 million people living with cancer (within 5 years of diagnosis) in 2012[2].

2.1.3. Biologic features

Breast cancer is a molecularly diverse disease with several clearly defined molecular subgroups (Perou et al 2000). The predominant subset is HR-positive, HER2-negative disease. Of the new breast cancer cases diagnosed worldwide each year, roughly 60% to 65% are HR-positive, 20% to 25% are HER2-positive, and 15% to 18% are triple-negative (Estrogen receptor-negative, Progesterone receptor-negative, HER2-negative)[3]. The expression of these biological markers in breast cancer is correlated with prognosis and response to treatment, and therefore plays an important role in treatment decisions.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

The diagnosis of breast cancer is based on clinical examination in combination with imaging, and confirmed by pathological assessment. Clinical examination includes bimanual palpation of the breasts and locoregional lymph nodes and assessment for distant metastases (bones, liver and lungs; a neurological examination is only required when symptoms are present)[4].

Metastatic breast cancer is an incurable disease with a median overall survival of 2~3 years and a 5-year survival of only~25%. Median overall survival in patients with advanced breast cancer patients with tumours expressing the estrogen receptor (ER) but not the human epidermal growth factor receptor 2 is better, i.e. approximately 2.5 to 4 years.

2.1.5. Management

Locally advanced or metastatic breast cancer patients derive benefit mainly from systemic treatments. Endocrine therapy remains the therapeutic backbone for the treatment of HR+ cancers. For postmenopausal women with HR+ advanced breast cancer, the endocrine therapy options include, but are not limited to, selective estrogen receptor modulators (SERM; e.g. tamoxifen), estrogen receptor antagonists (e.g. fulvestrant), selective non-steroidal aromatase inhibitors (NSAI; e.g. anastrozole and letrozole) and steroidal aromatase inhibitors (e.g. exemestane). TTP/PFS in the range of 5- 15 (20) months is typical in endocrine therapy trials in the postmenopausal population (Kümler ESMO Open 2016). Endocrine therapy may be given in first, second or later lines of therapy for advanced breast cancer[5],[6]. Progressive disease ultimately develops in all patients, either as early failure to respond to endocrine therapy (primary or de novo resistance) or as relapse/progression following an initial response (acquired resistance). A first in class cyclin dependent kinase (CDK) 4/6 inhibitor, palbociclib, was recently approved in the EU as an add-on to endocrine therapy (see EPAR Ibrance).

[1] Ferlay et. al., Int J Cancer, 2012
[2] GLOBOCAN Breast Cancer 2012
[3] Finn et al 2015
[4] ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
[5] ESO-ESMO 2nd International Consensus Guidelines for Advanced Breast Cancer (ABC2)
[6] National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology

According to treatment guidelines, chemotherapy should be reserved for cases of rapidly progressive disease or proven endocrine resistance[2,3].

About the product

Ribociclib (LEE011) is an orally bioavailable, small-molecule inhibitor of CDK 4 and 6.

Ribociclib is a selective inhibitor of cyclin dependent kinase (CDK) 4 and 6, resulting in 50% inhibition (IC50) values of 0.01 (4.3 ng/ml) and 0.039 µM (16.9 ng/ml) in biochemical assays, respectively. These kinases are activated upon binding to D cyclins and play a crucial role in signalling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb) (see SmPC 5.1).

In vitro, ribociclib decreased pRb phosphorylation, leading to arrest in the G1 phase of the cell cycle, and reduced cell proliferation in breast cancer cell lines. *In vivo*, treatment with single agent ribociclib led to tumour regressions which correlated with inhibition of pRb phosphorylation.

In vivo studies using patient-derived oestrogen-positive breast cancer xenograft model combinations of ribociclib and antioestrogens (i.e. letrozole) resulted in superior tumour growth inhibition with sustained tumour regression and delayed tumour regrowth after stopping dosing compared to each substance alone.

When tested in a panel of breast cancer cell lines with known ER status, ribociclib demonstrated to be more efficacious in ER+ breast cancer cell lines than in the ER- ones.

The initially applied indication for Kisqali 200 mg film-coated tablets was:

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 initial endocrine-based therapy.

The recommended 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.

The recommended dose is 600 mg (three 200 mg film-coated tablets) of ribociclib once daily for 21 consecutive days followed by 7 days off treatment, resulting in a complete cycle of 28 days. The treatment with Kisqali should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

Kisqali should be used together with 2.5 mg letrozole or another aromatase inhibitor. The aromatase inhibitor should be taken orally once daily continuously throughout the 28-day cycle. Please refer to the Summary of Product Characteristics of the aromatase inhibitor for additional details.

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption, reduction or discontinuation of Kisqali. If dose reduction is required, the recommended dose reduction guidelines are listed in the SmPC. Dose reduction can be made to 400 mg/day or 200 mg/day according to guidelines in the SmPC, section 4.2.

Treatment with Kisqali should be initiated by a physician experienced in the use of anticancer therapies.

Type of application and aspects on development

See section 1.1.

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. The applicant's claim that ribociclib was of major interest from the point of view of public health, in particular based on therapeutic innovation and an unmet medical need was not considered fulfilled taking into account the upcoming CHMP positive opinion on the approval of Ibrance (palbociclib) which is a CDK4/6 inhibitor indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing ribociclib succinate, equivalent to 200 mg of ribociclib as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone type A, magnesium stearate and colloidal anhydrous silica.

Film coat: partially hydrolysed polyvinyl alcohol, titanium dioxide (E171), talc, soya lecithin (E322), xanthan gum, iron oxide black (E172) and iron oxide red (E172).

The product is available in PVC/PCTFE (polyvinylchloride/polychlorotrifluoroethylene) and PA/Al/PVC (polyamide/aluminium/polyvinylchloride) blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of ribociclib succinate is butanedioic acid—7-cyclopentyl-*N*,*N*-dimethyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}-7*H*-pyrrolo[2,3-d]pyrimidine-6-carboxamide (1:1) corresponding to the molecular formula $C_{27}H_{36}N_8O_5$. It has a relative molecular mass of 552.6 g/mol and has the following structure:

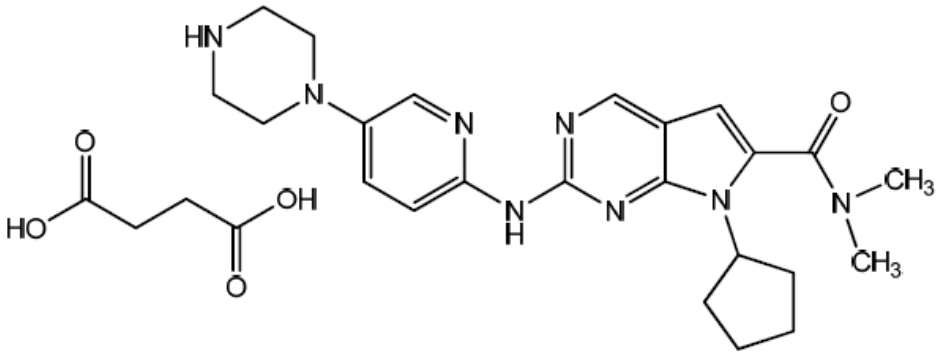


Figure 1 – Structure of ribociclib succinate

The chemical structure of ribociclib succinate was elucidated by a combination of ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, mass spectrometry, elemental analysis, infrared spectroscopy and ultraviolet spectroscopy. It is achiral. The solid state properties of the active substance were measured by differential scanning calorimetry, thermogravimetric analysis and x-ray powder diffraction.

The active substance is a slightly hygroscopic yellow to brown crystalline powder, soluble in acidic aqueous media, becoming less soluble as pH increases.

Polymorphism has been observed for ribociclib succinate. Production of the correct polymorphic form is ensured by an XRPD method in the active substance specification. As described under the stability section, ribociclib succinate form A has been demonstrated to be stable and not to convert into other polymorphic forms under long term and accelerated stability studies when stored in the proposed packaging.

Ribociclib is considered to be a new active substance. The applicant demonstrated that neither it, nor its derivatives and salts have ever been active substances in products authorised in Europe.

Manufacture, characterisation and process controls

Ribociclib is synthesized in nine main steps using four well defined starting materials with acceptable specifications.

The synthetic process uses a convergent approach with the four starting materials being converted in several steps to two intermediates, by two separate manufacturers. The intermediates are unified late in the sequence. In the final step, the succinate salt is formed, the conditions being carefully controlled in order to produce the desired polymorph. The process from the intermediates to ribociclib succinate is carried out by a third manufacturer.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Critical steps were identified and critical process parameters defined in order to ensure the quality of the active substance.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Elemental impurities are controlled in line with ICH Q3D and mutagenic impurities are controlled in line with ICH M7.

The active substance is packaged in polyethylene bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended, as well as the Ph. Eur. monograph on polyolefins. The bags are placed in quadruple laminated PE/PET/ALU/PET foil bags which are sealed and stored in drums. The selected packaging is very tight in order to prevent moisture ingress.

Specification

The active substance specification includes tests for appearance, identity (IR, XRPD), assay of ribociclib (HPLC), assay of succinic acid (titration), related substances (HPLC), residual solvents (GC), water content (KF), elemental impurities (ICP-MS), residue on ignition (Ph. Eur.), particle size distribution (laser diffraction), clarity of solution (Ph. Eur.) and microbial enumeration (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. As mentioned above, limits for elemental and mutagenic impurities are in line with the published guidance.

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

Batch analysis data from 38 batches of the active substance used in clinical trials, toxicology and stability studies, the last 8 of which used the proposed commercial process and were manufactured on production scale, are provided. The earlier batches used an earlier process which has since undergone only minor modifications and are considered representative. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three pilot scale batches of active substance stored in the intended commercial package for up to 12 months under refrigerated conditions (5 ºC), up to 6 months under long term conditions (25 ºC / 60% RH), up to 12 months under intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches were made at a different manufacturing site but are considered representative of commercial batches. A further stability program will be instigated using four production scale batches from the intended commercial manufacturers.

Batches were tested for appearance, identity (including crystalline form), related substances, water content, assay, clarity of solution and microbial enumeration. No significant changes to any of the measured parameters were observed and all attributes remained within specification under all the conditions tested. Polymorphic form A was demonstrated to be stable over the duration of the studies.

Photostability testing following the ICH guideline Q1B was performed on one batch. One impurity increased slightly but remained within its specification limit. No changes to any other measured parameter were observed. Therefore, ribociclib succinate is photostable.

Stress tests were carried out in both solid and solution state. Samples were exposed to heat, heat and humidity, acid, base, humidity, and an oxidant. Impurities remained well within specification. No degradation was observed when solid ribociclib succinate was heated with oxygen.

In aqueous solution, the active substance decomposed to a varying extent when heated with acid, base, water alone, or hydrogen peroxide. The results show that the analytical methods are stability indicating.

The stability results indicate that the active substance is sufficiently stable. The stability results justify the proposed retest period of 24 months not above 30 ^{o}C in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Kisqali is presented as film-coated tablets containing 200 mg ribociclib as succinate salt. The drug product is packaged in either PCTFE/PVC or PA/Al/PVC blisters.

The aim of development was to find a stable immediate release dosage form. A capsule formulation was used throughout clinical trials. In addition, an oral solution was developed for patients with difficulty swallowing capsules. The two were found to exhibit similar pharmacokinetic behaviour. To aid patient compliance and for convenience, a smaller tablet formulation was subsequently developed and shown to be bioequivalent to the 200 mg hard gelatin capsule in a clinical study.

The active substance is a BCS class 4 molecule with moderate permeability. It is soluble in acidic media below pH 5.5 but solubility decreases at neutral and basic pH and stable in the solid form. A dry granulation process was developed in order to prevent changes in polymorphic form which could impact bioavailability. Suitable controls are in place to prevent detrimental solid form changes and ensure manufacturability. Excipients were chosen to enable manufacture of a robust film-coated tablet which performs adequately *in vivo*. Compatibility of the active substance with the chosen excipients was demonstrated through stability studies.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. As mentioned above, they were selected based on compatibility studies with the active substance and knowledge gained from development of Kisqali and other tablet products.

Development of the dissolution method has been described. The method was evaluated against meaningful changes in process parameters and input material attributes. The method is considered sufficiently discriminatory and the associated specification limit is deemed adequate to ensure product quality.

The primary packaging is PVC/PCTFE and PA/Al/PVC blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product, providing adequate protection from moisture uptake and potential polymorph conversion.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: blending of intra-granular components; roller compaction; milling and blending with extra-granular excipients; compression; film-coating. The process is considered to be a standard manufacturing process.

The granulation, compression and film-coating steps are considered to be critical. Critical process parameters have been defined in order to ensure the process routinely delivers tablets of acceptable quality. In-process controls are carried out following compression and film-coating on in-process intermediates.

Major steps of the manufacturing process have been validated on three consecutive production scale batches of finished product at the intended commercial manufacturing site with a focus on the critical steps. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications re-produced below include appropriate tests for this kind of dosage form including appearance, identity (UV, HPLC), identity of colourants (colour reaction), mean mass, uniformity of dosage units (Ph. Eur.), assay (HPLC), degradation products (HPLC), water content (KF),

dissolution (UV) and microbial enumeration (Ph. Eur.). The omission of a test for polymorphic form is justified since no meaningful changes in solid state were found during stability studies. A risk assessment according to ICH Q3D and additional screening studies were performed indicating that elemental impurities are routinely below 1% of their PDE. Therefore, no tests for elemental impurities are carried out.

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

Batch analysis results were provided for two production scale batches from the intended manufacturer and three pilot scale batches from a different site (including the biobatch) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three pilot scale batches of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product were manufactured at a different site but using the same process as those proposed for marketing and were packed in both primary packaging formats intended for marketing.

Batches were tested for appearance, dissolution, assay, degradation products and microbial enumeration. Additional tests for water content, crushing strength and disintegration time were carried out for information. The analytical procedures used are stability indicating. No significant changes to any of the measured parameters were observed under long term or intermediate conditions, other than a slight decrease in crushing strength at 30 ^{o}C. Under accelerated conditions, no changes were observed to appearance, assay, impurities or dissolution time. A small increase in water content, well within the specification limit, and an increase in disintegration time was noted, with a concomitant decrease in crushing strength.

In addition, one batch was exposed unpacked to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant change to any of the measured parameters was observed, other than an increase in water content. Kisqali is not considered to be photosensitive.

A further study examined conditions likely to be experience during transportation, for example, termperature excursions. However, all quality characteristics remained within the proposed specifications indicating no likely issues.

Based on available stability data, the proposed shelf-life of 24 months without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. Magnesium stearate is of vegetal origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The correct polymorphic form of ribociclib succinate is ensured by the crystallization process, a test in the active substance specification, and the storage conditions. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in

turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical data consisted of *in vitro* and *in vivo* pharmacology studies, safety pharmacology studies, single-dose toxicity in dogs, and repeat-dose toxicity for up to 27 weeks in rats and 39 weeks in dogs, *in vitro* and *in vivo* genotoxicity, embryo-foetal development toxicity in rats and rabbits, *in vitro* phototoxicity. In addition, potential impurities have been addressed. The non-clinical pharmacokinetics of ribociclib was evaluated in a series of *in vitro* and *in vivo* studies conducted in mice, rats, dogs and cynomolgus monkeys.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro

The potency and selectivity of ribociclib as a CDK4/6 inhibitor were determined by biochemical assays using isolated enzyme complexes. Ribociclib inhibited CDK4/Cyclin D1 and CDK6/Cyclin D3 complexes with IC_{50} of 0.008 µM and 0.039 µM, respectively, while exhibiting less potent activity against other CDK family members. IC_{50} for binding to CDK9 was 1.52 µM. This concentration is similar to clinical free C_{max} at the therapeutic dose (600 mg) of ribociclib (1.2 µM).

Target inhibition and effects on proliferation and cell cycle were investigated in a number of different cancer cell lines, including breast cancer cell lines. In Jeko-1 cells (a retinoblastoma protein (pRb)-positive mantle cell lymphoma cell line containing translocated cyclin D1), ribociclib inhibited the CDK4/6 specific phosphorylation of pRb, with an IC_{50} of 0.18 µM. Ribociclib also inhibited BrdU uptake and induced a selective G1 cell cycle arrest in Jeko-1 cells, with an IC_{50} of 0.08 µM and 0.11 µM, respectively.

In other cancer cell lines the IC_{50} values between assays showed greater variation, for instance in two HER2-positive breast cancer cell lines (BT474, HCC1954) where the IC_{50} for proliferation was considerably higher (1.8-3.3 µM) than the IC_{50} for cell cycle arrest (0.07-0.46 µM).

The major metabolites of ribociclib observed in human hepatocytes are LEQ803 and the secondary metabolite CCI284. Both were tested in Jeko-1 cells, with G1 arrest IC_{50} of 0.240 uM (LEQ803) and 1.137 uM (CCI284). Thus both metabolites were less potent inhibitors of CDK4/6 than ribociclib.

In vivo

The anti-tumour activity of ribociclib *in vivo* was evaluated in mouse and rat xenograft models, including Jeko-1 cells, human breast cancer cell lines and patient-derived breast cancer xenografts. In the Jeko-1 cell model in SCID mice, ribociclib at 150 mg/kg/day orally for 21 days caused complete tumour regression, which correlated with 90% inhibition of pRb phosphorylation. After cessation of treatment, tumours re-grew rapidly. Despite an increase of the dose to 300 mg/kg/day during a 2-week extension phase, anti-tumour activity was suboptimal and at the end of dosing the tumour volume was increasing.

In the Jeko-1 cell model in male nude rats, ribociclib at 300 mg/kg/day orally was the maximum tolerated dose (MTD). Ribociclib at 10, 75 and 150 mg/kg/day reduced the phosphorylation of pRB by 35, 80 and 100%, respectively. At the highest dose level this effect was maintained over 24 h. Complete tumour regression was observed in the 75 and 150 mg/kg dose groups after 28 days of dosing. In the 30 mg/kg dose group, there was a 44% tumour volume reduction as compared to vehicle controls. Integration of PK/PD data suggests that a sustained plasma exposure corresponding to approximately $\geq$ 10 uM must be maintained over the dose interval for full effect.

In three estrogen receptor (ER)+ breast cancer cell line xenograft models (KPL-1, ZR751, MCF7) in athymic nude mice, ribociclib at 75 mg/kg/day orally for 28 days caused significant tumour growth inhibition. Plasma exposure in the MCF7 xenograft model was AUC 12513 ng·h/mL and C_{max} 2683 ng/mL, which is in a similar range as the exposure achieved at a dose of 600 mg once daily in humans. When ribociclib was combined with the ER antagonist fulvestrant, at 5 mg/week (subcutaneous injection), the anti-tumour effect was enhanced.

The anti-tumour activity of ribociclib was further tested in patient-derived ER+ breast cancer xenograft models (PDX191, HBCx-34) in athymic nude mice. Ribociclib administered at 75 mg/kg/day 6 days/week for 40 days caused significant tumour growth reduction in the PDX191 model. In the HBCx-34 model, ribociclib given alone at 75 mg/kg/day for 56 days did not cause any significant inhibition of tumour growth. In contrast, combination treatment with ribociclib at 75 mg/kg/day + the non-steroidal aromatase inhibitor letrozole at 2.5 mg/kg/day caused marked inhibition of tumour growth, without any tumour regrowth observed during a 1-month follow-up period. Ribociclib (75 mg/kg/day) was also administered in combination with the ER modulator tamoxifen (1 mg/kg/day) orally for 56 days in the HBCx-34 xenograft model. This treatment scheme resulted in significant tumour growth inhibition, with an enhanced anti-tumour activity as compared to monotherapy.

Secondary pharmacodynamic studies

Secondary pharmacodynamics

The effect of ribociclib on myelopoiesis and selected blood chemistry parameters was evaluated as part of the efficacy study in male nude rats. Ribociclib at all dose levels (30, 75 and 150 mg/kg/day) caused significant reductions of white blood cells (WBC) and absolute neutrophil count (ANC).

Ribociclib was assessed for its off-target activity on 147 G protein-coupled receptors (GPCRs), transporters, ion channels, nuclear receptors and enzymes. An activity of >50% inhibition at 10 µM was found on 4 targets. Of these, binding to PDE4d (IC_{50} = 0.59 µM) occurred at a concentration relevant to the clinical situation (free C_{max} 1.2 µM). IC_{50} values were not determined for the apelin and orexin-2 receptors.

LEQ803 was assessed for its off-target activity on 144 GPCRs, transporters, ion channels, nuclear receptors and enzymes. An activity of >50% inhibition at 10 µM was found on 7 targets; however, the IC_{50} concentrations were 20-900x above clinical free C_{max}.

Safety pharmacology programme

Studies in the rat did not reveal any effects on respiratory functions (tidal volume, respiratory rate, and minute volume) after a single oral gavage administration of ribociclib at 200 mg/kg. The Functional Observational Battery revealed slightly decreased rectal temperature 7h postdose, as well as reduced activity and rearing 7 and 24 h postdose after a single oral dose of ribociclib at 200 mg/kg.

Ribociclib decreased concentration-dependently hERG channel activity in stably transfected HEK293 cells with significant inhibition at concentrations $\geq$30 µM (13.0 µg/mL). The estimated IC_{25}-, IC_{50}- and IC_{75}-values for ribociclib-induced block of the hERG tail current were 26.0 µM (11.3 µg/mL), 53.0 µM (23.0 µg/mL) and 111.0 µM (48.1 µg/mL), respectively.

In vivo cardiac safety pharmacology (telemetry) studies in dogs demonstrated a clear signal for QT prolongation at doses of ribociclib $\geq$20 mg/kg. Mean changes of QTc at 20, 50 and 100 mg/kg versus vehicle for the time period of 1.75 h post dose until end of the recording period were +12.1 ms (+5.3 %), +23.4 ms (+10.2 %), +37.9 ms (+16.5 %), respectively. There were no effects on heart rate, blood pressure, ECG morphology, rhytm or duration of other intervals. The lowest C_{max} level where QTc prolongation was observed was 929 ng/mL (for comparison, C_{max} at steady state in patients following a 600 mg dose is 1820 ng/mL).

In an investigative follow-up telemetry study, a single dose of ribociclib at 100 mg/kg produced QTc prolongation (up to 12%), as well as QRS prolongation, increased heart rate and premature ventricular contractions (PVCs) in one dog. C_{max} in this dog was 9720 ng/mL.

The metabolite LEQ803 inhibited the hERG current with IC_{50} values of 4.8 µM and 15.8 µM in two experiments. It produced 76% inhibition at 30 µM, the highest concentration tested. In a non-GLP telemetry study in dogs, LEQ803 caused up to 16% increase in mean QT and QTc at a dose of 5 mg/kg, corresponding to mean C_{max} of 50 ng/mL. Mean human C_{max} at steady-state for LEQ803 following a 600 mg dose of ribociclib was 116 ng/mL.

Pharmacodynamic drug interactions

No drug interaction study was conducted in animals which was considered acceptable (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

Absorption

Ribociclib was rapidly absorbed after a single oral dose, with Tmax ranging from 0.25 to 4 h in the plasma of mice, rats, dogs and monkeys, which is similar to Tmax in humans (2-4 h). Oral bioavailability was moderate in mouse, rat and dog (65%, 37.1-55% and 63.8-85.6%, respectively) and low (16.6%) in monkey.

Ribociclib showed moderate to high clearance in the mouse, rat, dog and monkey following iv dosing. The plasma systemic half-life was moderate (1.91 to 5.0 h) in the mouse, rat and monkey and long in the dog

and human (12-38.8 h and 49.4 h, respectively). The volume of distribution was large (7.88 to 27.9 L/kg) across species. In rat a gender difference was observed. Clearance was faster in females compared to males due to a more pronounced sulfoconjugation pathway in females (see Metabolism). In female rats, blood clearance was higher than hepatic blood flow indicating extrahepatic sulfation.

In all species where LEQ803 was measured (rat, dog, monkey and human) exposure to LEQ803 was lower compared to that of ribociclib. LEQ803 AUC represented between 1% and 73% of ribociclib AUC in rat, dog and monkey and 27% in human. The LEQ803/ribociclib AUC ratio was higher in male rats compared to females because in males oxidative metabolic pathways leading to LEQ803 were more prominent (see Metabolism). In rat and dog, the relative exposure to LEQ803 was higher after oral dosing compared to iv dosing, indicating a first-pass effect in formation of this metabolite.

Distribution

Tissue distribution in albino and pigmented rats was evaluated by quantitative whole body autoradiography (QWBA). Ribociclib was widely distributed into tissues except for the brain and was rapidly eliminated from most tissues. Highest concentrations of radioactivity in albino rats after iv dosing were found in the thyroid gland, kidney, pineal body, pituitary gland, adrenal medulla, and spleen. After oral dosing, the highest tissue concentrations were found in the pituitary gland, preputial gland, thyroid gland, and spleen.

Pigmented rats showed a similar tissue distribution as albino rats, except that melanin-containing structures like the eye (choroid, ciliary body), meninges and hair follicles had high exposure to radiolabeled material and a slow elimination. In the choroid and ciliary body of the eye, radioactivity was still measurable after 840 h (the last time-point analysed).

Low or absent brain penetration in the rat was demonstrated after intracarotid injection; however, significant brain penetration was observed after intravenous injection. Plasma protein binding of ribociclib was moderate in all species. The unbound plasma fraction (fu) ranged from 0.20 in rat to 0.34 in dog (human: 0.30). The blood:plasma concentration ratios were between 0.90 in rat and 1.30 in dog (1.01 in human).

Ribociclib passed the placental barrier in rats and rabbits (see Toxicology). Fetal plasma concentrations were 4 to 29% of maternal plasma concentrations.

Metabolism

In vitro

The in vitro metabolism of ribociclib was evaluated in hepatocytes of mouse, rat, dog, monkey and human. Ribociclib was a substrate for liver metabolism in all species tested. CYP3A4 and, to a lesser extent, FMO3 were identified as the enzymes responsible for the majority of the metabolic clearance (see the Clinical Pharmacokinetics Assessment Report). The metabolism rate was highest in monkey, rat and human hepatocytes. All human metabolites identified in vitro were later detected in vivo with the exception of the glutathione conjugates M2 and M5. In dog intestinal microsomes, ribociclib was metabolically stable.

In vivo

Ribociclib underwent extensive metabolism in vivo in rat, dog and human. In the rat, metabolism was dominated by direct Phase II sulfation, whereas in the dog and human metabolic pathways were predominantly oxidative. Female rats had lower exposure to ribociclib compared to males due to a more pronounced Phase II metabolism to the sulfate metabolite M8. This pathway was minor in dog and human. The major component in plasma of rat, dog and human was unchanged ribociclib. The most prominent plasma metabolites in human were M4 (LEQ803) and M13 (CCI284). Exposure to these metabolites was covered in rat toxicology studies (see Toxicology).

Metabolites in milk

Metabolites in rat milk were assessed following a single oral dose of 50 mg/kg 14C-ribociclib. The major component in milk and maternal plasma was ribociclib. Major metabolites in milk were M12, M18 (5.0%), M11 and M15. The exposure to total radiolabeled material and to ribociclib was higher in milk compared to plasma. The milk/plasma ratio (AUCinf) was 4.87 for total radiolabeled components, and 3.56 for ribociclib. Based on the average concentrations in maternal milk and daily milk consumption by neonatal rats, a daily ribociclib intake of 0.08 mg/kg bw was estimated for the suckling pups.

Reactive intermediates in the liver

The potential of ribociclib to form reactive intermediates and as a consequence covalent drug-protein adducts was investigated in human liver microsomes as well as in human, rat and dog hepatocytes incubated with 3H-ribociclib. In human liver microsomes, low levels (below the pre-defined threshold) of covalent drug protein adducts were observed. In contrast, incubation of human, rat and dog hepatocytes with 3H-ribociclib led to high amounts of covalent drug protein adducts. Preincubation with the non-selective CYP450 inhibitor AXR642 as well as azamulin (CYP3A4 specific) were effective in blocking protein adduct formation leading to a decrease of 72% and 83%, respectively. Menadione (non-selective CYP inhibitor) and methimazole (FMO-3 specific) at a concentration of 10 µM, led to 91% and 58% decrease in protein adduct formation, respectively.

Analysis of the protein adducts in human hepatocytes revealed 20 target proteins in different mass ranges (20 – 150 kDa). The proteins were not identified by LC-MS/MS.

Analysis of the protein adducts in rat hepatocytes revealed a target pattern that was less complex when compared to human hepatocytes. Five major proteins in the range of 25-150 kDa were identified. In dog hepatocytes, 10 target proteins in the range of 20-75 kDa were detected. In all three species (human, rat, dog) there appeared to be an identical, intense protein band at around 25 kDa.

Excretion

Mass balance data was obtained from rats and male Beagle dogs.

The majority of absorbed drug-related radioactivity being eliminated by metabolism via bile, and a minor fraction by direct secretion into urine and feces. Following oral dosing in the rat, the majority of radiolabelled material was excreted within the first 24 h. In contrast, excretion in the dog was slow, with a sampling period of 336 h needed for good recovery.

2.3.4. Toxicology

Single dose toxicity

Table 4. Summary of single-dose toxicity studies performed with ribociclib in dogs.

Study ID/GLP	Species/ Sex/Number/ Group	Dose (mg/kg)/ Route	Observed max non-lethal dose	Approx. lethal dose
rd0870611 Non-GLP	Beagle dog 1 sex/group	25, 50, 100, 150 Oral gavage Vehicle: 0.5 % methyl cellulose	All doses were tolerated, but MTD considered to be 100 mg/kg	Not established

Noteworthy findings ≥50 mg/kg in M and at ≥ 100 mg/kg in F: emesis with dose formulation and mucus 100 mg/kg: salivation. ≥25 mg/kg: slight to severe decreases in food consumption				
rd0870721 Non-GLP	Beagle dog 1 sex/group	2, 5, 10 Intravenous Vehicle: citrate buffer /HCl	All doses were tolerated, but MTD considered to be 5 mg/kg	Not established
Noteworthy findings 2 mg/kg: reddened skin at the abdomen, testes, oral mucosa and gingiva in the male; abnormal posture, salivation, excessive licking, and reddened gingiva in the female. M & F: slight reduction in food consumption ≥ 5 mg/kg: partially closed eye lids and decreased motor activity (male: marked; female: slight) 10 mg/kg: head shaking, labored respiration, licking excessively, reddened ears, and eye lids partially closed. M: gasping, salivation, and reddened eyes. F: recumbency, trembling, vomiting, retching, reddened body, and soft feces. F: slight body weight loss; M & F: reduction in food consumption				

Repeat dose toxicity

Table 5. Summary of repeat-dose toxicity study performed with ribociclib

Study ID/GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg(day)/Route	Maximum tolerated dose
0870010 Non-GLP 2 weeks	Wistar rat 5M/group	0 (vehicle), 37.5x2, 100x2 Oral gavage, ~7 hrs apart Vehicle: 0.5% methylcellulose aqueous solution w/v	Not established
0870393 (pivotal) GLP 4 weeks + 4 weeks recovery	Han Wistar rat 10/sex/group (5/sex/group for recovery at ctrl and HD groups) + satellites for TK	0 (vehicle), 25, 75, 150 Oral gavage Vehicle: 0.5% methylcellulose aqueous solution w/v	75 mg/kg/day in M 150 mg/kg/day in F
1370292 (pivotal) GLP 15 weeks (3 weeks dosing, 1 week off) + 4 weeks recovery	Han Wistar rat 20/sex/group (10/sex/group for recovery at ctrl and HD groups) + satellites for TK	0 (vehicle), 25, 75, 150 in M and 0 (vehicle), 50, 150, 300 in F Oral gavage Vehicle: 0.5% methylcellulose aqueous solution w/v	25 mg/kg/day in M 300 mg/kg/day in F
1470078 (pivotal) GLP 27 weeks (3 weeks dosing, 1 week off)	Han Wistar rat 20/sex/group + satellites for TK	0 (vehicle), 25, 75, 150 in M and 0 (vehicle), 50, 150, 300 in F Oral gavage Vehicle: 0.5% methylcellulose aqueous solution w/v	25 mg/kg/day in M 150 mg/kg/day in F
0870165-01 Non-GLP 2 weeks	Beagle dog 1 or 2/sex/group	0 (vehicle), 5, 15, 25 Oral gavage Vehicle: 0.5% methylcellulose aqueous solution w/v	25 mg/kg/day
0870399 (pivotal) GLP 4 weeks + 4 weeks recovery	Beagle dog 3/sex/group (2/sex/group for recovery at ctrl and HD groups)	0 (vehicle), 5, 10, 20 Oral gavage Vehicle: 0.5% methylcellulose aqueous solution w/v	MTD 20 mg/kg/day
1370291 (pivotal) GLP 15 weeks (3 weeks	Beagle dog 4/sex/group + 2/sex for recovery at ctrl and HD	0 (vehicle), 1, 3, 10 Oral gavage Vehicle: 0.5%	No NOAEL for M 10 mg/kg/day for F

Study ID/GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg(day)/Route	Maximum tolerated dose
dosing, 1 week off) + 4 weeks recovery		methylcellulose aqueous solution w/v	
1470079 (pivotal) GLP 39 weeks (3 weeks dosing, 1 week off)	Beagle dog 4/sex/group	0 (vehicle), 1, 3, 10 Oral gavage Vehicle: 0.5% methylcellulose aqueous solution w/v	No NOAEL for M 10 mg/kg/day for F

In rat and dog toxicity studies, effects on bone marrow (hypocellularity), lymphoid tissue (lymphoid depletion), the hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) and testes (atrophy) were observed. In dog toxicity studies providing up to 4 weeks of treatment, a QT interval prolongation and effects on intestinal mucosa (atrophy), skin (atrophy) and bone/ribs (decreased bone formation) were also reported. In rat toxicity studies only, changes in the lung (increased incidence of alveolar macrophages) and kidney (concurrent degeneration and regeneration of tubular epithelial cells) were observed.

Mortality/clinical signs

In rats, no ribociclib-related mortality occurred in studies up to 15 weeks duration. In the 27-week study, two males given 150 mg/kg/day were euthanized in a moribund condition on Days 120 and 149, respectively. Their deaths were considered possibly due to a ribociclib-related infiltrate of alveolar macrophages resulting in respiratory distress. The group mean AUC exposure in males at 150 mg/kg/day corresponds to about 2-fold the clinical AUC. In the 4-week rat study, a dose-related increased salivation and rales was seen at ≥75 mg/kg/day and a slightly reduced body weight gain in males at 150 mg/kg/day. A reduced body weight gain was also observed in males given ≥75 mg/kg/day in the 15- and 27-week studies. However, during the dose-free weeks, body weight changes rebounded and were slightly higher than the controls.

In dogs, no mortalities were observed. In the preliminary 2-week non-GLP study, vomiting, increased salivation and severe body weight loss were observed at 25 mg/kg/day, corresponding to AUC exposures ~2-fold the clinical exposure. A marked body weight loss (up to -17%) was also observed at 20 mg/kg/day in the 4-week GLP study. In the 15- and 27-week studies at slightly lower dose levels, no ribociclib-related clinical signs or effects on body weight were observed.

Effects on the hepatobiliary system

Dose-related hepatobiliary toxicity was observed in both rats and dogs. Reversibility was demonstrated in rats, while partial reversibility was shown in dogs. In rats, the changes were characterized by bile duct epithelium vacuolation and/or hypertrophy with correlating increased plasma total bilirubin. In the 27-week rat toxicity study, immunohistochemistry for lysosome-associated membrane protein-2 (LAMP-2) was performed on the liver from selected animals. Increased LAMP-2 positivity suggested a ribociclib-related increase in lysosomes (phospholipidosis) in rats.

In dogs treated for up to 4 weeks, the changes consisted of hyperplasia/hypertrophy/proliferation of intra- and extra-hepatic bile ducts with periductular fibrosis, inflammatory cells and single cell degeneration, gallbladder hyperplasia/hypertrophy with wall and arterial necrosis, cholestasis; inspissated bile with calculi in gallbladder, arteriopathy with focal wall degeneration, and hemorrhage and fibrin in arteries near the liver hilus. Lysis of periportal hepatocytes and vacuolated macrophages in the wall of the common bile duct were also observed. Clinical chemistry changes indicative of hepatobiliary toxicity were observed and included increases in ALP, ALT, AST and total bilirubin, as well as an increased

cholesterol and decreased triglycerides, glucose and/or albumin and globulin. No liver histopathology or liver enzyme elevation were observed in dog 15- or 39-week studies at lower exposures.

Effects on the bone marrow and lymphoid system

In rat and dog studies, bone marrow hypocellularity, reduced extramedullary hemopoiesis in the spleen, lymphoid depletion in the thymus, spleen, gut-associated lymphoid tissues and lymph nodes with reduced germinal center development were observed. Correlating bone marrow smears and hematological changes were also seen with decreases in myeloid: erythroid ratio, reticulocyte count, red blood cell count, hemoglobin and hematocrit as well as decreases in lymphocytes, neutrophils, monocytes and eosinophils. These changes were reversible or showed a trend towards reversibility.

Effects on the kidney

In the 15- and 27-week rat toxicity studies, increased kidney weight and concurrent degeneration and regeneration of kidney tubular epithelial cells were observed. No effects were noted in dogs.

Effects on the lung and mesenteric lymph nodes

In the 4-week dog study, minimal to moderate (not dose-related) pulmonary inflammation with accumulation of alveolar macrophages was observed in several dogs of all dose groups. There was a trend towards reversibility during the recovery period. In rats, increased alveolar macrophages in the lungs and histiocytosis in the lymph nodes was observed in all studies with partial reversibility during the recovery period. In the 27-week rat study, additional immunohistochemistry for LAMP-2 was performed on the lung and mesenteric lymph node from selected animals. Increased LAMP-2 positivity suggests a ribociclib-related increase in lysosomes i. e. phospholipidosis. This was further confirmed by electron microscopy showing the presence of various sized and shaped lysosomes containing electron dense lamellar inclusion bodies.

Effects on the skin, intestinal mucosa, bone/ribs and ovaries

In dogs treated for up to 4 weeks, epidermal atrophy of the skin, mucosal atrophy mainly in the jejunum and decreased bone formation at the costochondral junction and increased number of ovarian corpora lutea (one dog only) were observed. All changes were fully reversible after a 4-week treatment free period. The effects on skin, intestinal mucosa, bone/ribs and ovaries were not present in the 15- or 39-week dog studies where slightly lower dose levels were used.

Effects on the testes

In rats and dogs (up to 26 and 39 weeks of treatment, respectively), focal/multifocal tubular vacuolation with spermatic giant cells, abnormal spermatids and germ cell depletion, predominantly affecting the spermatogonia and spermatocytes, were detected. At the end of recovery periods, signs of spermatogenesis regeneration in the testes (tubular regeneration) were noted with the reappearance of spermatogonia and pachytene spermatocytes in both species. However, a complete reversibility was not demonstrated.

Electrocardiography (ECG)

In the 4-week dog toxicity study, ECG revealed no overt treatment-related effects on morphology and heart rate. Prolongation in QT and QTc intervals in comparison with pre-test was observed in individual dogs. A dose- and concentration-related QT and QTc interval prolongation (up to 16%) was observed in the single-dose telemetry study in dogs. No QT effects were noted in the longer duration toxicity studies.

Genotoxicity

The *in vitro* mutagenicity studies, micronucleus test study, and chromosome aberration test study, in which either cytotoxic concentrations (mammalian cell tests) or the maximum recommended concentration (5000

µg/plate; AMES test) were used, were negative and did not reveal any evidence for a genotoxic potential of ribociclib. In the *in vivo* rat micronucleus test, ribociclib did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of male rats treated up to the estimated MTD of 350 mg/kg/day. Small but statistically significant increases in micronuclei in the polychromatic erythrocytes were observed in female rats at doses of ≥350 mg/kg/day. However, with the exception of a single animal at the intermediate dose (350 mg/kg/day), all individual animal micronuclei in the polychromatic erythrocytes frequencies fell within historical control ranges.

Carcinogenicity

No carcinogenicity study has been submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

Embryo-foetal development toxicology studies were conducted in pregnant rats and rabbits. In rats, a marked maternal toxicity was observed by clinical observations, markedly reduced body weight and food consumption and by mortality/moribundity at 1000 mg/kg/day and consequently the high dose group was terminated and not further evaluated. No significant maternal toxicity was observed at 300 mg/kg/day, but foetal toxicity evidenced by reduced foetal weights accompanied by skeletal changes considered to be transitory and/or related to the lower foetal weights were noted. There were no effects upon embryo-foetal mortality or adverse effects on foetal morphology at 50 or 300 mg/kg/day. The NOAEL for maternal toxicity was 300 mg/kg/day, corresponding to 0.5-fold the clinical AUC exposure and the NOAEL for embryo-foetal development was 50 mg/kg/day, corresponding to <0.1-fold the clinical AUC (maternal exposure).

In the pivotal rabbit study, no maternal toxicity was observed. At doses ≥30 mg/kg, there were significant adverse effects on the embryo-foetal development as evidenced by increased incidences of foetal abnormalities (malformations and external, visceral and skeletal variants) and reduced foetal weight. These findings included reduced/small lung lobes and additional vessel on the aortic arch and diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes and reduced/small accessory lung lobe (30 and 60 mg/kg), extra/rudimentary 13^{th} ribs and misshapen hyoid bone and reduced number of phalanges in the pollex. There was no evidence of embryo-foetal mortality. The NOAEL for maternal toxicity was 30 mg/kg/day corresponding to 1.5-fold clinical AUC exposure, and the NOAEL for embryo-foetal development was 10 mg/kg/day, corresponding to 0.3-fold the clinical AUC (maternal exposure).

Toxicokinetic data

Toxicokinetic assessment of ribociclib was included in all toxicology studies conducted in rats, dogs and rabbits. In addition, metabolite LEQ803 exposure was also included in all studies while metabolite CCI284 exposure was measured in plasma samples of the high dose males from the 27 week rat study using a non-validated non-GLP method.

In the rat 4-week study, all animals were exposed to ribociclib and LEQ803. In general, the exposure of ribociclib and LEQ803 in terms of AUC increased with increasing dose in a roughly proportional manner over the dosing regimen and irrespectively of the gender.

In the rat 27-week study, all animals were exposed to ribociclib and LEQ803 with a few exceptions where values were below the LLOQ. In general, the exposure to ribociclib and LEQ803 in terms of AUC increased with increasing dose in a rough proportional manner irrespective of dose, gender or study day.

The non-GLP analysis of metabolite CCI284 from high dose male samples revealed that all male rats were exposed to CCI284. The male rats were roughly 10 times more exposed to ribociclib than to LEQ803 and roughly 2 times more exposed to ribociclib than to CCI284.

In the dog 4-week study, all animals were exposed to ribociclib and LEQ803. In general, the exposure to ribociclib and LEQ803 in terms of AUC increased with increasing dose in a rough proportional manner irrespective of dose, sex or study day.

In the dog 39-week study, all animals were exposed to ribociclib and LEQ803, except for LEQ803 at the lowest dose where values were generally below the LLOQ. For this reason, no toxicokinetic profile could be calculated for LEQ803 at the lowest dose. In general, the exposure to ribociclib and LEQ803 in terms of AUC increased with increasing dose in a rough proportional manner irrespective of dose, sex, or study day. No accumulation of ribociclib or LEQ803 was noted after multiple administrations. No sex difference based on the AUC for ribociclib and LEQ803 was noted, irrespective of dose or study day. Based on the dose normalized AUC, dogs of both sexes were far more exposed to ribociclib than to LEQ803, from 23-fold to 33-fold.

Local Tolerance

Ribociclib did not show a skin irritation potential in rabbits, nor a sensitizing or irritating potential (after 3 days of topical administration) in the murine local lymph node assay.

Other toxicity studies

Phototoxicity

Ribociclib showed light absorption in the UVB and UVA range up to approximately 400 nm with MEC values above the threshold value. In pigmented rats, specific distribution and retention of ribociclib-derived radioactivity was observed in melanin-containing structures (choroid and ciliary body of the eye, meninges and hair follicles). An in vitro 3T3 neutral red uptake phototoxicity test did not identify a relevant phototoxicity potential for ribociclib, since neither under irradiation with simulated sunlight nor without irradiation any cytotoxicity was observed up to 1000 µM.

2.3.5. Ecotoxicity / environmental risk assessment

Table 6: Summary of main study results

Substance (INN / Invented Name): ribociclib succinate			
CAS-number (if available): NA			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log D at pH 4 < -0.8 log D at pH 7 = 0.6 log D at pH 9 = 2.2	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	0.6	not B
	BCF	N/A	–
Persistence	DT50 or ready biodegradability	not readily biodegradable (see OECD301B)	P
Toxicity	NOEC or CMR		T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	3.0	µg/L	> 0.01 threshold

					(Y)
Other concerns (e.g. chemical class)	N/A	N/A			N/A
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} $Soil_1$ = 41886 L/kg K_{oc} $Soil_2$ = 69250 L/kg K_{oc} $Soil_3$ = 301755 L/kg K_{oc} $Sludge_1$ =1873 L/kg K_{oc} $Sludge_2$ = 993 L/kg			K_{oc} > 10000 L/kg triggers terrestrial testing
Ready Biodegradability Test	OECD 301B	5 – 14%, not readily biodegradable			
Aerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ total\ system}$ = 0.31–0.35 days $DT_{90,\ total\ system}$ =1.2–2.3 days >10 % shifting to sediment			Shifting to sediment triggers sediment testing
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	EC_{10} NOEC	0.71 ≥10	mg/L mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	$NOEC_{21\ day}$	1.4	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	$NOEC_{30\ day}$	1.0	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	$EC_{50,\ 3h}$ $NOEC_{3h}$	>1000 ≥10	mg/L mg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	1000	mg/kg	*Chironimus riparius*

Ribociclib is not a PBT substance. Considering the above data, ribociclib is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The *in vivo* results in breast cancer xenograft models showed an enhanced tumour growth inhibition activity of ribociclib when given in combination with endocrine therapies used in breast cancer treatment (letrozole, fulvestrant, tamoxifen).

The potential biological consequences of the observed IC_{50} for binding to CDK9 (1.52 µM) was discussed. The Applicant clarified that the IC_{50} concentration *in vivo* is likely to be at least 10-fold higher than the IC_{50} *in vitro*, due to the considerably higher ATP concentration *in vivo*. In addition, the selectivity between CDK4 and CDK9 is estimated to be about 190-fold. Ribociclib was inactive (IC_{50} >10 µM) against 34 kinases and weakly active against Aurora A, HER1, and LCK with IC_{50} values of 2.0 µM, 9.0 µM, and 7.7 µM, respectively.

There is some concern over the findings in the Jeko-1 cell model in SCID mice, where ribociclib given as monotherapy at 150 mg/kg/day orally for 21 days caused complete tumour regression during the treatment period, correlating with 90% inhibition of pRb phosphorylation. However, after cessation of treatment, tumours re-grew rapidly. Despite an increase of the dose to 300 mg/kg/day during a 2-week extension phase, anti-tumour activity was suboptimal and at the end of dosing the tumour volume was increasing. It is known that inhibition of CDK4/6 may lead to the development of resistance, for instance via CDK2-mediated S-phase entry. The Applicant was therefore asked to discuss the potential mechanism(s) behind the observed re-growth of tumours in the Jeko-1 cell xenograft model, as well as the clinical relevance of this finding. The Applicant acknowledged that acquired resistance to treatment may occur with CDK4/6 inhibitors. The exact mechanism behind the rapid tumour re-growth in the Jeko-1 xenograft model could however not be

determined, due to lack of molecular analysis of tumours at the time of the study. This important aspect of ribociclib treatment was further discussed in the clinical section (see the Clinical assessment report).

Due to ribociclib's mechanism of action, the myelosupressive effect observed in secondary pharmacology study is not unexpected (CDKs are key players in driving cell cycle progression). Similar findings were observed in repeat dose toxicity studies (see Toxicology).

With regards to off target activity, binding to the apelin receptor is unlikely to be clinically relevant (only 53% inhibition at 10 µM). With regard to orexin-2, an IC_{50} value was extrapolated based on 70% inhibition at 10 µM. This value, 4 µM, is approximately 4-fold above the clinical free C_{max} at the therapeutic dose of ribociclib. Furthermore, brain penetration of ribociclib was low in rats. Regarding PDE4d, the Applicant acknowledged that nausea, vomiting and diarrhoea observed in the Phase III clinical trial with ribociclib could possibly be due to PDE4d binding, although direct effects of ribociclib on the intestinal mucosa are probably also involved. It is agreed that potential off-target binding to orexin-2 and PDE4d is not likely to be of major safety concern for humans. Off target binding of LEQ803 is also unlikely to be clinically relevant.

The *in vivo* cardiac safety pharmacology studies with ribociclib in dogs demonstrated dose and concentration related QTc interval prolongation at an exposure that would be expected to be achieved in patients following the recommended dose of 600 mg. There is also potential to induce incidences of premature ventricular contractions (PVCs) at elevated exposures (approximately 5 fold the anticipated clinical Cmax). QTc interval prolongation has been observed in patients and is included as an important identified risk in the RMP. The proposed SmPC contains information and warnings concerning this risk in sections 4.2, 4.4 and 4.8. From a non-clinical perspective, no further action is considered necessary.

In a rat safety pharmacology study, a single oral dose of ribociclib at 200 mg/kg produced slightly decreased rectal temperature as well as reduced activity and rearing. Overall, it is agreed that the reduced body temperature is not of major safety concern for humans.

Pharmacokinetics

In the distribution study in pigmented rats, melanin-containing structures like the eye (choroid, ciliary body), meninges and hair follicles had high exposure to radiolabeled material and a slow elimination (> 840 h in the eye). Given the lack of ocular adverse effects in the non-clinical toxicology studies or in the clinic, the binding of ribociclib to melanin does not appear to be associated with any obvious risk for ocular toxicity in patients. It is considered that brain penetration of ribociclib appears to be low in the rat.

Ribociclib and its metabolites passed readily into the milk of lactating rats (see SmPC section 5.3).

Formation of reactive intermediates in human, dog and rat hepatocytes was observed. It is noted in study report R0800264 (experiment with human microsomes and hepatocytes) that the observed levels of covalent drug-protein adduct formation in vitro could possibly be clinically relevant when given in a chronic regimen at doses > 50 mg. It is possible that the covalent protein adduct formation in the liver may be linked to liver toxicity in humans. Liver toxicity is adequately addressed in the SmPC (see section 4.8).

Toxicology

The toxicological profile of ribociclib has been evaluated in agreement with recommendations in ICH S9. The rat and dog were the selected as main rodent and non-rodent species, respectively, based on their suitable pharmacokinetic profiles and representation of the major metabolism pathways in humans. Based on demonstration of target-related findings, both species are considered as pharmacologically relevant.

The repeat-dose toxicity (treatment schedule of 3 weeks on/1 week off) of ribociclib after oral administration was investigated in studies up to 27 weeks in rats and 39 weeks in dogs. In repeat-dose studies in rats, the AUC multiples at the highest dose levels compared to the clinical AUC were ~2-fold in male rats, while in female rats and in dogs, the AUC exposure was less than equal to the clinical exposure at steady-state at the highest recommended therapeutic dose of 600 mg/day.

The hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) was revealed as the primary target organ of toxicity of ribociclib. Target organs associated with the pharmacological action of ribociclib in repeat dose studies include bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation), kidney (concurrent degeneration and regeneration of tubular epithelial cells) and testes (atrophy). Besides the atrophic changes seen in the testes, which showed a trend towards reversibility, all other changes were fully reversible after a 4 week treatment-free period (see SmPC section 5.3). Hepatobiliary toxicity has also been observed in patients and is included as an important identified risk in the RMP. The proposed SmPC contains information and warnings concerning this risk in sections 4.2, 4.4 and 4.8.

Potential additive or synergistic effects of ribociclib and two of its metabolites, LEQ803 or CCI284, with co-exposure with letrozole was examined in *in vitro* studies in human hepatocytes. The studies indicate no increased sensitivity of human hepatocytes to combined exposure of ribociclib or its metabolites and letrozole.

The toxicity in the bone marrow and lymphoid system is suggestive of a direct effect of ribociclib on hematopoiesis and lymphopoiesis and likely related to the pharmacological action of ribociclib. Hematological toxicity has been observed in patients and neutropenia is included as an important identified risk in the RMP. The proposed SmPC contains information and warnings concerning this risk in sections 4.2, 4.4 and 4.8.

Effects in the kidney were observed in the 15- and 27-week rat toxicity studies, but not in dogs. A closely related CDK inhibitor (palbociclib) was shown to transiently arrest renal tubular cells in G0/G1, thereby reducing DNA damage and apoptosis following acute kidney injury in rats. Renal effects were also identified in patients and further discussed in Clinical Safety section.

The effect noted in intestinal mucosa, skin, bone/ribs and potentially ovary in dogs are all considered likely related to the pharmacological anti-proliferative effects of ribociclib. No effect on bone or epidermis (atrophy) in humans has been observed. In clinical trials, rash (unrelated to epidermal atrophy) has been reported and was seen with a greater imbalance in ribociclib vs placebo treated patients, but was mild in nature and reversible.

In rats and dogs, adverse effects in the testis were observed. A complete reversibility was not demonstrated. Based on the testis toxicity, male fertility may be compromised by treatment with ribociclib. As Kisqali is indicated for treatment of postmenopausal women, further risk minimisation measures are not suggested. In the case of future indications including men, further risk minimization measures should be considered for the male patient population.

In dog studies providing up to 4 weeks of treatment, a QT interval prolongation was also reported. QTc interval prolongation has been observed in patients and is included as an important identified risk in the RMP. The proposed SmPC contains information and warnings concerning this risk in sections 4.2, 4.4 and 4.8.

Ribociclib was tested in a complete package of genotoxicity studies in agreement with ICH S2(R1) guidance. Genotoxicity studies in bacterial in vitro systems and in mammalian in vitro and in vivo systems with and

without metabolic activation did not reveal any evidence for a genotoxic potential of ribociclib (see SmPC section 5.3).

No carcinogenicity studies were performed which in view of the applied indication is acceptable given the intended treatment of patients with advanced cancer. However, if ribociclib is to be used in other indications with a longer life expectancy, studies to address carcinogenicity could be warranted.

Fertility and early embryonic development studies were not conducted with ribociclib in agreement with ICH S9. However, chronic toxicity studies in rats and dogs revealed atrophic changes of the testes after histopathological evaluation. These effects can be linked to a direct anti-proliferative effect on the testicular germ cells resulting in atrophy of the seminiferous tubules.

Ribociclib and its metabolites passed readily into rat milk. The exposure to ribociclib was higher in milk than in plasma.

Ribociclib showed foetotoxicity and teratogenicity at doses which did not show maternal toxicity in the rats or rabbits. In rats, reduced foetal weights accompanied by skeletal changes considered to be transitory and/or related to the lower foetal weights were noted. In rabbits, there were adverse effects on embryo-foetal development as evidenced by increased incidences of foetal abnormalities (malformations and external, visceral and skeletal variants) and foetal growth (lower foetal weights). These findings included reduced/small lung lobes and additional vessel on the aortic arch and diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes and reduced/small accessory lung lobe (30 and 60 mg/kg), extra/rudimentary thirteenth ribs and misshapen hyoid bone and reduced number of phalanges in the pollex. There was no evidence of embryo-foetal mortality (see SmPC section 5.3).

Based on these finding in animals, ribociclib can cause foetal harm when administered to pregnant women (see sections 4.6 and 5.3). Pregnancy status should be verified prior to starting treatment with Kisqali. In the case of future indications including pre-menopausal women, further risk minimization measures may be considered.

Based on the results of the phototoxicity test, ribociclib is considered to have a low phototoxic potential.

One impurity was found above the reporting threshold of 0.05% in all batches produced to date, is considered adequately qualified on a mg/kg basis in the 15-week repeat-dose studies in rats and dogs. The control strategy for the genotoxic or potentially genotoxic impurities are considered as adequate.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data submitted to evaluate the pharmacology, pharmacokinetic and toxicity are considered acceptable.

Ribociclib is not a PBT substance. Considering the submitted data, ribociclib is not expected to pose a significant risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered / compl.	Duration	Diagnosis Incl. criteria	Primary Endpoint
CLEE011 A2301	233 sites, 29 countries	Randomized, double-blind, placebo-controlled	• Ribociclib (or placebo) 600 mg once daily 21/28 days • Letrozole 2.5 mg once daily	Efficacy and safety	• Exp: 334/139 pts • Cont: 334/176 pts	• Ongoing. • Randomized: 24 Jan 2014 - 24 Mar 2015 • Data cut-off for interim: 29 Jan 2016 • Data cut-off for 2nd IA: 2 Jan 2017	• Advanced breast cancer • First line • HR- positive • HER2-negative • Post menopause	PFS
CLEE011 X1101 Phase 1	2 sites, Japan	Open-label dose escalation	• Ribociclib 400 mg 21/28 days • Ribociclib 600 mg 21/28 days	Max. tolerab. dose and dose for expansion	• 400 mg: 4 pts • 600 mg: 13 pts	• 20 June 2013 – 28 Jan 2015 • 17 Dec 2014 decision not to open dose-expansion; no effect in 9 esophageal cancer patients	• Solid tumours • No standard therapy available	MTD
CLEE011 X2101 Phase 1	7 sites, 3 countries	Open-label dose escalation	Ribociclib 21/28 days: 50, 70, 140, 260, 280, 350, 400, 600, 750, 900, 1200 mg Ribociclib 28/28 days: 300, 400, 600 mg	Max. Tolerable dose and dose for expansion	• 21/28 days: ⩽ 400 28 pts, 600 mg 76 pts, ⩾ 750 mg 30 pts • 28/28 days: 300 mg 6 pts 400 mg 6 pts 600 mg 7 pts	21 Dec 2010 - ongoing	• Advanced solid tumours or lymphomas • Intact pRB • No standard therapy available	MTD
CLEE011 X2107 Phase 1b/2	13 sites, 5 countries	Open-label, dose finding	• Ribociclib 600 mg once daily 21/28 days AND • letrozole 2.5 mg once daily	Max. tolerab. dose and rec. phase 2 dose	47 pts in the ribociclib + letrozole arm	22 Oct 2013 - ongoing	• Advanced breast cancer • Any line (escal.) or first (extens.) • HR- positive • HER2-negative Post menopause	MTD and/or RP2D
CLE001X US03 Phase 2	US, 61 centres	Open-label	• Ribociclib 600 mg once daily 21/28	Efficacy and safety	106 pts, 7 triple-negative	25 Aug 2014 - ongoing	• Advanced solid tumours and haematological	Clinical benefit (CB)

			days		breast cancer		malignancies	

2.4.2. Pharmacokinetics

The pharmacokinetics of ribociclib were investigated in patients with advanced cancer following oral daily doses of 50 mg to 1200 mg. Healthy subjects received single oral doses ranging from 400 mg to 600 mg or repeated daily doses (8 days) at 400 mg (see Table 7).

Table 7: Clinical studies with pharmacokinetic evaluation of ribociclib

Study code	Study description	Study population	Ribociclib daily dose
[Study A2101]	Phase I, open label, DDI study /CYP3A inhibitor, CYP3A inducer Single oral ribociclib dose / PK and safety	Healthy subjects (N=24)	400 mg, 600 mg
[Study A2102]	Phase I, open label, ADME / Single oral ribociclib dose / PK and safety	Healthy subjects (N=6)	600 mg
[Study A2103]	Phase I, open-label, bioequivalence and food effect study / FCT Single oral ribociclib dose / PK and safety	Healthy subjects (N=56)	600 mg
[Study A2106]	Phase I, open-label, DDI study / CYP3A4/5, CYP1A2 substrate Multiple oral ribociclib dose / PK and safety	Healthy subjects (N=25)	400 mg
[Study A2109]	Phase I, open-label, hepatic impairment study / Single oral ribociclib dose / PK and safety	Healthy subjects with normal hepatic function and subjects with impaired hepatic function [1] (N=28)	400 mg
[Study A2111]	Phase I, open-label, food effect study / DiC Single oral ribociclib dose / PK and safety	Healthy subjects (N=24)	600 mg

ADME: absorption, distribution, metabolism and excretion; CYP: cytochrome P450; DDI: drug-drug interaction; FCT: film-coated tablet; PK: pharmacokinetics.

[1] Study is ongoing and an interim clinical study report was prepared

Study code	Study description	Study population	Ribociclib daily dose (IS[d])
[Study X1101]	Phase I, open label / Oral ribociclib dose-escalation study, monotherapy / MTD, PK, PK/PD, efficacy and safety	Asian patients with advanced solid tumors (N=17)	400[b], 600 mg
[Study X2101]	Phase I, open label / Oral ribociclib dose-escalation study, monotherapy / MTD, PK, PK/PD, efficacy and safety	Adult patients with advanced solid tumors or lymphomas (N=134)	50[b], 70, 140, 260, 280, 300[e], 350, 400[e], 600[c,e], 750, 900, 1200 mg
[Study X2107]	Phase Ib/II, open label / Oral ribociclib dose-escalation study, combination with letrozole / MTD, PK, efficacy and safety	Adult patients with advanced ER+ breast cancer (N=47)	600 mg[a]
[Study A2301] (sparse data)	Phase III, randomized double-blind, placebo-controlled, combination with letrozole / Oral ribociclib flat-fixed dose / PK, efficacy and safety	Postmenopausal women with hormone receptor-positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease (N=334)	600 mg

ER+: estrogen receptors positive; HER2: human epidermal growth factor receptor 2; IS: intermittent schedule; MTD: maximum tolerated dose; PD: pharmacodynamics; PK: pharmacokinetics.

[a] Only data from treatment Arm 1 is included in this document (i.e., 600 mg ribociclib + letrozole)

[b] Starting dose

[c] Oral solution formulation also tested

[d] Once daily 3 weeks on/1 week off

[e] Continuous daily dosing of ribociclib at 300, 400 and 600 mg was also evaluated

In all studies in patients, except study X2107, ribociclib pharmacokinetics were determined during cycle one only. Preliminary PK data from a Phase 1b study of ribociclib in combination with everolimus and exemestane in breast cancer patients (Study X2106). There are no single-dose studies in patients.

Furthermore, *in vitro* studies included investigation of ribociclib as a substrate for CYP450 enzymes, UGTs, FMO and clinically important transporters. The potential of ribociclib and the metabolites LEQ803 and CCI284 to inhibit or induce CYP450 and to inhibit important transporters were also investigated *in vitro*.

Absorption

Ribociclib succinate is classified as a biopharmaceutics classification system (BCS) class IV compound. Ribociclib succinate exhibited high solubility in aqueous buffer at or below pH 4.5 and in bio-relevant media at pH 5.0 and pH 6.5, and lower solubility in aqueous buffer at pH 6.8 and pH 7.5.

In vitro, the apparent passive permeability of ribociclib was determined to be moderate in Caco-2 cell monolayers and high in human hepatocytes.

The absolute bioavailability of ribociclib in humans is not known. Based on an in vivo interaction study with a strong CYP3A4 inhibitor, there is some degree of first-pass metabolism.

The time to reach Cmax (Tmax) following ribociclib oral administration was between 1 and 4 hours. Ribociclib exhibited slightly over-proportional increases in exposure (Cmax and AUC) across the dose range tested (50 to 1200 mg). Following repeated once daily dosing, steady state was generally achieved after 8 days and ribociclib accumulated with a geometric mean accumulation ratio of 2.51 (range: 0.97 to 6.40).

Compared to the fasted state, oral administration of a single 600 mg dose of ribociclib film-coated tablets (commercial tablet) with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib. When ribociclib was administered as the clinical trial capsule formulation, the geometric mean Cmax was lower (23% and 32% for ribociclib and LEQ803, respectively) in the fed state versus the fasted state and median Tmax was delayed, while food had no effect on AUC.

Bioequivalence

Ribociclib was initially developed as hard-gelatin capsule formulation. In most of the clinical studies including the registration trial (Study A2301), the capsule formulation at a strength of 200 mg was used. In parallel, a smaller tablet was developed for commercial use. In Study A2103, bioequivalence was shown between the capsule and the commercial tablet, with 90% confidence intervals within 0.80-1.25 for the geometric mean ratio of Cmax and AUC of the tablet vs. the capsule.

Distribution

Based on population pharmacokinetic analysis, the apparent volume of distribution for ribociclib at steady state (Vss/F) was 1090 L.

Ribociclib is a substrate for Pgp in vitro, but based on mass-balance data inhibition of Pgp or BCRP is unlikely to affect ribociclib exposure at therapeutic doses. Ribociclib was not a substrate for hepatic uptake transporters OATP1B1, OATP1B3 or OCT-1 *in vitro* (see SmPC section 5.2).

In vitro, human plasma protein binding of ribociclib was moderate, about 70%, with no apparent concentration dependency (10 to 10000 ng/ml). The protein binding of the metabolites LEQ803 and CCI284 was somewhat higher, 88% and 92%, respectively.

Ribociclib was equally distributed between red blood cells and plasma with a mean in vivo blood-to-plasma ratio of 1.04.

Elimination

Estimated mean half-life of ribociclib was 30-55 hr in studies in healthy volunteers. The highest value was observed in the mass-balance study, which had the longest sampling period (504 hr). The geometric mean apparent plasma terminal half-life (T1/2) of ribociclib ranged from 29.7 to 54.7 hours and the geometric mean CL/F of ribociclib ranged from 39.9 to 77.5 l/hr at 600 mg across studies.

The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63% CV) and the geometric mean apparent oral clearance (CL/F) was 25.5 l/hr (66% CV) at steady-state at 600 mg in patients with advanced cancer.

In vitro and *in vivo* studies indicated ribociclib is eliminated primarily via hepatic metabolism. Ribociclib and its metabolites are eliminated mainly via faeces, with a small contribution of the renal route.

The metabolism of ribociclib appears to be mediated primarily by CYP3A4 (including formation of the major metabolite LEQ803) and to minor extent by FMO3 and (extra-hepatic) FMO1 (including formation of the major metabolite CCI284), but based on *in vitro* data there are also other enzymes involved, such as CYP1A2, CYP2J2 and phase II enzymes UGT2B7 and UGT1A1.

Following oral administration of a single 600 mg dose of [14C] ribociclib to humans, the primary metabolic pathways for ribociclib involved oxidation (dealkylation, C and/or N oxygenation, oxidation (-2H)) and combinations thereof. Phase II conjugates of ribociclib phase 1 metabolites involved N-acetylation, sulfation, cysteine conjugation, glycosylation and glucuronidation.

Reactive metabolites are formed through CYP3A and FMO catalysed metabolism, with indications of covalent adduct formation in hepatocytes. Metabolite data from the human mass-balance study indicate that the reactive intermediates are rapidly converted via a detoxifying pathway into glutathione adducts. These are likely excreted via bile into faeces, where they are degraded to cysteine metabolites.

Mass-balance

A mass-balance study was performed in six healthy male subjects, who received a 600 mg single oral dose of [^{14}C]-ribociclib as 200 mg capsules. Subjects were fasted.

Based on the recovery in urine and of radiolabelled metabolites in faeces, absorption of ribociclib was estimated to be at least around 60%. Absolute bioavailability may be lower due to first-pass metabolism.

Of the total administered radioactive dose, 91.7% was recovered within 22 days; faeces was the major route of excretion (69.1%), with 22.6% of the dose recovered in urine. Ribociclib was extensively metabolised with unchanged drug accounting for 17.3% and 12.1% of the dose in faeces and urine, respectively. Metabolite LEQ803 was a significant metabolite in excreta and represented approximately 13.9% and 3.74% of the administered dose in faeces and urine, respectively. Numerous other metabolites were detected in both faeces and urine in minor amounts (≤ 2.78% of the administered dose). CCI284 was not detected in excreta.

Direct Phase II conjugates of the parent compound observed were sulfate conjugates and cysteine conjugates but these were minor, each representing ≤2.2% of the dose.

Metabolites in plasma

In the mass-balance study, parent ribociclib was the major circulating drug-derived entity in plasma accounting for 23% of the total radioactivity in plasma over 508 hour. The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide). By metabolite profiling over 48 hr post-dose, these metabolites each represented an estimated 9.39%, 8.60%, and 7.78% of total radioactivity, and 21.6%, 19.8%, and 17.9% of ribociclib exposure. Other metabolite peaks were only minor. In other single-dose studies in healthy volunteers, LEQ803 accounted for about 23-31% of the AUC of parent ribociclib.

At steady state in cancer patients at the 600 mg dose level, LEQ803 generally accounted for <10% of the parent AUC. CCI284 accounted for 27% of the parent AUC at steady state. Metabolite M1 was not analysed in steady state studies.

Metabolites LEQ803 and CCI284 are Phase I metabolites and were evaluated for inhibition of major CYPs (see Interactions below). M1 is a Phase II metabolite and was not evaluated for CYP inhibition potential.

Dose proportionality and time dependencies

Ribociclib displays dose- and time-dependent pharmacokinetics due to time-dependent auto-inhibition of CYP3A4-mediated metabolism.

A power model was used to assess dose proportionality across the dose range of 50 mg to 1200 mg. After a single dose, the slope of ln (Cmax) or ln (AUC) versus ln (dose) was estimated to be 1.19 and 1.26, respectively, indicating a lack of dose proportionality. At steady state the slope was 1.37 and 1.42 for Cmax and AUC, respectively, indicating a greater non-linearity after multiple dosing.

Based on a population pharmacokinetic model, ribociclib clearance would be 19% lower at 1200 mg and 24% higher at 300 mg than at the reference dose (600 mg). At lower doses, the effect was more pronounced; CL would be 116% higher at 50 mg than at 600 mg.

Evaluation of trough concentrations of ribociclib and LEQ803 showed that the steady state of ribociclib was generally reached in approximately 7 days. The calculated geometric mean accumulation ratio (Racc) based on AUC_{0-24h} ranged from 1.35 to 2.75 across the 50 to 1200 mg dose groups. Data on metabolic ratio indicated that CYP3A4-mediated formation of LEQ803 is smaller at steady state than after a single dose.

Being a CYP3A4 substrate, and subject to some degree of first-pass metabolism, ribociclib displays relatively large pharmacokinetic variability. Based on the population pharmacokinetic analysis, the inter-patient variability in CL/F is 51%. Intra-patient (inter-occasion) variability was not assessed.

The exposure of ribociclib in healthy subjects in single dose studies was slightly lower compared to patients with cancer, but within the range of values observed in studies with patients with cancer. Following a single 600 mg dose, the geometric mean Cmax and AUC_{0-24h} in healthy subjects (different studies) ranged from 507 to 792 ng/mL and 5910 to 9350 h•ng/mL, respectively. In comparison, the geometric mean Cmax and AUC0-24h in patients with cancer was 992 ng/mL and 9700 h•ng/mL, respectively.

At steady state, with the 400 mg dose, exposure to ribociclib was relatively similar in patients with advanced cancer and in healthy volunteers, with steady state AUC values of 12800 and 11100 ng*hr/ml, respectively.

Special populations

Renal impairment

No dedicated pharmacokinetic study in subjects with renal impairment was submitted.

Based on a population pharmacokinetic analysis that included 77 patients with normal renal function (eGFR≥ 90 ml/min/1.73 m^2), 76 patients with mild renal impairment (eGFR 60 to <90 ml/min/1.73 m^2) and 35 patients with moderate renal impairment (eGFR 30 to <60 ml/min/1.73 m2), mild and moderate renal impairment had no effect on the exposure of ribociclib. The effect of eGFR on CL/F was estimated to be 0.987 (95% CI: 0.845, 1.135). The pharmacokinetics of ribociclib in patients with severe renal impairment have not been studied.

Hepatic impairment

Based on a pharmacokinetic study in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.50 for C_{max}; 1.32 for AUC_{inf}) and severe (GMR: 1.34 for C_{max}; 1.29 for AUC_{inf}) hepatic impairment. Based on a population pharmacokinetic analysis that included 160 breast cancer patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib, further supporting the findings from the dedicated hepatic impairment study (see section 4.2).

Gender, weight and age

The population pharmacokinetic analysis indicated no relevant effects of gender or age on the pharmacokinetics of ribociclib.

Body weight had a statistically significant effect on CL, volume of distribution of the peripheral compartment (V2), and inter-compartmental clearance (Q). Simulations suggested that a change of body weight from the reference value of 70 kg to 50 kg or 100 kg would cause up to a 22% change in steady-state pharmacokinetic parameters. Based on a cross-study comparison, the exposure of ribociclib in Japanese patients in Study X1101 was higher on average, but the individual values were within the range observed in Caucasian patients in Study X2101. Following multiple doses of ribociclib 600 mg, the geometric mean AUC0-24h for ribociclib was 51600 hr•ng/mL in Japanese patients and 23800 hr•ng/mL in Stud X2101.

No pharmacokinetic data in children were submitted. The population pharmacokinetic analysis included patients ranging in the age from 23 to 82 years old. Age had no statistically significant effect on the pharmacokinetics of ribociclib. The simulated effect of age on CL/F was 1.018 (95%CI: 0.875, 1.324).

Pharmacokinetic interaction studies

Ribociclib as a victim for drug-drug interactions

Co-administration of the strong CYP3A4 inhibitor ritonavir (100 mg twice daily for 14 days) with a single 400 mg dose of ribociclib increased ribociclib exposure (AUC_{inf}) and the peak concentration (C_{max}) in healthy subjects 3.2 and 1.7-fold, respectively, relative to a single 400 mg ribociclib dose given alone. C_{max} and AUC_{last} for LEQ803 (a prominent metabolite of ribociclib accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively.

Physiologically based pharmacokinetic (PBPK) simulations were performed to model the effect of a strong CYP3A4 inhibitor at steady state of ribociclib, and the effect of moderate CYP3A4 inhibitors. The key parameter in these simulations was fm_{CYP3A4} at multiple dose conditions. This parameter is dependent on fm

at single-dose conditions as well as the time dependent inhibition potency (K_I) and inactivation rate (k_{inact}). The parameters are correlated.

The PBPK simulations suggested that at steady state, a dose reduction to 400 mg ribociclib with a strong CYP3A4 inhibitor will lead to a ribociclib exposure range that overlaps the exposure range at the 600 mg dose without a inhibitor.

The PBPK simulations suggested that at a 600 mg dose of ribociclib, a moderate CYP3A4 inhibitor (erythromycin) may increase ribociclib steady state Cmax and AUC 1.2 fold and 1.3 fold, respectively. For patients who had their ribociclib dose reduced to 400 mg once daily, the increase in steady-state Cmax and AUC was estimated to be 1.4 and 2.1-fold, respectively. The effect at the 200 mg qd dose was predicted to be a 1.7- and 2.8-fold increase, respectively.

Co-administration of the strong CYP3A4 inducer rifampicin (600 mg daily for 14 days) with a single 600 mg dose of ribociclib decreased the ribociclib AUCinf and Cmax by 89% and 81%, respectively, relative to a single 600 mg ribociclib dose given alone in healthy subjects. LEQ803 Cmax increased 1.7-fold and AUCinf decreased by 27%, respectively.

Non-compartmental analysis of PK data from the pivotal efficacy/safety study indicated no effect of concomitant treatment with proton-pump inhibitors (PPIs) on ribociclib exposure. Also population pharmacokinetic analysis indicated no effect of PPIs on ribociclib bioavailability.

Ribociclib as a perpetrator of drug-drug interactions

In vitro

In vitro, ribociclib was a reversible inhibitor of CYP1A2, CYP2E1 and CYP3A4/5 and a time-dependent inhibitor of CYP3A4/5, at clinically relevant concentrations. *In vitro* evaluations indicated that Kisqali has no potential to inhibit the activities of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 at clinically relevant concentrations. It has no potential for time-dependent inhibition of CYP1A2, CYP2C9, and CYP2D6.

In vitro evaluations indicated that Kisqali has a potential to inhibit the activities of drug transporters PgP, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1 and BSEP. Ribociclib did not inhibit OAT1, OAT3 or MRP2 at clinically relevant concentrations *in vitro*.

The *in vitro* hepatocyte induction data were inconclusive as sufficiently high ribociclib concentrations could not be studied due to effects on cell viability. Induction of CYP1A2 could be excluded based on *in vivo* data. In a cell-free induction study, no agonist activity of ribociclib on the PXR at concentrations up to 100 µM (i.e. covering the 50*Cmax, u cutoff of 74 µM) were observed. CAR data were considered inconclusive.

Table 8. *In vitro* enzyme inhibition by ribociclib

Competitive inhibition		TDI	Basic model: In vivo relevant?	In vivo data
Enzyme	Ki¤/IC50 (µM)	KI (µM) and Kinact (min-1)		
CYP1A2	12¤	Yes	Yes	Weak inhibition
CYP2B6	>>50	No	No*)	
CYP2C8	>100	No	No	
CYP2C9	>100	No	No	
CYP2C19	>100	No	No	
CYP2D6	>>50	No	No*)	
CYP2E1	49¤	No	Yes	Not studied**)
CYP3A4	35¤	Yes KI = 5.06 µM, kinact = 0.0245 min-1 ¤	Intestine and liver: Competitive Yes TDI Yes	Moderate to strong inhibition

¤ *fu mic compensated*

**) although highest tested concentration did not cover the 50*Cmax,u of 74 µM, virtually no inhibition was observed at 50 µM and it is considered unlikely that IC50 can be < 74 µM*

***) few known clinically relevant interactions*

Table 9 *In vitro* transporter inhibition by ribociclib and metabolites

	Ribociclib			**LEQ803**			**CII284**			**Σ**
Transporter	Ki* (µM)	IC50 (µM)	In vivo relevance	Ki* (µM)	IC50 (µM)	In vivo rel.	Ki* (µM)	IC50 (µM)	In vivo rel.	Outcome
P-gp	Ca 72	143	Yes intestine Borderline systemic		37	No		<50	-	Yes intestine Borderline systemic
BCRP	Ca 12	24	Yes intestine Yes systemic		<50	-		<50	-	Yes, Intestine and systemic
OATP1B1		43	Yes	24		No	4		Yes	Yes
OATP1B3		>300	?	46		No	22		No	?
OAT1		>400	No	>50		-	>50		-	No
OAT3		>400	No	38		No	>50		-	No
OCT2		1.9	Yes	2.2		No	1.0		Yes	Yes
MRP2		>300	-	>50		-		>50	-	No
OCT1		17	Yes	6.4		No	3.5		Yes	Yes
MATE1		1.7	Yes		0.3	Yes		0.6	Yes	Yes
MATE2K		31	Yes	Ca 1.05	2.1	Yes		6.2	No	Yes
BSEP		4.7	Yes		>47	-		3.9	Yes	Yes

*When "Ca" is used, this means that Ki was roughly estimated by the assessor as $IC_{50}/2$. This appears not completely accurate for transporters but the basic conditions for this estimation were fulfilled.

In vivo

In a clinical study with midazolam, a sensitive CYP3A4 substrate, 8 days of dosing at the 400 mg ribociclib dose to healthy volunteers led to a 3.8-fold increase (280%) in AUC of midazolam, indicating that the net effect (inhibition + possible induction) of ribociclib at steady state on CYP3A4 is inhibition, and that ribociclib at the 400 mg dose is a moderate CYP3A4 inhibitor. Results of a PBPK simulation suggested that ribociclib is a strong CYP3A4 inhibitor at the therapeutic dose of 600 mg (an estimated 5.2-fold increase in midazolam AUC).

A study of the effect of 8 daily doses of 400 mg ribociclib on caffeine, a CYP1A2 substrate showed that ribociclib increased the caffeine exposure by 20% (1.20-fold) in healthy subjects, compared with administration of caffeine alone. At the clinically relevant dose of 600 mg, simulations using PBPK models predicted only weak inhibitory effects of ribociclib on CYP1A2 substrates (<2-fold increase in AUC).

The potential effect of ribociclib on letrozole pharmacokinetics was evaluated by comparing letrozole PK data (2 hr and trough values only) between treatment arms in the phase III study A2301. Letrozole C 2hr and Ctrough values on Day 15 were similar between treatment arms. In addition, a cross study comparison of letrozole PK data from study X2107 (dose escalation in combination with letrozole) and historical data was performed. Letrozole exposure on Day 21 following multiple dose administration of ribociclib (600 mg) and letrozole (2.5 mg) was consistent with or numerically lower than data reported in historical studies with letrozole.

The potential interaction between ribociclib and exemestane was evaluated by comparison of data from a phase 1 dose-finding study with ribociclib+exemestane with historical PK data for monotherapy ribociclib and exemestane, respectively. No interaction was observed.

No pharmacokinetic data of ribociclib and anastrozole in combination were submitted.

2.4.3. Pharmacodynamics

Mechanism of action

No studies submitted.

Primary and Secondary pharmacology

Relationship between plasma concentration and effect

In the CLEE011A2301/MONALEESA-2, an analysis of PFS in subgroups defined by above or below median in cycle 1 day 15 Ctrough was provided, with fewer events in the higher exposure group (see also dose finding studies). Dose-exposure-PD relationships were investigated primarily in CLEE011X2101, utilizing skin and tumour biopsies assessed for IHC expression of RB and KI67. In doses above 600 mg, a larger decrease from baseline in the proportion of cells expressing KI67 was observed.

Relationship between ribociclib exposure and neutrophil response

An indirect, concentration dependent effect of ribociclib on absolute neutrophil count (ANC) was modeled. A low baseline neutrophil count was associated with a higher risk of neutropenia although the sensitivity to

drug exposure (slope) was independent of the baseline ANC level. Simulations showed that a lower ribociclib dose on average would lead to less ANC reduction.

Relationship between ribociclib exposure and QT prolongation

The risk of QT-prolongation associated with ribociclib was identified in non-clinical studies (see non-clinical section). A thorough QT/QTc study was not submitted. The relationship between ribociclib exposure and changes from baseline in QT corrected for heart rate using pooled data from studies in patients with cancer was evaluated. The pooled analysis in patients included a total of 267 patients with cancer treated with ribociclib at doses ranging from 50 to 1200 mg including 193 subjects treated with ribociclib 600 mg. The pooled analysis in healthy subjects included a total of 187 healthy subjects treated with ribociclib at doses of 400 or 600 mg.

Ribociclib was associated with concentration-dependent QT interval prolongation effect with a largest ΔQTcF reached at steady state (during cycle 1). The estimated mean ΔQTcF was 22.87 ms (90% CI: 21.6, 24.1) in patients at the mean Cmax at steady-state (2237 ng/mL) following a therapeutic dose of 600 mg daily for 3 weeks on/ one week off therapy (i.e. the proposed regimen). A similar relationship was observed in healthy subjects (an estimated mean ΔQTcF of 13.59 ms [90% CI: 12.8, 14.4 ms] for subjects at the mean Cmax following a single dose of 600 mg (652 ng/mL).These results were consistent with data from the pivotal A2301 study where the largest mean ΔQTcF in the ribociclib-containing arm was observed at Cmax at steady-state during Cycle 1 (19.6 ms; 95% CI 17.6, 21.5).

With respect to supratherapeutic exposure, for example an approximate 50% increase in exposure from 2237 ng/mL (the mean Cmax for 600 mg) to 3460 ng/mL would result in an estimated mean ΔQTcF of 28.13 ms (90% CI: 26.7, 29.5).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Given the data from the food effect studies indicating no relevant food effect on either the clinical study formulation or on the commercial formulation, Ribociclib should be taken orally once daily with or without food (see SmPC section 4.2). This was the recommendation also in the pivotal efficacy study. The tablets should be swallowed whole and should not be chewed, crushed or split prior to swallowing. No tablet should be ingested if it is broken, cracked or otherwise not intact. Patients should also be encouraged to take their dose at approximately the same time each day, preferably in the morning. If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

Ribociclib succinate exhibits high solubility in aqueous buffer at or below pH 4.5 and in bio-relevant media (at pH 5.0 and 6.5) but lower solubility in aqueous buffer at pH 6.8 and pH 7.5. The effect of agents that alter gastric pH was not evaluated in a dedicated drug interaction study. However, non-compartmental analysis of PK data from the pivotal efficacy/safety study indicated no effect of concomitant treatment with proton-pump inhibitors (PPIs) on ribociclib exposure. Also population pharmacokinetic analysis indicated no effect of PPIs on ribociclib bioavailability.

The major part of the dose was recovered in faeces as parent and metabolites. It is not known whether the 17% of the dose found in faeces as unchanged ribociclib is unabsorbed drug or excreted via biliary or gastrointestinal secretion (likely via Pgp or BCRP). Thus, biliary excretion may contribute to up to 17% of the elimination. The effect of inhibitors of biliary excretion on ribociclib exposure is expected to be minor. Twelve

percent of the dose was recovered as unchanged ribociclib in urine. If absolute bioavailability is <50%, as suggested by the Applicant, renal excretion could contribute to 25% or more of the elimination.

Ribociclib exhibited slightly over-proportional increases in exposure (C_{max} and AUC) across the dose range of 50 mg to 1200 mg following both single dose and repeated doses. This analysis is limited by the small sample sizes for most of the dose cohorts with a majority of the data coming from the 600 mg dose cohort.

The excretion data together with the results of *in vitro* metabolism studies, data in mild-moderate renal impairment and the interaction study with ritonavir indicate that ribociclib is eliminated primarily via metabolism. The most important enzyme appears to be CYP3A4.

With regards to special populations, no dedicated pharmacokinetic study in renal impairment was provided. If bioavailability is 0.5, with 12% of a single dose excreted unchanged in the urine, renal elimination may account for 25% of the elimination. Complete blocking of a pathway accounting for 25% of clearance would lead to about 30% increase in AUC. The effect of mild-moderate renal impairment would be expected to be limited, which was also confirmed by the population pharmacokinetic analysis. Severe renal impairment may, in addition to blocking the renal elimination pathway, affect also the hepatic elimination of ribociclib. However, the effect is not expected to be greater than it can be handled by the general monitoring for side effects recommended in the SmPC. Awaiting data from the ongoing pharmacokinetic study in severe renal impairment (see RMP measures), the warning proposed for the SmPC is considered sufficient. Caution should be used in patients with severe renal impairment with close monitoring of signs of toxicity as there is no experience with Kisqali in this population (see sections 4.2 and 5.2). No dose adjustment is necessary in patients with mild or moderate renal impairment (see section 5.2). A pharmacokinetic study in hepatic impairment indicated no relevant effect of mild hepatic impairment on ribociclib exposure. The average increase in moderate and severe hepatic impairment was small (30%) and the ranges of individual AUC values in the hepatic impairment groups were largely overlapping the individual values in the normal hepatic function group. Given also the observed hepatotoxicity of ribociclib, it is agreed to take a cautious approach in this patient group. The SmPC states that, no dose adjustment is necessary in patients with mild hepatic impairment (Child Pugh class A). Patients with moderate (Child Pugh class B) and severe hepatic impairment (Child Pugh class C) can have increased (less than 2-fold) exposure to ribociclib and the starting dose of 400 mg Kisqali once daily is recommended. Ribociclib has not been studied in breast cancer patients with moderate and severe hepatic impairment (see sections 4.2 and 5.2).

A population pharmacokinetic analysis showed that there are no clinically relevant effects of age, body weight or gender on the systemic exposure of ribociclib that would require a dose adjustment. Data on differences in pharmacokinetics due to race are too limited to draw conclusions. No dose adjustment is required in patients over 65 years of age (see SmPC sections 4.2 and 5.2).

The comparison between Caucasian and Japanese patients is limited due the small sample size. Based on tolerability, the recommended dose in Japanese patients was defined as 600 mg once daily on a 21-days on/7-days off schedule, i.e. the same as in Caucasian patients.

As ribociclib is primarily metabolised by CYP3A, medicinal products that can influence CYP3A4 enzyme activity may alter the pharmacokinetics of ribociclib. The strong CYP3A4 inhibitor ritonavir increased the exposure to ribociclib by 3.2-fold, after administration of a single 400 mg dose of ribociclib. Ribociclib at the 600 mg dose is a strong time-dependent CYP3A4 inhibitor with auto-inhibition leading to time-dependent pharmacokinetics. The contribution of CYP3A4 to the overall elimination is likely smaller at steady state than after a single dose due to time-dependent auto-inhibition of the CYP3A4-mediated metabolism of ribociclib. Thus, in the ritonavir study the effect of ritonavir on ribociclib at steady state might have been

overestimated. The effect of a strong CYP3A4 inhibitor on ribociclib at steady state was therefore simulated using Physiologically-based pharmacokinetic modelling (PBPK).

Although there are some remaining uncertainties with the PBPK simulations, the models for prediction of the effect of CYP3A4 inhibitors are considered sufficiently well justified for guiding recommendations in the SmPC.

Given the effects on QTc interval, the concomitant use of strong CYP3A4 inhibitors including, but not limited to the following must be avoided: clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, verapamil and voriconazole (see section 4.4). Alternative concomitant medicinal products with less potential to inhibit CYP3A4 should be considered and patients should be monitored for ADRs (see sections 4.2, 4.4 and 5.2).

Based on these PBPK simulations, if patients must be given a strong CYP3A4 inhibitor concomitantly with ribociclib, the Kisqali dose should be reduced to 400 mg once daily (see SmPC sections 4.2 and 4.5). In patients who have had their dose reduced to 400 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, the dose should be further reduced to 200 mg. In patients who have had their dose reduced to 200 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, Kisqali treatment should be interrupted.

Of particular importance is the fact that C_{max}, which would be expected to be the most important pharmacokinetic parameter for potential QT prolongation, is not predicted to be increased at the 400 mg dose with inhibitor as compared with the 600 mg dose without inhibitor.

Due to inter patient variability, the recommended dose adjustments may not be optimal in all patients, therefore close monitoring for ribociclib related AEs is recommended. In the event of ribociclib related toxicity, the dose should be modified or treatment should be interrupted until toxicity is resolved (see sections 4.2 and 5.2). If the strong inhibitor is discontinued, and after at least 5 half lives of the CYP3A4 inhibitor (refer to product information of the inhibitor in question) the Kisqali dose should be resumed at the dose used prior to the initiation of the strong CYP3A4 inhibitor (see sections 4.4, 4.5 and 5.2).

The PBPK-predicted increase in exposure was 1.3-fold when combining ribociclib 600 mg with moderate CYP3A4 inhibitors. For patients who already had their dose reduced to 400 mg or 200 mg, the predicted effect of a moderate CYP3A4 inhibitor was predicted to be larger than at the 600 mg dose, a 2.1-fold and 2.8 fold increase in AUC, respectively, i.e. > the 50% increase. Nevertheless, given some remaining uncertainty in these predictions and the expected variability in the effect of different inhibitors, it is agreed not to add a recommendation of a dose reduction at concomitant treatment with a moderate CYP3A4 inducer. Overall, no dose adjustments of ribociclib are required at initiation of treatment with mild or moderate CYP3A4 inhibitors. However, monitoring of ribociclib related AEs is recommended.

Patients should also be instructed to avoid pomegranates or pomegranate juice and grapefruit or grapefruit juice. These are known to inhibit cytochrome CYP3A4 enzymes and may increase the exposure to ribociclib (see SmPC section 4.5).

The strong PXR inducer rifampicin had a large effect on ribociclib AUC, with the exposure only 11% of that observed after treatment of ribociclib alone. This may be due to induction of several elimination pathways for ribociclib, including CYP3A4, FMO, Pgp and UGTs. The effect at steady state of ribociclib is not known. Such a large decrease cannot be compensated for by dose adjustments. Concomitant treatment with strong CYP3A4 inducers was prohibited in the pivotal efficacy/safety study. The concomitant use of strong CYP3A4 inducers may therefore lead to decreased exposure and consequently a risk for lack of efficacy. The concomitant use of strong CYP3A4 inducers should be avoided, including, but not limited to, phenytoin, rifampicin,

carbamazepine and St John's Wort (Hypericum perforatum). An alternative concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered.

The effect of a moderate CYP3A4 inducer on ribociclib exposure has not been studied. Physiologically based pharmacokinetic simulations suggested that a moderate CYP3A4 inducer (efavirenz) may decrease steady state ribociclib Cmax and AUC by 51% and 70%, respectively. The concomitant use of moderate CYP3A4 inducers may therefore lead to decreased exposure and consequently a risk for impaired efficacy, in particular in patients treated with ribociclib at 400 mg or 200 mg once daily.

Ribociclib was found to inhibit CYP1A2 and CYP3A4, the latter enzyme both competitively and through time-dependent inhibition. After 8 days of dosing with 400 mg ribociclib once daily, midazolam AUC increased about 3.8-fold, suggesting that ribociclib at the 400 mg dose is a moderate CYP3A4 inhibitor. Based on PBPK simulation, midazolam AUC is predicted to increase 5.2-fold at daily dosing with 600 mg ribociclib, suggesting that ribociclib at the 600 mg dose should be categorised as a strong CYP3A4 inhibitor.

The SmPC reflects that Ribociclib is a strong CYP3A4 inhibitor at the 600 mg dose and a moderate CYP3A4 inhibitor at the 400 mg dose. Thus, ribociclib may interact with medicinal products which are metabolised via CYP3A4, which may lead to increased serum concentrations of CYP3A4 substrates (see section 4.5). Caution is recommended in case of concomitant use with sensitive CYP3A4 substrates with a narrow therapeutic index and the SmPC of the other product should be consulted for the recommendations regarding co administration with CYP3A4 inhibitors. (see SmPC section 4.4). The dose of a sensitive CYP3A4 substrate with a narrow therapeutic index, including but not limited to alfentanil, ciclosporin, everolimus, fentanyl, sirolimus and tacrolimus, may need to be reduced as ribociclib can increase their exposure (see SmPC section 4.5). Concomitant administration of ribociclib at the 600 mg dose with the following CYP3A4 substrates should be avoided: alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam.

CYP2E1 was also inhibited by ribociclib but this signal is not further pursued as there are few clinically relevant CYP2E substrates.

There was only a small 20% increase in caffeine AUC when administered with multiple 400 mg doses of ribociclib. Also a PBPK simulation indicated a small effect. Thus, the available *in vivo* data shows that the net effect on CYP1A2 is weak inhibition that is unlikely to be clinically relevant. There are no other important drug-metabolising enzymes regulated via the AhR receptor, and the AhR induction signal is therefore not further pursued.

In vitro evaluations indicated that ribociclib has a potential to inhibit the activities of drug transporters Pgp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1 and BSEP. The *in vivo* relevant net effect may be Pgp and BCRP inhibition both at intestinal level and "systemic" level, OATP1B1 and 1B3 inhibition, OCT1 and 2 inhibition, MATE1 and MATE2K inhibition and BSEP inhibition. Caution and monitoring for toxicity are advised during concomitant treatment with sensitive substrates of these transporters which exhibit a narrow therapeutic index, including but not limited to digoxin, pitavastatin, pravastatin, rosuvastatin and metformin.

In vitro data indicate that ribociclib has no potential to induce UGT enzymes or the CYP enzymes CYP2C9, CYP2C19 and CYP3A4 via PXR. Therefore, Kisqali is unlikely to affect substrates of these enzymes. In vitro data are not sufficient to exclude a potential of ribociclib to induce CYP2B6 via CAR.

Ribociclib was teratogenic in animal studies. A DDI study with an oral contraceptive is not considered necessary at present, given the proposed target population (postmenopausal women). The SmPC reflects

that it is currently unknown whether Kisqali may reduce the effectiveness of systemically acting hormonal contraceptives.

Data from a clinical study in patients with breast cancer and population pharmacokinetic analysis indicated no drug interaction between ribociclib and letrozole following co-administration of these medicinal products. Letrozole exposure on Day 21 following multiple dose administration of ribociclib (600 mg) and letrozole (2.5 mg) was consistent with or numerically lower than data reported in historical studies with letrozole. The latter evaluation should be interpreted with caution, as it is based on comparison with historical data.

No pharmacokinetic data of ribociclib and anastrozole in combination were submitted. Based on theoretical/mechanistic considerations, the risk for a clinically relevant interaction between the two drugs is expected to be low.

The potential interaction of ribociclib on exemestane was evaluated by comparison of data from a phase 1 dose-finding study with ribociclib+exemestane with historical PK data for monotherapy ribociclib and exemestane, respectively. No interaction was observed. The results should be interpreted with caution, as they are based on comparison with historical data. From a mechanistic point of view, an interaction risk appears to be low.

Pharmacodynamic

Genetic differences in PD response

A molecular correlate of variable sensitivity has not been identified clinically and there is no compelling evidence of differential effects in subgroups defined by Cyclin D1, RB or P16 mRNA or protein expression in CLEE011A2301/MONALEESA-2 (see clinical efficacy).

The applicant has investigated mRNA expression levels for CCNA2, CCND1, CCND2, CCND3, CCNE1, CDK2, CDK4, CDK6, CDKN1A, CDKN2A, CDKN2B, CDKN2C, E2F1, E2F3, RB1, TFDP1, BCL6, FGF2, FGFR1, LMO2, MCL1, MET, PDGFA, PDGFRA, YY1 in relation to PFS without identifying potential biomarkers for differential efficacy (data not shown).

Relationship between plasma concentration and effect

There was a strong association between ΔQTcF and ribociclib plasma concentration. Co-administration of Kisqali with medicinal products with a known potential to prolong the QT interval such as anti-arrhythmic medicinal products (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine and sotalol), and other medicinal products that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and intravenous ondansetron) should be avoided (see SmPC sections 4.4 and 4.5).

No relationship was observed between ribociclib exposure parameters and efficacy, which may be due to limitations in the evaluation, such as lack of relevant exposure data.

Overall, a 50% increase in exposure, e.g. due to an interaction, is considered manageable by monitoring for toxicity (except in patients with patients with pre-existing hepatic impairment, see above).

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics, pharmacodynamic and interaction potential of ribociclib are considered sufficiently characterised and the relevant information has been included in the SmPC section 4.4, 4.6 and 5.2.

2.5. Clinical efficacy

2.5.1. Dose response studies

Study CLEE011X1101

A phase I, multi-center, open-label dose-escalation study to estimate the MTD/RDE and to assess the dosing schedule as a single agent of LEE011, enrolling patients at two centres in Japan. LEE011 was administered orally once daily for 21 days followed by a 7-day rest period (28-day cycle) in patients with solid tumours that have progressed despite standard therapy or for which no further effective standard therapy is available.

Approximately 30 patients were planned to be treated in the entire study (a minimum of 12 patients in the dose escalation part and at least 12 esophageal squamous cell carcinoma (ESCC) patients who had not been treated with a CDK4/6 inhibitor in the dose expansion part). The dose expansion part was not opened as no sign of antitumor activity was observed in the 9 ESCC patients; between 20 June 2103 and 17 December 2014 4 patients were enrolled in the 400 mg dose group and 13 in the 600 mg group. The last patient last visit was 28 January 2015.

Dose-limiting toxicities (DLTs)

Four DLTs occurred in 4 patients: 1 patient each in the 400 mg and the 600 mg dose groups had grade 3 febrile neutropenia, 2 patients in the 600 mg dose group had grade 3 electrocardiogram QT prolonged, 1 patient in the 600 mg dose group had grade 4 neutropenia, and 1 patient in the 600 mg dose group had grade 4 thrombocytopenia.

Maximum tolerated dose (MTD) and recommended dose for expansion (RDE)

Doses above 600 mg were not studied and MTD was not determined. The RDE was determined to be 600 mg QD on the 21-days on/7-days off schedule in Japanese patients with solid tumors. The Bayesian logistic regression model (BLRM) analysis predicted that 750 mg had the highest posterior probability of the true DLT rates falling in the target toxicity interval among the doses satisfying the escalation with overdose control (EWOC) principle. However, all investigators and the Sponsor agreed to declare the RDE as 600 mg without further dose-escalation based on the following reasons: (1) 600 mg satisfied MTD/RDE determination criteria specified in the protocol; (2) 600 mg fulfilled the EWOC principle; and (3) the observed DLT rate at 600 mg in this study was 23%.

Efficacy

None of the patients achieved confirmed CR or PR. A best overall response of SD was observed in 4 of 13 patients in the 600 mg dose group. In 13 patients dosed at 600 mg, the median PFS per Investigator assessment was 2.0 months with 95% CI of 1.0-3.7 months.

Study CLEE011X2101

A Phase 1 multicenter, open label, dose-escalation study of oral LEE011 in patients with advanced solid tumors or lymphomas

This was a Phase I, multi-center, open-label dose-escalation study of ribociclib administered orally once daily for either 21 days followed by a 7 day rest period or continuous daily dosing (28-day cycle) in adult patients with solid tumors or lymphomas that have progressed despite standard therapy and for which no standard therapy was available. Enrollment was restricted to patients with tumors that have intact retinoblastoma protein (pRb). The study is ongoing. As of the data cut-off date (18-Sep-2015), 153 patients have been treated in this study. A total of 134 patients were treated on the once daily 3 weeks on/1 week off regimen.

Dose-limiting toxicities

As of the data cut-off date (18-Sep-2015), for patients treated in the once daily 3 weeks on/1 week off regimen, the incidence of DLTs was higher in patients who received >600 mg (17.9%) compared to those who received 600 mg (8.3%). The most common DLTs (≥ 1%) observed were thrombocytopenia (3.2%), neutropenia (2.4%), QT prolongation and febrile neutropenia (1.6% each).

All other DLTs occurred in one patient each, with an incidence of 0.8% (platelet count decreased, stomatitis, herpes simplex, and pulmonary embolism). The stomatitis and herpes simplex DLTs occurred in the same patient. In this case, the event was initially thought to be drug related stomatitis.

Maximum tolerated dose (MTD) and recommended dose for expansion (RDE)

The MTD was declared at 900 mg. The dose and regimen of 600 mg once daily 3 weeks on/1 week off was declared as the RDE based on the emerging DLT data from the 64 patients in the dose determining set, Bayesian logistic regression model (BLRM) results along with the escalation with over-dose control (EWOC) principle, and the review of all available safety and PK data. At the time of RDE declaration, the MTD (900 mg) had a risk of excessive toxicity of 1.2%, whereas the RDE (600 mg) had a risk of excessive toxicity of <0.1%. The decision to declare RDE below the MTD was driven primarily by the lower rate of QTcF prolongation observed at 600 mg/day compared with higher doses.

Efficacy

Across all dose levels, the ORR was 3.0% [90% CI: 1.0, 6.7], and the disease control rate was 38.1% [90% CI: 31.0, 45.5] for patients who were treated on the once daily 3 weeks on/1 week off regimen.

Best overall response of CR was not observed, however, four patients (3.0%), all at the 600 mg dose level, achieved a PR. These patients included: one patient with melanoma, one patient with thymic carcinoma, one patient with ER+ breast cancer, and one patient with head and neck acinar carcinoma. Stable disease was observed in patients across all dose levels (n=47, 35.1%).

Pharmacodynamics

Reduction in Ki67 and phosphorylated pRb were observed in skin biopsies in all dose cohorts. Tumour biopsies did not show a consistent decrease in phosphorylated Rb but reductions in Ki67 were observed in the majority of samples treated at doses ≥ 600 mg.

Study CLEE011X2107

A phase Ib/II, multicenter, study of the combination of LEE011 and BYL719 with letrozole in adult patients with advanced ER+ breast cancer

This was a multi-center, open-label, dose finding Phase Ib study to estimate the MTD and/or RP2D for two double combinations: LEE011 with letrozole and BYL719 with letrozole followed by estimation of the MTD and/or RP2D of the triple combination of LEE011 + BYL719 with letrozole.

The study was conducted in adult post-menopausal women with locally advanced or metastatic ER+/HER2-negative breast cancer. In the dose escalation part of the study, patients could have any number of prior lines of endocrine therapy with up to one prior cytotoxic regimen in the metastatic or locally advanced setting, whereas in the dose expansion patients should not have received prior systemic treatment for advanced disease (allowing < 1 month of letrozole).

The dose escalation part was followed by a dose expansion in all three arms to further characterize the safety, tolerability, PK and preliminary clinical anti-tumor activity of the combinations.

An interim analysis was submitted, where only the analysis related to the Arm 1 doublet (ribociclib with standard dose letrozole) dose escalation and dose expansion is reported.

In Arm 1, LEE011 was administered orally, once daily for 21 consecutive days followed by a 7-day planned break (28-day cycle, 3 weeks on/1 week off). Letrozole was administered orally on all 28 days (2.5 mg oral once daily).

Since 22 October 2013, 47 patients have been enrolled on Arm 1 of this study (19 patients in the dose escalation phase and 28 patients in the dose expansion phase of the study). All patients were dosed ribociclib 600 mg plus letrozole 2.5 mg.

Dose-limiting toxicities

Two patients (10.5%) in the escalation phase experienced a dose limiting toxicity of grade 4 neutropenia, both grade 4 events started after 21 days on study (and lasted 4 and 10 days).

Maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D)

The starting dose of ribociclib was 600 mg qd 3 weeks on 1 week off in combination with standard dose of letrozole. Based on the DLT data at the completion of the first cycle for the 19 patients evaluable for the dose-determining set at the time of MTD determination, one DLT was observed (grade 4 neutropenia). Based on the safety and PK data, and the recommendations of the Bayesian logistic regression model (BLRM), ribociclib 600 mg/day (3 weeks on, 1 week off) and letrozole 2.5 mg/day (continuous) was RP2D for Arm 1 expansion.

Efficacy

In the escalation phase, one patient (5.3%) had a partial response (PR); no patients had complete response (CR). In the expansion phase, one patient (3.6%) had a CR and 10 patients (35.7%) had a PR; overall response rate was 39.3%.

As of the cut-off date of 30-Oct-2015, 15 PFS events has been observed in the dose escalation phase; the median PFS was 5.2 months (95% CI: 2.3, 8.0). A total of 8 PFS events were observed in the dose expansion phase and the median PFS was not estimable at the time of data cut-off.

Pharmacodynamics

PD markers were available for a small number of paired samples, limiting usefulness. No patient had a mutation in the RB1 gene.

2.5.2. Main study

Pivotal study CLEE011A2301 (MONALEESA-2)

A randomized double-blind, placebo-controlled study of LEE011 in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer, who received no prior therapy for advanced disease.

Methods

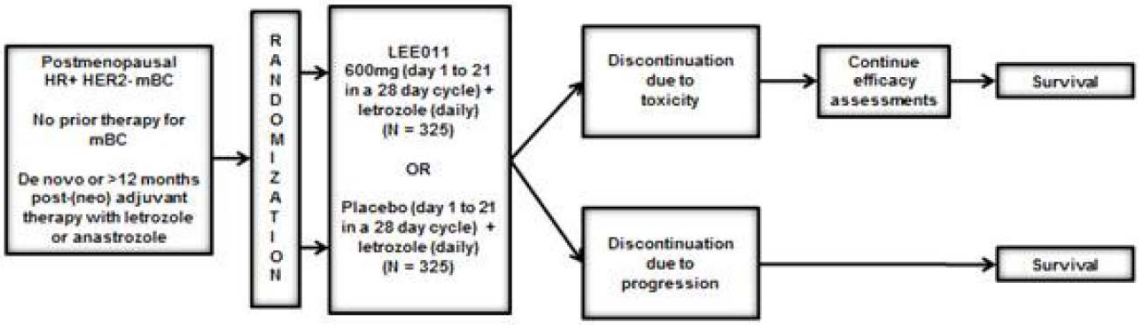


Figure 2: Study design – Study CLEE011A2301

Study Participants

The patient population consisted of postmenopausal women with HR-positive, HER2- negative, advanced breast cancer, who had previously received no prior therapy for their advanced breast cancer.

The main inclusion criteria were the following:

- Adult postmenopausal women (≥ 18 years) at the time of informed consent.
- Women with advanced (loco regionally recurrent or metastatic) breast cancer not amenable to curative therapy.
- Postmenopausal status was defined either by:
  - Prior bilateral oophorectomy
  - Age ≥ 60
  - Age < 60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression) and follicle stimulating hormone (FSH) and estradiol in the postmenopausal range per local normal range.
- Histological and/or cytological confirmation of estrogen receptor (ER)-positive - and/or progesterone receptor positive breast cancer by local laboratory.

- Patients diagnosed with HER2-negative breast cancer defined as a negative in situ hybridization test or an Immunohistochemistry (IHC) status of 0, 1+ or 2+. If IHC was 2+, a negative in situ hybridization (fluorescent in situ hybridization [FISH], chromosome in situ hybridization [CISH], or silver-enhanced in situ hybridization [SISH]) test was required by local laboratory testing.

Patient had either:

- Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria (Tumor lesions previously irradiated or subjected to other loco regional therapy were only to be considered measurable if disease progression at the treated site after completion of therapy was clearly documented)

OR

- At least one predominantly lytic bone lesion (Patients with only one predominantly lytic bone lesion that was previously irradiated were eligible if there was documented evidence of disease progression of the bone lesion after irradiation).
- ECOG performance status 0 or 1

<u>The main exclusion criteria were:</u>

- Patients who received any CDK4/6 inhibitor previously.
- Patients with inflammatory breast cancer.
- Patients who received any prior systemic anti-cancer therapy (including hormonal therapy and chemotherapy) for advanced breast cancer
- Patients who received (neo) adjuvant therapy for breast cancer were eligible. If the prior neo (adjuvant) therapy included letrozole or anastrozole the disease free interval had to be greater than 12 months from the completion of treatment until randomization. Patients who received ≤ 14 days of letrozole or anastrozole for advanced disease prior to randomization were allowed.
- Any prior (neo) adjuvant anti-cancer therapy had to be stopped at least 5 half-lives or 7 days, whichever was longer, before randomization
- Patients currently receiving other anti-cancer therapy.
- Patients with central nervous system (CNS) metastases.
- Patients who had active cardiac disease or a history of cardiac dysfunction including any of the following:
    - History of angina pectoris, symptomatic pericarditis, or myocardial infarction within 12 months prior to study entry
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Documented cardiomyopathy
    - Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)

- History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality in the previous 12 months.
- On Screening, any of the following cardiac parameters: bradycardia (heart rate <50 at rest), tachycardia (heart rate >90 at rest), pulse rate interval >220 msec, QRS interval >109 msec, or QTcF >450 msec.
- Systolic blood pressure >160 or <90 mmHg.

- Patients that were currently receiving any of the following medications and could not be discontinued seven days prior to the start of the treatment:
  - Known strong inducers or inhibitors of CYP3A4/5.
  - Those with a known risk to prolong the QT interval or induce Torsades de Pointes.
  - Those with a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.
  - Herbal preparations/medications.
  - Dietary supplements (except vitamins).
- Patients that were currently receiving or those who had received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.

Note: The use of following corticosteroids was permitted: single doses of topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), and eye drops or local injections (e.g., intra-articular).

Treatments

Arm A: Ribociclib (600 mg once daily, days 1-21 of a 28-day cycle) + letrozole (2.5 mg once daily, days 1-28 of a 28-day cycle).

Arm B: Placebo (once daily, days 1-21 of a 28-day cycle) + letrozole (2.5 mg once daily days 1-28 of a 28-day cycle continuously).

The ribociclib/placebo dose could be reduced to 400 mg (first reduction) and 200 mg (second reduction), whereas no dose modification for letrozole was planned in the study.

Patients received study treatment until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.

Objectives

Primary objective

The primary objective was to compare progression-free survival (PFS) in patients treated with ribociclib and letrozole to that of patients treated with placebo and letrozole, according to investigators' review.

Secondary objectives

The key secondary objective of the study was to compare the two treatment arms with respect to overall survival (OS).

Other secondary objectives were:

- To evaluate the two treatment arms with respect to overall response rate (ORR) and clinical benefit rate (CBR).
- To evaluate the two treatment arms with respect to time to deterioration of Eastern Cooperative Oncology Group (ECOG) performance status.
- To evaluate the safety and tolerability of ribociclib in combination with letrozole.
- To evaluate patient reported outcomes (PROs) for health-related quality of life (QoL) in the two treatment arms.

Exploratory objectives

Time to response, duration of response, exposure for ribociclib and letrozole, effects on estradiol suppression for combination vs. monotherapy, exposure-response relationship, hospital resource utilization, signaling pathway alterations, circulating DNA, mechanisms of resistance.

Outcomes / endpoints

PFS was determined through investigators review of radiology data using RECIST version 1.1 criteria. Tumour assessments (CT with iv contrast or without iv contrast combined with MRI, visual assessment, photograpy) were made every 8 weeks during the first 18 months, and every 12 weeks thereafter until disease progression and at end-of-treatment.

PFS was defined as the time from the date of randomization to the date of first documented disease progression or death due to any cause. Discontinuation for non-RECIST progression was not counted as a PFS event. If a patient started other anti-neoplastic therapy or had two or more missing tumour assessments, PFS was censored at the last adequate tumour assessment, regardless of subsequent events.

A blinded independent review committee (BIRC) was utilized for review of radiology (and photography) data. At the start of the study, the BIRC consisted of a single radiology reader and an oncologist who would review all data for select patients where radiological progression could not be fully confirmed. The decision regarding patient management remained with the investigator.

Overall survival (OS) was a key secondary endpoint. Overall survival (OS) was defined as the time from date of randomization to date of death due to any cause.

Other secondary efficacy variables were ORR, CBR, and ECOG performance status. ORR was defined as the proportion of patients with best overall response of confirmed CR or PR according to RECIST 1.1, and CBR defined as the proportion of patients with a best overall response of confirmed CR or PR or stable disease (SD) lasting 24 weeks or longer, according to RECIST 1.1 criteria.

Patient-reported outcomes (PROs) were evaluated using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3.0) questionnaire along with the disease-specific breast cancer module (EORTC QLQ-BR23, version 1.0) and the EuroQoL 5-level instrument (EQ-5D-5L, Version 4.0) to explore impacts on health-related quality of life, functioning, disease symptoms, and treatment-related side effects.

Sample size

It was initially planned to randomise 500 patients. Within a study protocol amendment (amendment 2, 25-Nov-2014) the sample size of the study was increased to 650 in order to better characterize the effect of ribociclib and letrozole on overall survival.

It was estimated that the median duration of PFS in the control group (placebo plus letrozole) would be 9.0 months, and treatment with test treatment arm (ribociclib plus letrozole) would result in a 33% reduction in the hazard rate (corresponding to an increase in median PFS to 13.43 months).

If the true hazard ratio was 0.67 (under alternative hypothesis), a total of 302 PFS events were required to have 93.5% power at a one-sided overall 2.5% level of significance to reject the null hypothesis (HR=1) using a log-rank test and a 2-look group sequential design with Haybittle-Peto to determine efficacy boundary for the interim analysis. Considering a recruitment period of approximately 16 months at a uniform rate of 37 patients/month 592 patients needed to be randomized to the two treatment arms in a 1:1 ratio. Assuming about 10% patients were to be lost to follow-up for PFS, a total of 650 patients needed to be randomized. Given the above assumptions, it was estimated that the 302th PFS event were to be observed at approximately 20 months from the date of first patient randomized in the study.

The median OS in the letrozole only arm was expected to be around 34 months. It was hypothesized that test treatment arm (ribociclib plus letrozole) resulted in a 28% reduction in the hazard rate for overall survival (corresponding to an increase in median survival to 47.2 months). If the true hazard ratio was 0.72 (under alternative hypothesis), a total of 400 deaths needed to be observed to have 90% power at a one-sided overall 2.5% level of significance to reject the null hypotheses (HR=1) using a log-rank test and a 4-look group sequential design.

Randomisation

Eligible patients were randomized using IRT system in a 1:1 ratio.

Randomization was stratified by the presence of liver and/or lung metastases (yes versus no).

Blinding (masking)

Double-blind study.

Statistical methods

This was a superiority trial, powered to detect a difference (at least) corresponding to a median PFS of 13.43 months (experimental arm) vs. 9 months (control arm), with 93.5% probability (HR 0.67, one-sided overall 2.5% level of significance, log-rank test). This also involved a 2-look group sequential design with an interim analysis for superiority. The interim analysis was planned to be performed after approximately 211 events, requiring a $p < 0.0000129$ for conclusion of superiority, whereas the final analysis was planned after 302 events, requiring a p-value of 0.02499 for statistical significance.

Assuming a median OS of 47.2 months for the experimental arm vs. 34 for the control arm (HR of 0.72), 400 events would be necessary for 90% power to detect a difference (one-sided overall 2.5% level of significance, log-rank test, 4-look group sequential design). The four OS analyses were planned to be performed after 76 (interim PFS analysis), 120 (final PFS analysis), 300 and 400 deaths.

Investigators and patients will remain blinded to study treatment and all patients will continue to be followed for OS until the final OS analysis (or earlier if OS reaches statistical significance at any of the interim analyses).

A hierarchical testing strategy, where OS was to be statistically evaluated only if the primary efficacy endpoint PFS was statistically significant, was used to control the overall type-I error rate.

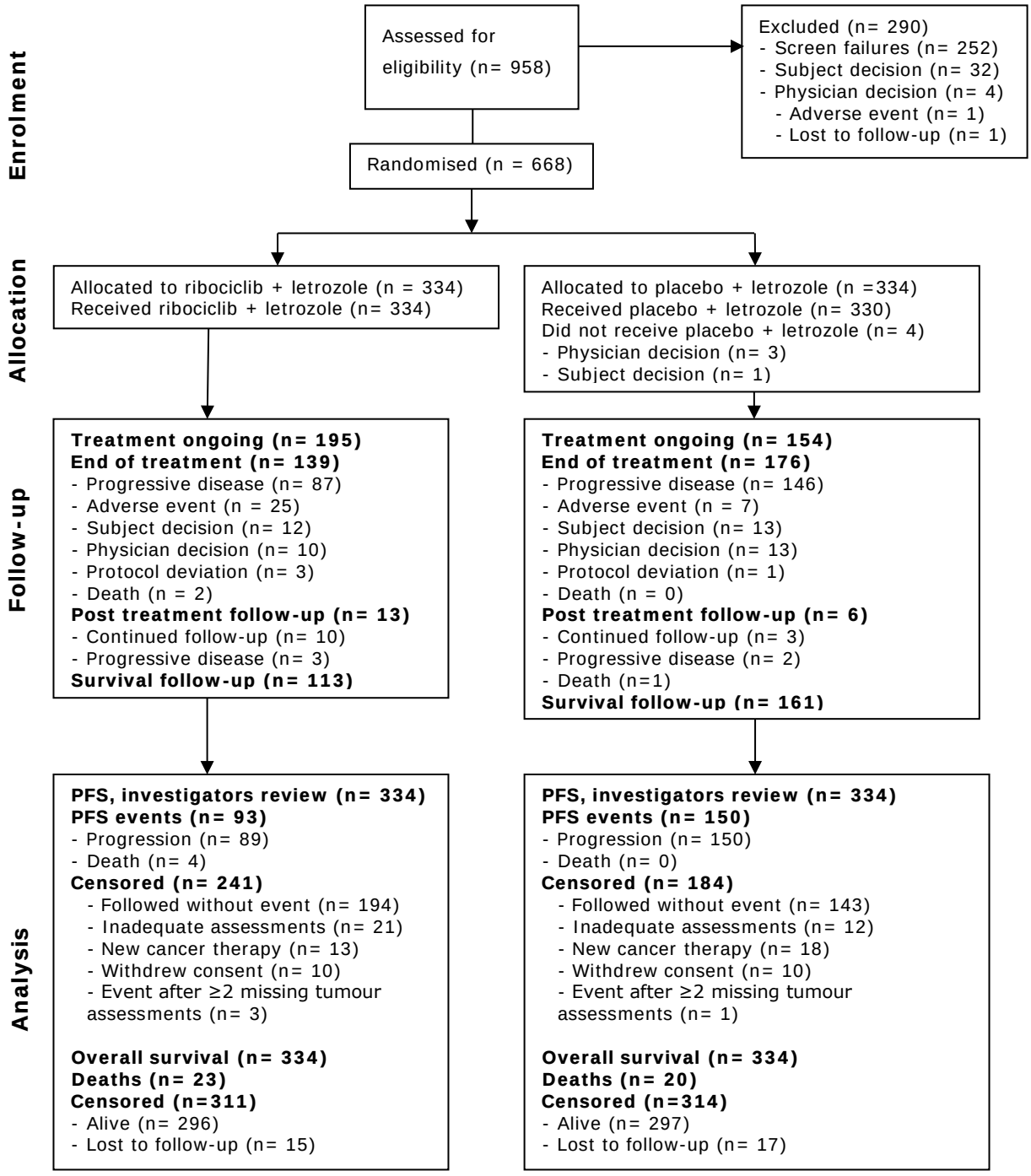
All efficacy analyses were performed using the Full Analysis Set (FAS) which consisted of all randomised patients. According to the intent to treat principle, patient data were analysed according to the treatment and stratum they had been assigned to at randomisation. Efficacy analyses included all data observed in patients from FAS regardless whether it was observed on-treatment or after the study treatment discontinuation till the analysis cut-off date.

As a supportive analysis, the primary PFS analysis was to be repeated using data from BIRC assessments using FAS and using the same conventions as for the primary analysis.

Several sensitivity analyses were planned to assess the overall robustness of the primary efficacy results. These analyses included repeating the primary efficacy analysis using the Per Protocol Set, using an unstratified log-rank test and using different censoring rules.

Results

Participant flow



Recruitment

First patient enrolled: 17-Dec-2013 (first patient first visit)

Last patient completed: Study ongoing

Data cut-off date for interim analysis: 29-Jan-2016

223 sites across 29 countries enrolled patients, the country and respective no. of sites are as follows: Argentina (3 sites), Australia (3), Austria (3), Belgium (5), Brazil (3), Canada (8), Czech Republic (4), Denmark (4), Finland (2), France (12), Germany (20), Hungary (4), Ireland (2), Israel (3), Italy (16), Lebanon (4), Netherlands (10), Norway (2), Province of China Taiwan (5), Republic of Korea (5), Russian Federation (3), Singapore (1), South Africa (1), Spain (12), Sweden (6), Thailand (1), Turkey (5), United Kindom (2), United States (74).

Conduct of the study

There were 4 protocol amendments and 2 changes in the SAP:

20 Sep 2013	Original protocol
24 Jan 2014	First patient randomized
23 Apr 2014	Protocol amendment 1 (17 patients randomized) Clarification of inclusion/exclusion criteria and study assessments after feedback from IRBs/ECs/health authorities. Update of nonclinical and clinical data for ribociclib.
25 Nov 2014	Protocol amendment 2 (407 patients randomized) Dose modification guidance for hepatic toxicity. Guidance for management of QTcF interval prolongation. Revision of sample size from 500 to 650 patients to increase power to detect OS HR 0.72 from 80% to 90% (please refer to sample size section). Highlighting of the need to consult the letrozole SPC in case of AEs. Updated the protocol requirements for consistency with the most recent preclinical information (thyroid laboratory monitoring no longer mandated, kidney monitoring added).
24 Mar 2015	Last patient randomized
9 Apr 2015	Protocol amendment 3 Additional cardiac monitoring (ECG first day each cycle, electrolyte monitoring, concomitant medication, ribociclib dosing). Management of neutropenia. Elimination of planned futility analysis and revision of the interim analysis for efficacy (refer to the statistical methods section). Editorial changes.
29 Jan 2016	Analysis cut off
8 Feb 2016	Protocol amendment 4 Additional monitoring and dose-adjustment guidelines for hepatic toxicity. Advice consultation with local cardiologist for certain cases of grade 3 QTcF values. Removal of the requirement for a central radiology assessment by a medical oncologist (please refer to the following section). Updates for consistency with ribociclib IB regarding

	concomitant medication, safety pharmacology and toxicology.
21 December 2016	Protocol amendment 5 Updated information that collection of unscheduled PK has been discontinued. Updated the timing of the second OS interim analysis, the corresponding power and the overall study power.

Protocol deviations

Overall, 42.4% of patients reported at least one protocol deviation with major protocol deviations being reported in 44 patients (6.6%).

Table 10: Major protocol deviations (FAS)

Protocol deviation	Ribociclib + letrozole N=334 n (%)	Placebo + letrozole N=334 n (%)	All patients N= 668 n (%)
Patients with at least one major protocol deviation	**24 (7.2)**	**20 (6.0)**	**44 (6.6)**
Selection criteria not met	**24 (7.2)**	**20 (6.0)**	**44 (6.6)**
Criteria for prior therapy for advanced breast cancer not met[1]	15 (4.5)	9 (2.7)	24 (3.6)
Postmenopausal status not met	2 (0.6)	6 (1.8)	8 (1.2)
Criteria for measureable disease or lytic bone lesion not met	6 (1.8)	3 (0.9)	9 (1.3)
Breast cancer type (HER2 status) not met	1 (0.3)	1 (0.3)	2 (0.3)
Concurrent malignancy or malignancy in last 3 years of randomization	0	1 (0.3)	1 (0.1)
Criteria for advanced disease not met	1 (0.3)	0	1 (0.1)

[1]These patients included those who took letrozole/anastrozole for more than 14 days or patients who were on any prior (neo) adjuvant anti-cancer therapy which were not stopped at least 5 half-lives or 7 days before randomization

Baseline data

Table 11: Demographics and baseline characteristics

Demographic variable	Ribociclib + letrozole N=334	Placebo + letrozole N=334	All patients N=668
Age (years)			
Mean (SD)	61.4 (10.98)	61.9 (10.52)	61.6 (10.75)
Median (min-max)	62 (23 - 91)	63 (29 - 88)	62 (23 - 91)
Age category (years) – n (%)			
<65	184 (55.1)	189 (56.6)	373 (55.8)
≥ 65	150 (44.9)	145 (43.4)	295 (44.2)
Race – n (%)			
Caucasian	269 (80.5)	280 (83.8)	549 (82.2)

Asian	28 (8.4)	23 (6.9)	51 (7.6)
Black	10 (3.0)	7 (2.1)	17 (2.5)
Native American	1 (0.3)	0	1 (0.1)
Pacific Islander	1 (0.3)	0	1 (0.1)
Other	12 (3.6)	8 (2.4)	20 (3.0)
Unknown	13 (3.9)	16 (4.8)	29 (4.3)
ECOG performance status – n (%)			
0	205 (61.4)	202 (60.5)	407 (60.9)
1	129 (38.6)	132 (39.5)	261 (39.1)
Region			
Europe	150 (44.9)	146 (43.7)	296 (44.3)
North America	108 (32.3)	121 (36.2)	229 (34.3)
Asia	35 (10.5)	33 (9.9)	68 (10.2)
Latin America	7 (2.1)	7 (2.1)	14 (2.1)
Other	34 (10.2)	27 (8.1)	61 (9.1)

Source: Table 14.1-3.1

Table 12: Patient and disease characteristics at baseline (FAS)

Disease history	Ribociclib + letrozole N=334	Placebo + letrozole N=334	All patients N=668
Primary site of cancer – n (%)			
Breast	334 (100.0)	334 (100.0)	668 (100.0)
Histological grade – n (%)			
Well differentiated	30 (9.0)	35 (10.5)	65 (9.7)
Moderately differentiated	143 (42.8)	128 (38.3)	271 (40.6)
Poorly Differentiated	59 (17.7)	75 (22.5)	134 (20.1)
Undifferentiated	3 (0.9)	5 (1.5)	8 (1.2)
Unknown	99 (29.6)	89 (26.6)	188 (28.1)
Missing	0	2 (0.6)	2 (0.3)
Stage at initial diagnosis – n (%)			
0	7 (2.1)	6 (1.8)	13 (1.9)
I	55 (16.5)	48 (14.4)	103 (15.4)
II	98 (29.3)	107 (32.0)	205 (30.7)
III	58 (17.4)	62 (18.6)	120 (18.0)
IV	115 (34.4)	108 (32.3)	223 (33.4)
Unknown	0	3 (0.9)	3 (0.4)
Missing	1 (0.3)	0	1 (0.1)
Stage at time of study entry– n (%)[1]			
III	1 (0.3)	3 (0.9)	4 (0.6)
IV	333 (99.7)	331 (99.1)	664 (99.4)
Time since initial diagnosis of primary site (months)			
n	334	333	667
Mean (SD)	74.7 (75.42)	75.2 (82.84)	74.9 (79.15)
25th Percentile	2.0	2.0	2.0
Median	58.1	52.1	55.2
75th Percentile	126.1	115.9	122.6
Disease free interval - n(%)			
De novo	114 (34.1)	113 (33.8)	227 (34.0)
Non De novo	220 (65.9)	221 (66.2)	441 (66.0)
≤ 12 months	4 (1.2)	10 (3.0)	14 (2.1)
>12 to ≤ 24 months	14 (4.2)	15 (4.5)	29 (4.3)
>24 months	202 (60.5)	195 (58.4)	397 (59.4)
Unknown	0	1 (0.3)	1 (0.1)
Types of lesions at Baseline-n (%)			
Target only	32 (9.6)	28 (8.4)	60 (9.0)
Non-target only	77 (23.1)	88 (26.3)	165 (24.7)
Both target and non-target	224 (67.1)	217 (65.0)	441 (66.0)
Unknown	1 (0.3)	1 (0.3)	2 (0.3)
HER2 receptor status – n (%)			
Positive	1 (0.3)	1 (0.3)	2 (0.3)

Negative[2]	333 (99.7)	333 (99.7)	666 (99.7)
Estrogen receptor status – n (%)			
Positive	332 (99.4)	333 (99.7)	665 (99.6)
Negative	2 (0.6)	1 (0.3)	3 (0.4)
Progesterone receptor status – n (%)			
Positive	271 (81.1)	278 (83.2)	549 (82.2)
Negative	55 (16.5)	49 (14.7)	104 (15.6)
Unknown	8 (2.4)	7 (2.1)	15 (2.2)
Estrogen and/or progesterone receptor status – n (%)			
At least one positive	334 (100.0)	334 (100.0)	668 (100.0)
Current extent of disease (metastatic sites) – n (%)			
Breast	8 (2.4)	11 (3.3)	19 (2.8)
Bone marrow	0	2 (0.6)	2 (0.3)
Bone	246 (73.7)	244 (73.1)	490 (73.4)
Bone only (no other metastatic sites)	69 (20.7)	78 (23.4)	147 (22.0)
Visceral	197 (59.0)	196 (58.7)	393 (58.8)
Liver	59 (17.7)	73 (21.9)	132 (19.8)
Lung	153 (45.8)	150 (44.9)	303 (45.4)
Other	22 (6.6)	18 (5.4)	40 (6.0)
Skin	15 (4.5)	10 (3.0)	25 (3.7)
Lymph nodes	133 (39.8)	123 (36.8)	256 (38.3)
Others	20 (6.0)	10 (3.0)	30 (4.5)
None	2 (0.6)	1 (0.3)	3 (0.4)
Number of metastatic sites involved – n (%)			
0	2 (0.6)	1 (0.3)	3 (0.4)
1	100 (29.9)	117 (35.0)	217 (32.5)
2	118 (35.3)	103 (30.8)	221 (33.1)
3	64 (19.2)	72 (21.6)	136 (20.4)
4	36 (10.8)	22 (6.6)	58 (8.7)
≥ 5	14 (4.2)	19 (5.7)	33 (4.9)

[1]Of the stage III patients, two had no metastatic sites, but the other two reported metastatic sites of axillary lymph nodes and bone, respectively. Furthermore, one of the stage IV patients was reported to have no metastatic sites.
[2]HER2-negative breast cancer defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+. If IHC was 2+, a negative in situ hybridization (FISH, CISH, or SISH) test was required by local laboratory testing.
Source: Table 14.1-3.2

All patients had an ECOG performance status of 0 or 1. 43.7% of patients had received chemotherapy in the neoadjuvant or adjuvant setting and 52.4% had received antihormonal therapy in the neoadjuvant or adjuvant setting prior to study entry. 34.1% of patients were *de novo* (see table below).

Table 13: Prior anti-neoplastic therapy by treatment – Overall (FAS)

Characteristic	Ribociclib + letrozole N=334 n (%)	Placebo + letrozole N=334 n (%)	All patients N=668 n (%)
Any therapy			
Yes	334 (100.0)	334 (100.0)	668 (100.0)
Surgery (including biopsy)			
Yes	334 (100.0)	334 (100.0)	668 (100.0)
Radiotherapy			
No	156 (46.7)	167 (50.0)	323 (48.4)
Yes	178 (53.3)	167 (50.0)	345 (51.6)
Medication setting[1]			
Adjuvant	195 (58.4)	189 (56.6)	384 (57.5)
Neoadjuvant	41 (12.3)	28 (8.4)	69 (10.3)
Palliative	20 (6.0)	21 (6.3)	41 (6.1)
Prevention	3 (0.9)	2 (0.6)	5 (0.7)
Other	24 (7.2)	18 (5.4)	42 (6.3)
Medication: chemotherapy setting[1]			
Adjuvant	118 (35.3)	127 (38.0)	245 (36.7)
Neoadjuvant	41 (12.3)	25 (7.5)	66 (9.9)
Palliative	1 (0.3)	1 (0.3)	2 (0.3)
Other	1 (0.3)	0	1 (0.1)
Medication: hormonal therapy setting[1]			
Adjuvant	173 (51.8)	166 (49.7)	339 (50.7)
Neoadjuvant	0	4 (1.2)	4 (0.6)
Palliative	19 (5.7)	20 (6.0)	39 (5.8)

Prevention	3 (0.9)	2 (0.6)	5 (0.7)
Other	23 (6.9)	18 (5.4)	41 (6.1)
Medication: other therapy setting[1]			
Adjuvant	5 (1.5)	2 (0.6)	7 (1.0)
Neoadjuvant	1 (0.3)	0	1 (0.1)
Type of last therapy			
Chemotherapy	7 (2.1)	10 (3.0)	17 (2.5)
Hormonal therapy	129 (38.6)	134 (40.1)	263 (39.4)
Radiotherapy	75 (22.5)	64 (19.2)	139 (20.8)
Surgery – non biopsy	57 (17.1)	62 (18.6)	119 (17.8)
Setting at last therapy			
Adjuvant	136 (40.7)	135 (40.4)	271 (40.6)
Neoadjuvant	1 (0.3)	2 (0.6)	3 (0.4)
Palliative[2]	45 (13.5)	45 (13.5)	90 (13.5)
Prevention	2 (0.6)	5 (1.5)	7 (1.0)
Other	21 (6.3)	18 (5.4)	39 (5.8)

[1]A patient may have multiple setting
[2]These were the patients who received palliative therapy (including medication and radiotherapy) as last therapy prior to randomization.
-'Other therapy' included any other prior antineoplastic medications that do not fall into chemotherapy, hormonal therapy, targeted therapy, or immunotherapy
-Last therapy was defined as the last therapy prior to the first dose.
- Setting at last therapy was not applicable if the type of last therapy was surgery.
Patients who took letrozole/anastrozole for more than 14 days or patients who were on any prior (neo) adjuvant anti-cancer therapy which were not stopped at least 5 half-lives or 7 days before randomization were excluded from the per protocol set.
Source: Table 14.1-3.6

Numbers analysed

Table 14: Analysis sets

Analysis set	Ribociclib + letrozole N=334 n (%)	Placebo + letrozole N=334 n (%)	All patients N=668 n (%)
Full analysis set	334 (100)	334 (100)	668 (100)
Per protocol set	310 (92.8)	311 (93.1)	621 (93.0)
Safety set	334 (100)	330 (98.8)	664 (99.4)
Pharmacokinetic analysis set	73 (21.9)	85 (25.4)	158 (23.7)

Source: Table 14.1-2.1

Stratification according to presence of liver and/or lung metastases (yes/no) was incorporated into the randomisation design. Overall, 43.7% of the enrolled patients had liver and/or lung metastases and 56.3% did not have liver and/or lung metastases.

Table 15: Randomisation by stratification factor and treatment (FAS)

	Ribociclib + letrozole N=334	Placebo + letrozole N=334	All patients N=668
Stratification factor	n (%)	n (%)	n (%)
Liver and/or lung metastases (Yes)	146 (43.7)	146 (43.7)	292 (43.7)
Liver and/or lung metastases (No)	188 (56.3)	188 (56.3)	376 (56.3)

Outcomes and estimation

Primary endpoint: progression-free survival

Table 16: Analysis of PFS per investigator review using the Kaplan-Meier method (full analysis set, 29-Jan-2016 data cut-off)

Table 11-6 Analysis of PFS per Investigator review using the Kaplan-Meier method (Full analysis set)

Category	Ribociclib + letrozole N=334	Placebo + letrozole N=334
Number of events - n (%)	93 (27.8)	150 (44.9)
Progression	89 (26.6)	150 (44.9)
Death[1]	4 (1.2)	0
Number censored - n (%)	241 (72.2)	184 (55.1)
P-value ribociclib vs. Placebo[2]	3.29×10^{-6}	
Hazard ratio (95% CI) ribociclib vs. Placebo[3]	0.556 (0.429, 0.720)	
Percentiles (95% CI)		
25th	11.1 (9.2, 13.1)	7.2 (5.6, 9.1)
50th	NE (19.3, NE)	14.7 (13.0, 16.5)
75th	NE (NE, NE)	21.0 (21.0, NE)

Figure 11-1 Kaplan-Meier plot of PFS based on Investigator assessment (FAS)

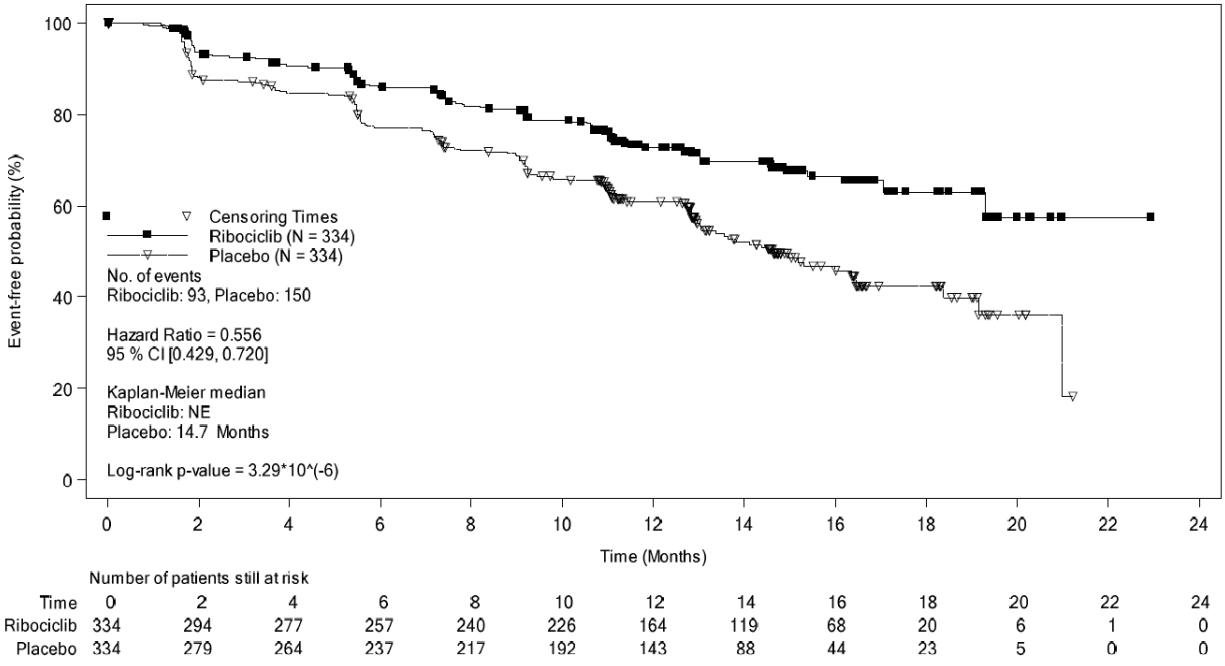


Figure 3: Kaplan-Meier plot of PFS based on investigator assessment (full analysis set, 29-Jan-2016 data cut-off)

PFS updates

- The first efficacy update (corresponding to a 22-Jun-2016 data cut-off)

This analysis was based on 297 local PFS events. The median follow-up time was 20.1 months. Median PFS was prolonged by 7.1 months, from 15.3 months (95% CI: 13.4, 16.7) in the placebo plus letrozole arm to 22.4 months (95% CI: 20.8, NE) in the ribociclib plus letrozole arm. HR 0.559; 95% CI: 0.443 - 0.706; $p=3.73\times10^{-7}$

- A second updated PFS analysis was carried out at the time of the second interim analysis for overall survival (OS) based on a data cut-off of 02-Jan-2017

Table 17: Analysis of PFS per investigator (FAS, 2-Jan-2017 cut-off)

Table 2-1 Analysis of PFS per Investigator (Full Analysis Set)

	Interim PFS analysis: 29-Jan-2016 data cut-off		Updated PFS analysis: 02-Jan-2017 data cut-off	
	Ribociclib plus letrozole	Placebo plus letrozole	Ribociclib plus letrozole	Placebo plus letrozole
	N=334	N=334	N=334	N=334
Number of PFS events – n (%)	93 (27.8)	150 (44.9)	140 (41.9)	205 (61.4)
Progression	89 (26.6)	150 (44.9)	135 (40.4)	204 (61.1)
Death before progression	4 (1.2)	0	5 (1.5)	1 (0.3)
Censored – n (%)	241 (72.2)	184 (55.1)	194 (58.1)	129 (38.6)
Median PFS (mo) (95% CI)	**NR (19.3, NE)**	**14.7 (13.0, 16.5)**	**25.3 (23.0, 30.3)**	**16.0 (13.4, 18.2)**
Improvement in median PFS (mo)	**NE**		**9.3**	
Hazard ratio (95% CI)	**0.556 (0.429, 0.720)**		**0.568 (0.457, 0.704)**	
p-value	3.29×10^{-6}		9.63×10^{-8}	

Figure 3-4 Updated Kaplan-Meier plot of PFS per Investigator: 02-Jan-2017 data cut-off (Full Analysis Set)

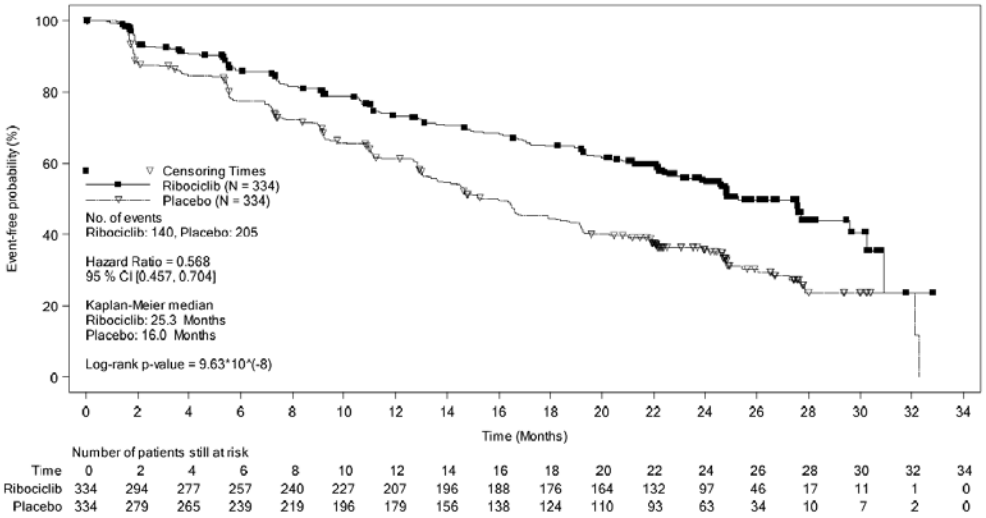


Figure 4: Kaplan-Meier plot of PFS based on investigator assessment (full analysis set, 2-Jan-2017 data cut-off)

54.7% of patients receiving ribociclib plus letrozole were estimated to be progression free at 24 months compared with 35.9% in the placebo plus letrozole arm (see SmPC 5.1).

Table 18: Summary of type of events for PFS as per local investigator's assessment, by treatment (FAS, 2-Jan-2017 cut-off)

Table 1.2-3 (Page 1 of 1)
Summary of type of events for PFS as per local investigator's assessment, by treatment
Full Analysis Set

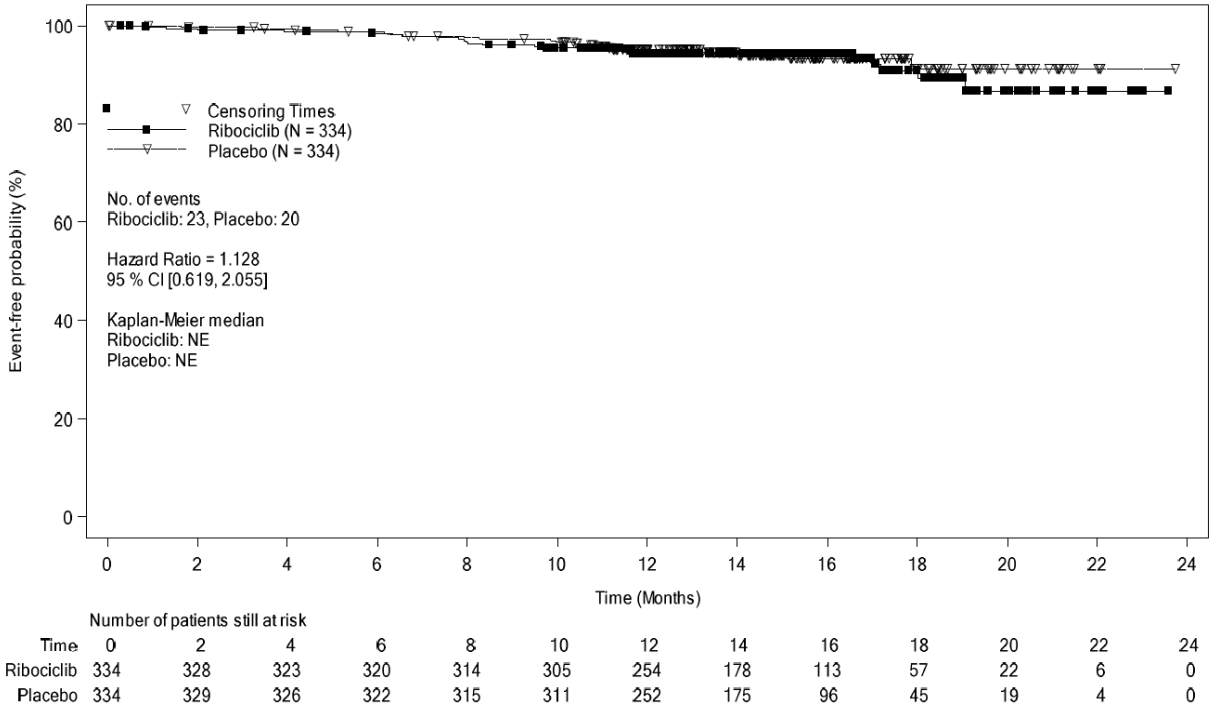
	Ribociclib 600mg + letrozole 2.5mg N=334 n (%)	Placebo + letrozole 2.5mg N=334 n (%)
No. of PFS events	140 (41.9)	205 (61.4)
PD	135 (40.4)	204 (61.1)
Death	5 (1.5)	1 (0.3)
Type of PD events		
New lesion only	71 (21.3)	94 (28.1)
Enlarged lesion only	33 (9.9)	76 (22.8)
Combination	30 (9.0)	33 (9.9)
Others	1 (0.3)	1 (0.3)
No. censored	194 (58.1)	129 (38.6)

Key secondary endpoint: overall survival

Table 19: Analysis of OS using the Kaplan-Meier method (FAS, 29-Jan-2016 data cut-off)

Category	Ribociclib + letrozole N=334	Placebo + letrozole N=334
Number of events - n (%)	23 (6.9)	20 (6.0)
Number censored - n (%)	311 (93.1)	314 (94.0)
P-value ribociclib vs. Placebo[1]	0.653	
Hazard ratio (95% CI) ribociclib vs. Placebo[2]	1.128 (0.619, 2.055)	

Figure 11-4 Kaplan-Meier plot of overall survival (FAS)



-Log-rank test and Cox model were stratified by liver and/or lung metastases status as per IRT.
Source: Figure 14.2-1.10

Figure 5: Kaplan-Meier plot of OS (full analysis set, 29-Jan-2016 data cut-off)

OS update

Table 20: Updated analysis of OS using Kaplan-Meier methodology (FAS, 02-Jan-17 cut-off)

Table 2-2 Updated analysis of OS using Kaplan-Meier methodology: 02-Jan-2017 data cut-off (Full Analysis Set)

	Ribociclib plus letrozole	Placebo plus letrozole
Overall survival (OS)	**N=334**	**N=334**
Number of events – n (%)	50 (15.0)	66 (19.8)
Number censored – n (%)	284 (85.0)	268 (80.2)
Median OS (months)	**NR**	**33.0**
95% confidence interval	**NE, NE**	**33.0, NE**
Hazard ratio	**0.746**	
95% confidence interval	**0.517, 1.078**	
p-value	0.059	

Table 21: Censoring reasons for OS (FAS, 02-Jan-17 cut-off)

Table 2-3 Censoring reasons for OS: 02-Jan-2017 data cut-off (Full Analysis Set)

Censoring reason	Ribociclib plus letrozole N=334		Placebo plus letrozole N=334	
Number censored – n (%)	284	(85.0)	268	(80.2)
Reason for censoring:				
Alive	260	(77.8)	246	(73.7)
Lost to follow-up	24	(7.2)	22	(6.6)

Figure 2-1 Updated Kaplan-Meier plot of OS: 02-Jan-2017 data cut-off (Full Analysis Set)

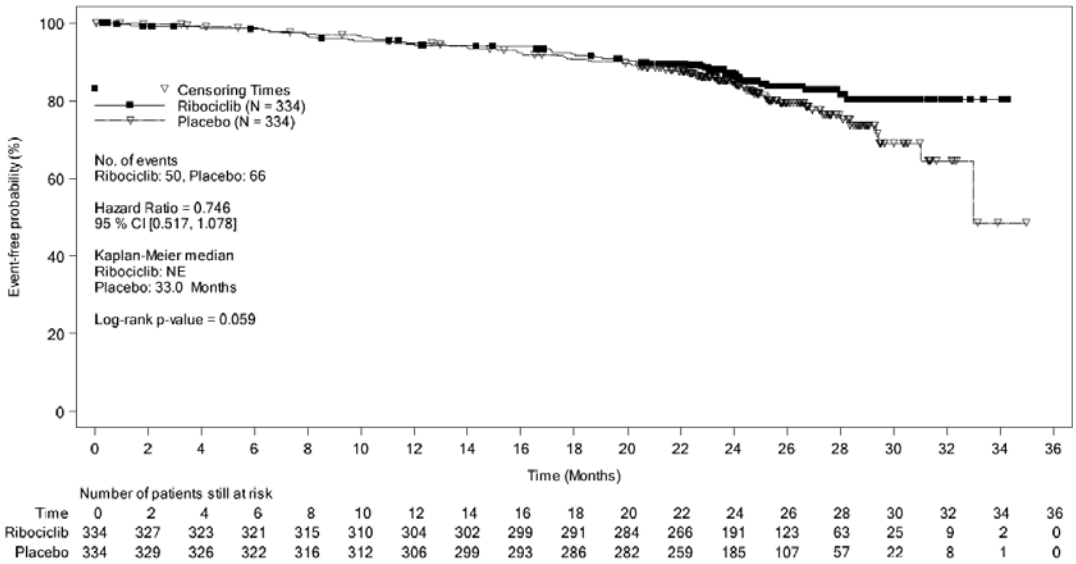


Figure 6: Kaplan-Meier plot of OS (full analysis set, 02-Jan-2017 data cut-off)

Other secondary endpoints

- The overall response rate (ORR) was 40.7% in the experimental arm, and 27.5% in the control arm, whereas the clinical benefit rate (CBR) was 79.6% in the experimental arm, and 72.8% in the control (data cut off of primary analysis). The updated analysis is presented below.

Table 22: MONALEESA-2 efficacy results (ORR, CBR) based on investigator assessment (02 January 2017 cutoff)

Analysis	Kisqali + letrozole (%, 95% CI)	Placebo + letrozole (%, 95% CI)	p-value[c]
Full analysis set	**N=334**	**N=334**	
Overall response rate[a]	42.5 (37.2, 47.8)	28.7 (23.9, 33.6)	9.18×10^{-5}
Clinical benefit rate[b]	79.9 (75.6, 84.2)	73.1 (68.3, 77.8)	0.018
Patients with measurable disease	**N=257**	**N=245**	
Overall response rate[a]	54.5 (48.4, 60.6)	38.8 (32.7, 44.9)	2.54×10^{-4}
Clinical benefit rate[b]	80.2 (75.3, 85.0)	71.8 (66.2, 77.5)	0.018

[a] ORR: Overall response rate = proportion of patients with complete response + partial response

[b] CBR: Clinical benefit rate = proportion of patients with complete response + partial response (+ stable disease or non-complete response/Non-progressive disease ≥24 weeks)

[c] p-values are obtained from one-sided Cochran-Mantel-Haenszel chi-square test

Time to deterioration of ECOG PS

Time to definitive deterioration of ECOG performance status was similar between two treatment arms, with an HR of 0.917 (95% CI: 0.640, 1.314) (one -sided p=0.319).

Patient reported outcome

The global health status/global QoL scale score of the EORTC QLQ-C30 was the primary PRO variable of interest. Physical functioning, emotional functioning and social functioning sub-scale scores of the EORTC QLQ-C30, the breast cancer symptoms scale of the EORTC QLQ-BR23, and the VAS of the EQ-5D-5L were secondary PRO variables of interest.

Overall compliance rates of patients completing the EORTC QLQ-C30 questionnaires during the treatment period were high in both treatment arms with Baseline rates 97.0% and 97.9% in ribociclib plus letrozole arm and placebo plus letrozole arm, respectively. The compliance rate was above 90% at the first post-baseline assessment and throughout the first year of treatment. Overall compliance rates of patients completing the QLQ-BR23, and EQ-5D-5L questionnaires were also high for patients on study at the time of assessment for both treatment arms during the study treatment.

Mean (SD) Baseline global health status/QOL scores from the EORTC QLQ-C30 were well balanced between treatment arms (64.5 [20.25]) and 64 [21.07]) in the ribociclib plus letrozole arm and in the placebo plus letrozole arm, respectively). Global health status/QoL scores were generally similar between the two treatment arms throughout the study; there was a slight improvement (i.e. increased) in scores for patients in both the treatment arms and the improvement was sustained over the study treatment period.

A longitudinal analysis of changes from Baseline in the global health status data of EORTC QLQ-C30 was performed by fitting a linear mixed effect model with Baseline value, stratification factors, treatment, visit time and treatment by visit time interaction factors in the model. The results revealed no significant effect of treatment, time or treatment by time interactions. The estimated mean difference in the changes in global health status/QoL scale score between the two treatment arms was -1.50 with 95% CI: (-4.0, 1.0).

Time to definitive 10% deterioration of the global health status/QOL scale (EORTC QLQ - C30) score was similar between the two treatment arms, with an HR of 0.890 (95% CI: 0.670, 1.182) slightly favouring the ribociclib plus letrozole arm.

Ancillary analyses

PFS per BIRC review

Table 23: Analysis of PFS per BIRC review using the Kaplan-Meier method (full analysis set, 29-Jan-2016 data cut-off)

Category	Ribociclib + letrozole N=334	Placebo + letrozole N=334
Number of events - n (%)	50 (15.0)	72 (21.6)
Progression	46 (13.8)	72 (21.6)
Death[1]	4 (1.2)	0
Number censored - n (%)	284 (85.0)	262 (78.4)
P-value ribociclib vs. Placebo[2]	0.002	
Hazard ratio (95% CI) ribociclib vs. Placebo[3]	0.592 (0.412, 0.852)	
Percentiles (95% CI)		
25th	22.9 (15.0,22.9)	14.5 (10.8, NE)
50th	22.9 (NE, NE)	NE (NE, NE)
75th	22.9 (NE, NE)	NE (NE, NE)

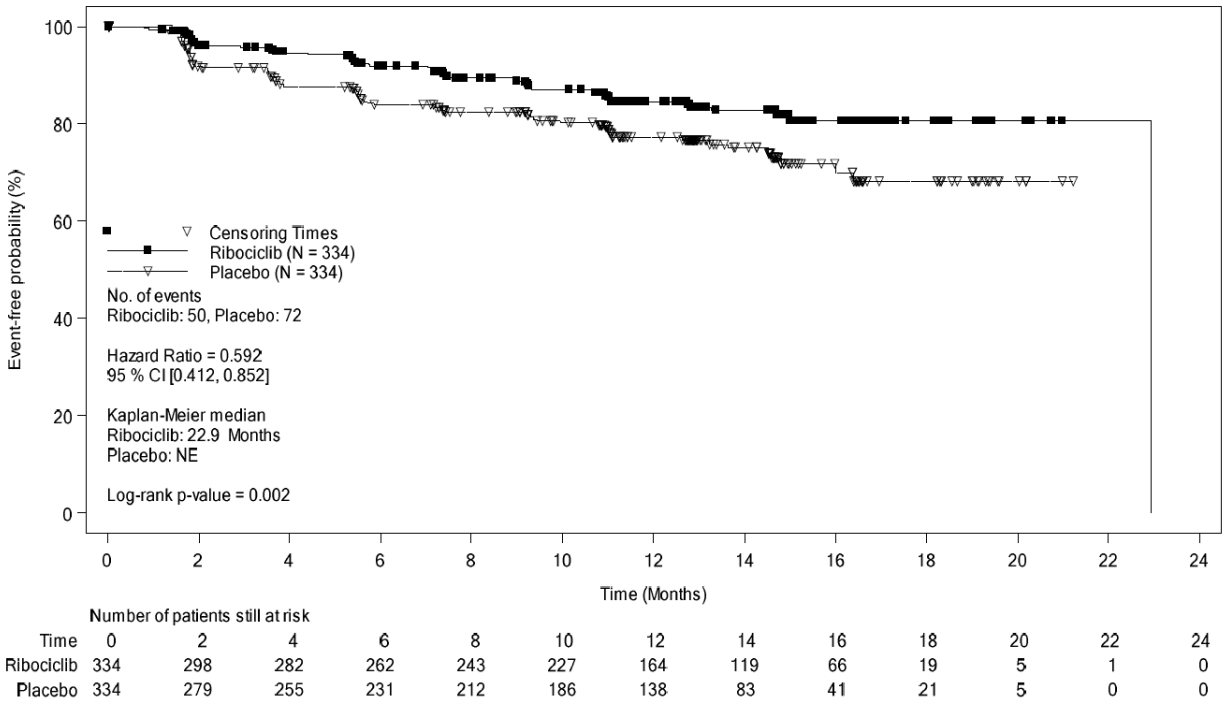


Figure 7: Kaplan-Meier plot of PFS based on central BIRC review (full analysis set, 29-Jan-2016 data cut-off)

Table 24: Summary of reasons for censoring patients in PFS per investigator assessment and BIRC review (full analysis set, 29-Jan-2016 data cut-off)

Table 11-9 Summary of reasons for censoring patients in PFS per Investigator assessment and BIRC review (Full analysis set)

	Investigator assessment		BIRC review	
	Ribociclib letrozole	Placebo + letrozole	Ribociclib + letrozole	Placebo + letrozole
	N=334	N=334	N=334	N=334
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number censored	241 (72.2)	184 (55.1)	284 (85.0)	262 (78.4)
Reason of censoring				
Ongoing without event[1]	194 (58.1)	143 (42.8)	195 (58.4)	139 (41.6)
Adequate assessment no longer available[2]	21 (6.3)	12 (3.6)	25 (7.5)	20 (6.0)
New cancer therapy added	13 (3.9)	18 (5.4)	51 (15.3)	90 (26.9)
Withdrew consent	10 (3.0)	10 (3.0)	10 (3.0)	11 (3.3)
Event documented after two or more missing tumor assessments	3 (0.9)	1 (0.3)	3 (0.9)	2 (0.6)

[1]Patients without event and had adequate follow-up as of data cut-off.
[2]Patients censored without adequate evaluations for a specified period prior to data cut-off or without adequate Baseline assessment.
Source: Table 14.2-1.13, Table 14.2-1.14.

PFS concordance between investigator assessment and BIRC reviews (29-Jan-2016 data cut-off)

The overall concordance rate (considering the proportion of patients with same PFS outcome of PD, death or censor), between the Investigator assessment and BIRC was 80.5% in ribociclib plus letrozole arm and 69.5% in placebo plus letrozole arm respectively. A similar proportion of locally assessed PDs were not confirmed by the BIRC: 54 out of 89 (60.7%) in the ribociclib plus letrozole arm and 90 out of 150 (60.0%) in the placebo plus letrozole arm.

Table 25: Comparison of PFS event type/censor and PFS date between local investigator and central BIRC, by treatment Full Analysis Set

PFS event type		Ribociclib 600mg + letrozole 2.5mg N=334 n (%)				Placebo + letrozole 2.5mg N=334 n (%)			
Investig. (INV)	Central review (BIRC)	Same time	BIRC after INV	BIRC before INV	Total	Same time	BIRC after INV	BIRC before INV	Total
PD	PD	22 (6.6)	4 (1.2)	9 (2.7)	35 (10.5)	39 (11.7)	0	21 (6.3)	60 (18.0)
Death	Death	4 (1.2)	0	0	4 (1.2)	0	0	0	0
Censor	Censor	212 (63.5)	13 (3.9)	5 (1.5)	230 (68.9)	156 (46.7)	9 (2.7)	7 (2.1)	172 (51.5)
PD	Censor	44 (13.2)	5 (1.5)	5 (1.5)	54 (16.2)	74 (22.2)	13 (3.9)	3 (0.9)	90 (26.9)
PD	Death	0	0	0	0	0	0	0	0
Death	PD	0	0	0	0	0	0	0	0
Censor	PD	7 (2.1)	0	4 (1.2)	11 (3.3)	5 (1.5)	0	7 (2.1)	12 (3.6)
Total		289 (86.5)	22 (6.6)	23 (6.9)	334 (100)	274 (82.0)	22 (6.6)	38 (11.4)	334 (100)

The most frequent reason for PD according to investigator, subsequently not confirmed by BIRC, was new or worsening bone lesion. The concordance in investigator and BIRC PD, in patients with bone lesion(s) only at baseline was investigated, and found to be lower than the overall concordance rates; approximately 75% (12 / 16 investigator PDs with bone-only disease at baseline) and 78.1% (25 / 32 investigator PDs with bone-only disease at baseline) of the PDs considered by local investigators were not subsequently confirmed by BIRC, in the ribociclib + letrozole and placebo + letrozole arms, respectively.

Early and late discordance rates between investigator and BIRC were also calculated, according to Amit O. et al. 2011:

Ribociclib + letrozole: **Early discordance rate (EDR): 65%** **Late discordance rate (LDR): 26%**	**Placebo + letrozole:** **Early discordance rate (EDR): 60%** **Late discordance rate (LDR): 27%**
Definitions according to O. Amit, F. Mannino, A.M. Stone, et. al.; European Journal of Cancer, 2011	

Table 26: Analysis of PFS per Investigator and BIRC assessments using Kaplan-Meier methodology – Full Analysis Set

Table 1-5 Analysis of PFS per Investigator and BIRC assessments using Kaplan-Meier methodology – Full Analysis Set

	Original submission: 29-Jan-2016 data cut-off				Efficacy Update: 22-Jun-2016 data cut-off			
	Investigator assessment		BIRC assessment		Investigator assessment		BIRC assessment	
	Ribociclib plus letrozole N=334	Placebo plus letrozole N=334	Ribociclib plus letrozole N=334	Placebo plus letrozole N=334	Ribociclib plus letrozole N=334	Placebo plus letrozole N=334	Ribociclib plus letrozole N=334	Placebo plus letrozole N=334
Number of PFS events - n (%)	93 (27.8)	150 (44.9)	50 (15.0)	72 (21.6)	118 (35.3)	179 (53.6)	61 (18.3)	86 (25.7)
Progression	89 (26.6)	150 (44.9)	46 (13.8)	72 (21.6)	112 (33.5)	179 (53.6)	55 (16.5)	86 (25.7)
Death[1]	4 (1.2)	0	4 (1.2)	0	6 (1.8)	0	6 (1.8)	0
Number censored - n (%)	241 (72.2)	184 (55.1)	284 (85.0)	262 (78.4)	216 (64.7)	155 (46.4)	273 (81.7)	248 (74.3)
Percentiles (95% CI)								
25th	11.1 (9.2, 13.1)	7.2 (5.6, 9.1)	22.9 (15.0, 22.9)	14.5 (10.8, NE)	11.1 (9.2, 14.6)	7.2 (5.6, 9.1)	21.9 (19.3, NE)	13.6 (9.4, 16.4)
50th	NE (19.3, NE)	14.7 (13.0, 16.5)	22.9 (NE, NE)	NE (NE, NE)	22.4 (20.8, NE)	15.3 (13.4, 16.7)	NE (22.9, NE)	NE (NE, NE)
75th	NE (NE, NE)	21.0 (21.0, NE)	22.9 (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (24.8, NE)	NE (NE, NE)	NE (NE, NE)
Kaplan-Meier estimate (95% CI)								
Month 6	85.8 (81.4, 89.2)	77.1 (72.1, 81.4)	91.8 (88.1, 94.4)	83.8 (79.1, 87.5)	85.8 (81.4, 89.3)	77.2 (72.1, 81.4)	91.5 (87.7, 94.1)	83.5 (78.8, 87.2)
Month 12	72.8 (67.3, 77.6)	60.9 (55.1, 66.2)	84.5 (79.7, 88.3)	77.3 (71.9, 81.9)	73.4 (68.1, 78.1)	61.3 (55.6, 66.5)	84.4 (79.6, 88.1)	77.0 (71.6, 81.5)
Month 18	63.0 (54.6, 70.3)	42.2 (34.8, 49.5)	80.7 (74.8, 85.4)	68.1 (59.6, 75.2)	63.5 (57.5, 69.0)	43.7 (37.8, 49.5)	80.4 (75.1, 84.6)	67.6 (61.1, 73.3)
Month 20	57.3 (43.4, 68.9)	36.1 (26.1, 46.2)	80.7 (74.8, 85.4)	68.1 (59.6, 75.2)	59.0 (52.3, 65.1)	36.7 (30.4, 43.1)	77.2 (70.8, 82.4)	66.1 (59.0, 72.2)
Month 22	57.3 (43.4, 68.9)		80.7 (74.8, 85.4)		54.2 (46.5, 61.3)	34.1 (27.3, 41.0)	73.6 (65.5, 80.2)	61.2 (51.6, 69.5)
Month 24	0	0	0	0	42.5 (30.6, 53.9)	34.1 (27.3, 41.0)	63.7 (47.6, 76.1)	61.2 (51.6, 69.5)
Months 26	0	0	0	0	42.5 (30.6, 53.9)	25.6 (12.0, 41.6)	63.7 (47.6, 76.1)	61.2 (51.6, 69.5)
p-value ribociclib vs. placebo[2]	**3.29×10^{-6}**		**0.002**		**3.73×10^{-7}**		**9.62×10^{-4}**	
Hazard ratio (95% CI) ribociclib vs. placebo[3]	**0.556 (0.429, 0.720)**		**0.592 (0.412, 0.852)**		**0.559 (0.443, 0.706)**		**0.597 (0.430, 0.830)**	

NE=not estimable
[1]Death before progression
[2]One-sided p-value obtained from log-rank test stratified by liver and/or lung metastasis as per IRT

Per protocol and sensitivity analyses

In a per protocol analysis, with 84/310 PFS events in the experimental arm and 144/311 in the control arm, findings were similar, HR 0.536, stratified log-rank test. Sensitivity analyses were also performed (see Table below).

Table 27: Overview of sensitivity analyses of PFS as per investigator (FAS)

Table 11-11 Overview of sensitivity analyses of PFS as per Investigator (FAS)

Sensitivity analysis	Median PFS (95% CI)	p-value	Hazard ratio (95% CI)
Primary analysis			
Ribociclib + letrozole	NE (19.3, NE)	$3.29x10^{-6}$	0.556 (0.429, 0.720)
Placebo + letrozole	14.7 (13.0, 16.5)		
Unstratified log-rank test and Cox PH model			
Ribociclib + letrozole	NE (19.3, NE)	$3.53x10^{-6}$	0.557 (0.430, 0.721)
Placebo + letrozole	14.7 (13.0, 16.5)		
Stratified Cox PH model, adjusting for Baseline covariates			
Ribociclib + letrozole	NE (19.3, NE)	$3.29x10^{-6}$	0.551 (0.424, 0.714)
Placebo + letrozole	14.7 (13.0, 16.5)		
Actual event			
Ribociclib + letrozole	NE (19.3, NE)	$7.00x10^{-6}$	0.571 (0.442, 0.737)
Placebo + letrozole	14.7 (13.0, 16.5)		
Backdating			
Ribociclib + letrozole	NE (19.3, NE)	$6.67x10^{-6}$	0.570 (0.441, 0.737)
Placebo + letrozole	14.7 (13.0, 16.5)		
No censoring for antineoplastic therapy			
Ribociclib + letrozole	NE (19.3, NE)	$2.82x10^{-6}$	0.557 (0.431, 0.720)
Placebo + letrozole	14.5 (13.0, 16.5)		

Source: Table 14.2-1.1, Table 14.2-1.4, Table 14.2-1.5, Table 14.2-1.6, Table 14.2-1.8, Table 14.2-1.9

Subgroup analysis of PFS, per investigator

Table 28: Analysis of PFS per Investigator by subgroup – Full Analysis Set

Exploratory subgroup analyses of PFS based on local investigator's assessment using Cox model
Full Analysis Set

Subgroup	Ribociclib 600mg + letrozole 2.5mg N=334 N	No of events/ Median	Placebo + letrozole 2.5mg N=334 N	No of events/ Median	Ribociclib vs. Placebo Cox model Hazard ratio (1)	(95% CI)
All patients	334	140 / 25.3	334	205 / 16.0	0.568	(0.457, 0.704)
Baseline ECOG performance status						
0	205	82 / 27.7	202	123 / 16.5	0.581	(0.439, 0.769)
1	129	58 / 24.6	132	82 / 14.7	0.543	(0.385, 0.766)
Age						
<65 Years	184	82 / 24.9	189	127 / 13.0	0.518	(0.392, 0.684)
>=65 Years	150	58 / 27.6	145	78 / 19.3	0.658	(0.466, 0.928)
Race						
Asian	28	14 / 23.9	23	19 / 9.2	0.370	(0.180, 0.760)
non-Asian	281	121 / 24.8	287	171 / 16.5	0.614	(0.486, 0.775)
Region						
Asia	35	13 / NE	33	27 / 11.1	0.265	(0.135, 0.520)
Europe	150	64 / 27.6	146	93 / 16.5	0.562	(0.407, 0.775)
Latin America	7	4 / 22.5	7	3 / NE	1.800	(0.381, 8.504)
North America	108	44 / 27.6	121	67 / 15.0	0.608	(0.414, 0.892)
Other	34	15 / 25.3	27	15 / 24.6	0.900	(0.423, 1.915)

Adjuvant or neoadjuvant chemotherapy						
No	188	69 / 27.6	189	102 / 19.1	0.640	(0.470, 0.871)
Yes	146	71 / 23.9	145	103 / 13.0	0.501	(0.368, 0.681)
Hormonal agent in (neo)adjuvant setting (2)						
NSAI and others	30	15 / 23.0	23	17 / 13.8	0.430	(0.205, 0.901)
None	158	62 / 27.6	162	86 / 19.1	0.651	(0.468, 0.904)
Tamoxifen and/or Exemestane	146	63 / 24.6	149	102 / 13.0	0.516	(0.376, 0.708)
Progesterone receptor status						
+	271	110 / 27.6	278	163 / 16.6	0.605	(0.475, 0.772)
-	55	27 / 21.3	49	38 / 11.1	0.369	(0.217, 0.628)
Estrogen receptor and progesterone receptor status						
++	269	109 / 27.6	277	162 / 16.6	0.606	(0.475, 0.774)
Other	65	31 / 23.0	57	43 / 12.7	0.358	(0.217, 0.591)
Number of metastasis sites						
<3	220	88 / 27.6	222	131 / 16.6	0.618	(0.471, 0.811)
>=3	114	52 / 24.6	112	74 / 12.9	0.467	(0.325, 0.671)
Liver involvement						
No	275	104 / 27.6	262	152 / 17.9	0.545	(0.424, 0.699)
Yes	59	36 / 10.7	72	53 / 11.0	0.735	(0.478, 1.129)
Lung involvement						
No	181	77 / 25.3	184	111 / 16.4	0.609	(0.455, 0.816)
Yes	153	63 / 24.9	150	94 / 14.6	0.531	(0.385, 0.731)
Liver or Lung involvement						
No	152	59 / 27.6	143	80 / 18.2	0.597	(0.426, 0.837)
Yes	182	81 / 24.8	191	125 / 13.4	0.561	(0.424, 0.743)
Bone lesion only metastasis						
No	265	114 / 24.9	256	159 / 14.6	0.551	(0.432, 0.702)
Yes	69	26 / 27.7	78	46 / 16.9	0.642	(0.393, 1.048)
De Novo						
No	220	97 / 23.9	221	144 / 14.6	0.579	(0.447, 0.749)
Yes	114	43 / 27.7	113	61 / 18.6	0.569	(0.384, 0.843)
Ki67						
<= 14%	108	41 / 29.6	109	59 / 19.5	0.623	(0.417, 0.931)
> 14%	127	60 / 24.6	125	87 / 12.8	0.478	(0.341, 0.669)
Cyclin D1						
<= 2001.6	103	42 / 27.7	100	59 / 16.0	0.533	(0.356, 0.798)
> 2001.6	95	44 / 22.9	97	64 / 14.5	0.555	(0.377, 0.818)
Total Rb by H-score						
High	208	88 / 25.3	214	131 / 15.2	0.565	(0.431, 0.743)
Low	35	17 / 23.9	28	22 / 14.7	0.529	(0.277, 1.009)
P16 mRNA by nanostring						
<= 31.5	98	40 / 27.7	104	62 / 17.9	0.583	(0.391, 0.870)
> 31.5	100	46 / 22.9	93	61 / 13.4	0.526	(0.357, 0.775)
P16 protein by H-score						
High	30	9 / NE	28	19 / 7.4	0.372	(0.161, 0.860)
Low	89	41 / 24.8	76	46 / 16.6	0.597	(0.388, 0.920)
Medium	90	36 / 27.6	95	60 / 15.2	0.521	(0.343, 0.792)

Subgroup analyses of PFS in strata defined by median expression of selected transcripts in the cyclin-CDK-RB-E2F axis

Table 29: Subgroup analysis of association of PFS vs mRNA expression levels of specified individual gene measured by NanoString technology

Biomarker subgroup	Ribociclib + letrozole			Placebo + letrozole			Ribociclib + letrozole vs. placebo + letrozole
	n	No of events	Median PFS	n	No of events	Median PFS	HR (95% CI)
CCNA2 high (>170.7)	101	30	NE	104	61	11.07	0.411 (0.264,0.640)
CCNA2 low (≤ 170.7)	106	28	NE	99	34	20.99	0.773 (0.466,1.282)
CCND1 high (>2001.6)	105	30	NE	100	48	14.13	0.597 (0.375,0.950)
CCND1 low (≤ 2001.6)	102	28	NE	103	47	15.97	0.497 (0.309,0.798)
CCND2 high (>265.8)	109	30	NE	96	48	13.37	0.461 (0.291,0.730)
CCND2 low (≤ 265.8)	98	28	NE	107	47	15.97	0.637 (0.397,1.023)
CCND3 high (>258.9)	107	33	NE	98	54	12.85	0.469 (0.303,0.726)
CCND3 low (≤ 258.9)	100	25	NE	105	41	16.36	0.635 (0.385,1.048)
CCNE1 high (>45.7)	103	33	NE	102	59	12.71	0.454 (0.295,0.697)
CCNE1 low (≤ 45.7)	104	25	NE	101	36	20.99	0.689 (0.412,1.151)
CDK2 high (>136.4)	102	34	NE	103	60	12.85	0.508 (0.332,0.779)
CDK2 low (≤ 136.4)	105	24	NE	100	35	NE	0.603 (0.358,1.017)
CDK4 high (>433.2)	106	32	NE	99	53	12.85	0.476 (0.305,0.745)
CDK4 low (≤ 433.2)	101	26	NE	104	42	20.99	0.586 (0.357,0.963)
CDK6 high (>107.3)	99	30	NE	106	52	13.04	0.527 (0.334,0.832)
CDK6 low (≤ 107.3)	108	28	NE	97	43	16.36	0.546 (0.338,0.883)
CDKN1A high (>404.6)	105	31	NE	100	55	13.01	0.458 (0.293,0.717)
CDKN1A low (≤ 404.6)	102	27	NE	103	40	20.99	0.655 (0.400,1.072)
CDKN2A high (>31.5)	106	33	NE	99	49	13.37	0.568 (0.364,0.886)
CDKN2A low (≤ 31.5)	101	25	NE	104	46	15.97	0.522 (0.320,0.853)
CDKN2B high (>178.2)	111	34	NE	94	42	15.97	0.674 (0.426,1.065)
CDKN2B low (≤ 178.2)	96	24	NE	109	53	13.63	0.447 (0.276,0.725)
CDKN2C high (>182.0)	103	32	NE	102	55	12.98	0.502 (0.323,0.780)
CDKN2C low (≤ 182.0)	104	26	NE	101	40	16.36	0.608 (0.371,0.997)
E2F1 high (>106.7)	101	32	NE	104	62	11.43	0.463 (0.301,0.713)
E2F1 low (≤ 106.7)	106	26	NE	99	33	NE	0.725 (0.433,1.214)
E2F3 high (>95.3)	103	30	NE	102	61	11.04	0.379 (0.244,0.589)
E2F3 low (≤ 95.3)	104	28	NE	101	34	20.99	0.860 (0.519,1.424)
RB1 high (>311.3)	102	28	NE	103	56	12.98	0.438 (0.277,0.692)
RB1 low (≤ 311.3)	105	30	NE	100	39	20.99	0.718 (0.444,1.163)
TFDP1 high (>417.7)	100	26	NE	105	56	12.98	0.420 (0.263,0.671)
TFDP1 low (≤ 417.7)	107	32	NE	98	39	15.97	0.743 (0.464,1.190)

Low and high levels of mRNA expression was defined by median cut-off for each gene.
NE=not estimable
(1) Median (time to event) are generated by Kaplan-Meier survival method.
(2) Cox PH model is stratified by liver and/or lung metastasis status as per IRT.
(3) Hazard Ratio for Ribociclib 600mg + letrozole 2.5mg versus Placebo + letrozole 2.5mg.

- First subsequent antineoplastic therapy

Table 30: First subsequent antineoplastic therapy by medication type (2 Jan 2017 cut off)

Characteristic	Ribociclib + letrozole N=334 n (%)	Placebo + letrozole N=334 n (%)
Patients discontinued study treatment	203	246
Any antineoplastic therapy	172 (84.7)	212 (86.2)
Chemotherapy	32 (15.8)	55 (22.4)
Chemotherapy + other [1]	7 (3.4)	8 (3.3)
Hormonal therapy alone	90 (44.3)	87 (35.4)
Hormonal therapy + targeted therapy/other [2]	37 (18.2)	58 (23.6)
Targeted therapy alone	6 (3.0)	2 (0.8)
Other	0	2 (0.8)

Denominator=number of patients who discontinued study treatment

[1] include patients who received chemotherapy + hormonal therapy

[2] include patients who received hormonal therapy + targeted therapy + other

Figure 2-1 Kaplan-Meier plot of time to first subsequent line of antineoplastic therapy (02-Jan-2017 data cut-off)

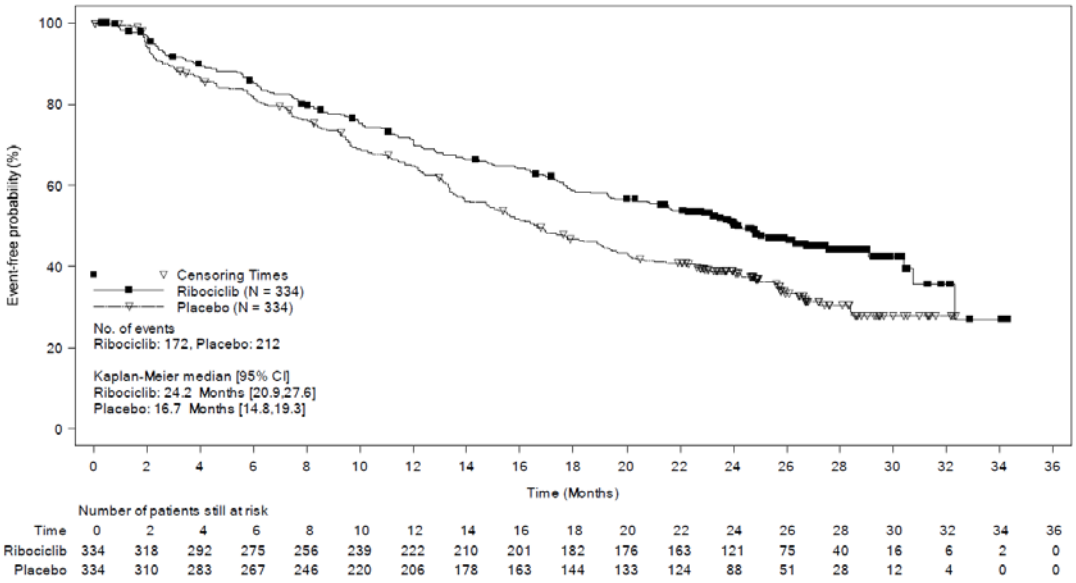


Figure 8: Kaplan-Meier of time to first subsequent antineoplastic therapy by medication type (2 Jan 2017 cut off)

- Second subsequent antineoplastic therapy

Table 31: Second subsequent antineoplastic therapy by medication type (2 Jan 2017 cut off)

Characteristic	Ribociclib + letrozole N=334 n (%)	Placebo + letrozole N=334 n (%)
Patients discontinued study treatment	203	246
Any antineoplastic therapy	45 (22.2)	68 (27.6)
Chemotherapy	20 (9.9)	36 (14.6)
Chemotherapy + other[1]	4 (2.0)	7 (2.8)
Hormonal therapy alone	6 (3.0)	11 (4.5)
Hormonal therapy + targeted therapy[2]	12 (5.9)	11 (4.5)
Targeted therapy alone	2 (1.0)	2 (0.8)
Other	1 (0.5)	1 (0.4)

Denominator= number of patients who discontinued study treatment

[1] include patients who received chemotherapy + hormonal therapy

[2] include patients who received hormonal therapy + targeted therapy + other

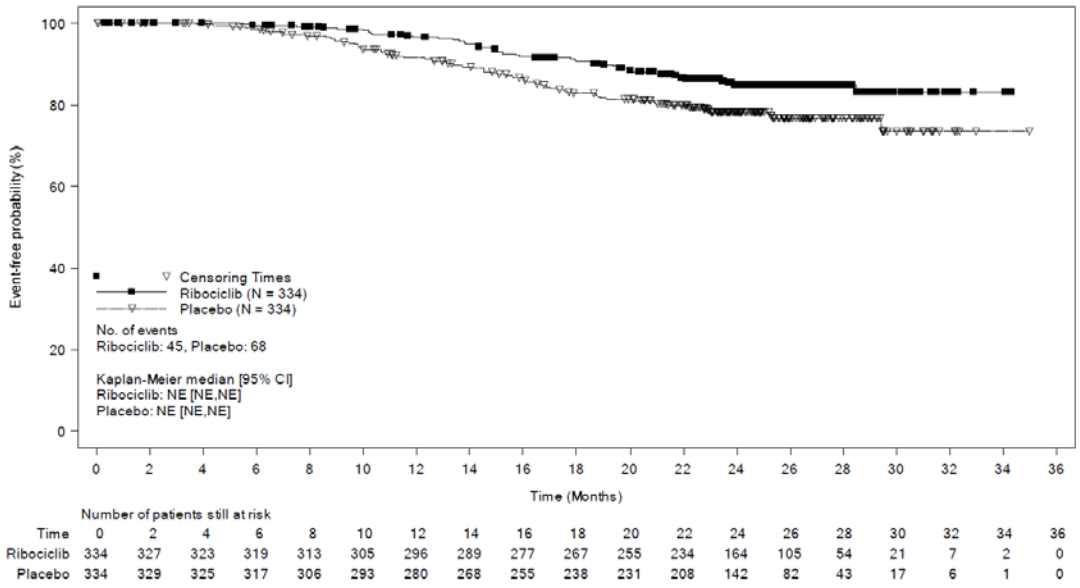


Figure 9: Kaplan-Meier plot of time to second subsequent line of antineoplastic therapy (2 Jan 2017)

- Time since treatment discontinuation to time to disease progression or death for patients discontinuing study treatment for reasons other than disease progression or death.

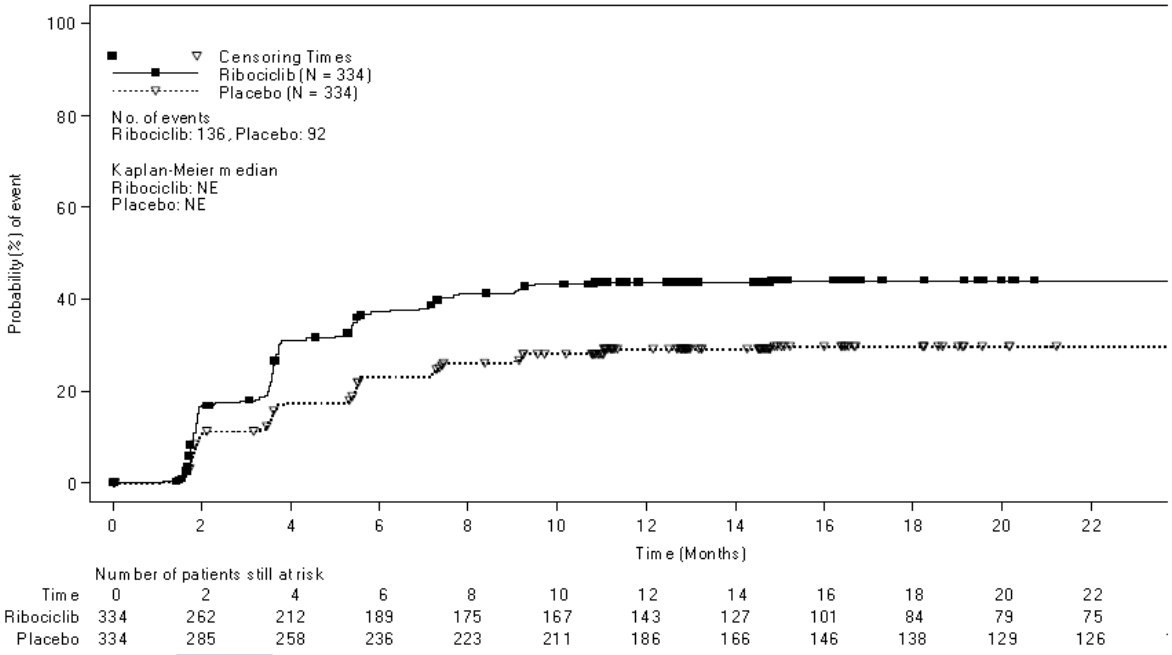
Table 32: Patients in post-treatment follow-up (2 Jan 2017 cut off)

Disposition Reason	Ribociclib plus letrozole N=334 n (%)	Placebo plus letrozole N=334 n (%)	All patients N=668 n (%)
Patients discontinued the study treatment for reasons other than disease progression or death [1]	66 (19.8)	42 (12.6)	108 (16.2)
Entered post-treatment follow-up [2]	18 (27.3)	7 (16.7)	25 (23.1)
Discontinued from post-treatment follow-up [3]	6 (33.3)	4 (57.1)	10 (40.0)
Reason for end of post-treatment follow-up[4]			
Death	0	1 (25.0)	1 (10.0)
Progressive disease	4 (66.7)	3 (75.0)	7 (70.0)
Subject/guardian decision	2 (33.3)	0	2 (20.0)
Time to disease progression/death since discontinuation of study treatment	m=4	m=4	m=8
Median (min, max) (months)	5.9 (0.8, 12.0)	3.3 (0.3, 12.4)	5.5 (0.3, 12.4)

[1] All percentages in this section use the number randomized as the denominator.
[2] The percentages of patients who entered post-treatment follow-up use the number discontinued from treatment as the denominator
[3] Patients who entered and then discontinued from the post-treatment follow-up phase at the end of post-treatment follow-up. In this section the denominator=the number of patients who entered post-treatment follow-up.
[4] In this section the denominator= the number of patients who discontinued from post-treatment follow-up

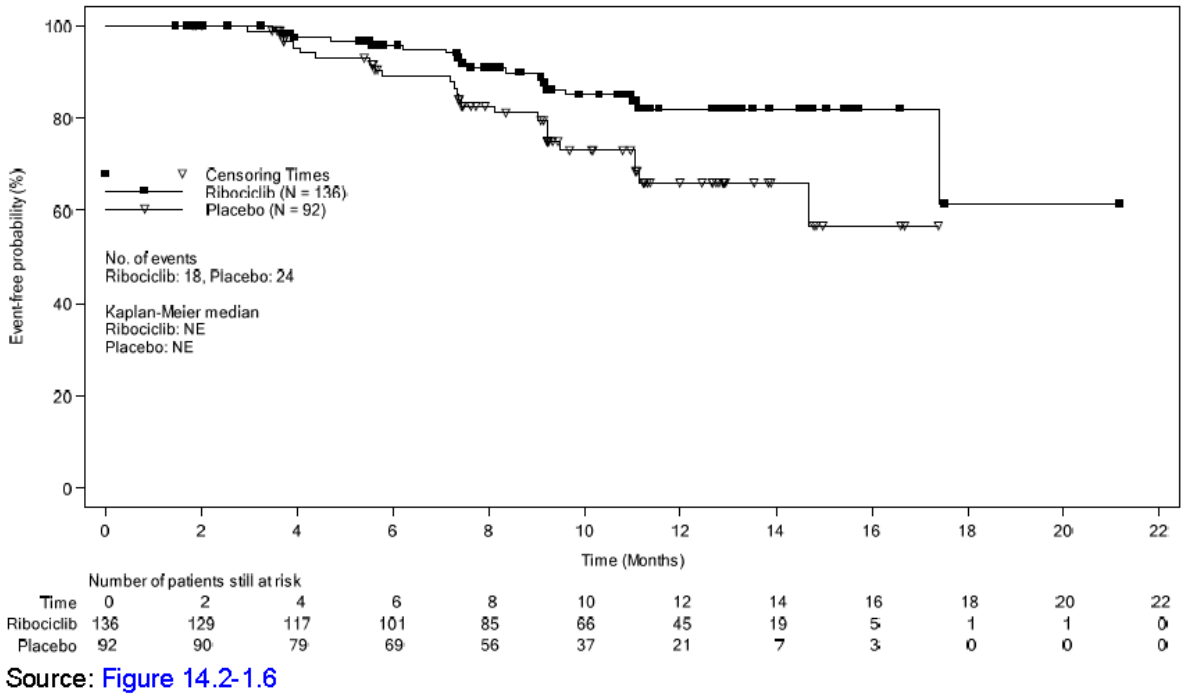
Exploratory endpoints

Time-to-response and duration of response



Source: Figure 14.2-1.5

Figure 10: Kaplan-Meier plot of time to response per Investigator assessment by treatment (FAS)



Source: Figure 14.2-1.6

Figure 11: Kaplan-Meier plot of duration of response per Investigator assessment by treatment (FAS)

Effect on estradiol suppression

The effect on estradiol (E2) suppression relative to baseline with or without co-administration with ribociclib was investigated. The proportion of values below the lower limit of quantitation were 11% in both arms at baseline and comparable – 98% and 94% in the ribociclib plus letrozole and letrozole arms, respectively – at day 15, cycle 1.

H-scores (pRb and p16) and Ki67

Total of 479 Baseline samples (241 in the ribociclib plus letrozole arm and 238 in the placebo plus letrozole arm) and 405 Baseline samples (208 in the ribociclib plus letrozole arm and 197 in the placebo plus letrozole arm) were evealuated for pRb and p16 by IHC (immunohistochemistry) respectively. The mean H-score for the total Rb was similar between the ribociclib plus letrozole and placebo plus letrozole arm (166 vs 167, respectively) and the mean H-score for total p16 was similar in both ribociclib plus letrozole and placebo plus letrozole arms (76.8 vs 82.4, respectively). Total of 463 Baseline samples (234 in the ribociclib plus letrozole arm and 229 in the placebo plus letrozole arm) were assessed for Ki67 by IHC. The mean percentage of cells positive for Ki67 from tissue was similar between the two treatment arms (20.1 vs 19.3, respectively).

mRNA expression of CCND1 and CDKN2A

Total of 410 Baseline samples (207 in the ribociclib plus letrozole arm and 203 in the placebo plus letrozole arm) were evaluated for levels of mRNA expression for CCND1 (Cyclin D1) and CDKN2A (p16) by Nanostring technology. The mean PCN count measuring the levels of mRNA expression for CCND1 (Cyclin D1) and CDKN2A (p16) in the ribociclib plus letrozole arm and in the placebo plus letrozole arm were:

- Cyclin D1: 3860 and 4250, respectively

- P16: 38.7 and 45.7, respectively

Summary of main study

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

Table 33: Summary of efficacy for trial CLEE011A2301 (MONALEESA-2)

Title: A randomized double-blind, placebo-controlled study of LEE011 in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer, who received no prior therapy for advanced disease.			
Study identifier	CLEE011A2301 (MONALEESA-2)		
Design	International, multi-center, randomized, double-blinded, placebo-controlled Phase III study. Randomization 1:1 to either ribociclib (600 mg once daily, days 1-21 in a 28-day cycle) plus letrozole (2.5 mg once daily) or placebo (once daily, days 1-21 in a 28-day cycle) plus letrozole (2.5 mg once daily). Randomization was stratified by the presence of liver and/or lung metastases (yes versus no). Treatment crossover from placebo to ribociclib was not permitted in this study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	not applicable not applicable not applicable	
Hypothesis	Superiority in PFS for the ribociclib plus letrozole vs. letrozole alone arm. Currently, results of an interim analysis are reported after 243 events. The final PFS analysis will be conducted after 302 events.		
Treatments groups	Arm A (Investigational arm)	Ribociclib (600 mg once daily, days 1-21 of a 28-day cycle) + letrozole (2.5 mg once daily, days 1-28 of a 28-day cycle). 334 patients randomized.	
	Arm B (Comparator arm)	Placebo (once daily, days 1-21 of a 28-day cycle) + letrozole (2.5 mg once daily days 1-28 of a 28-day cycle continuously). 334 patients randomized.	
Endpoints and definitions	Primary endpoint	PFS	Progression-free survival as assessed by the investigators
	Secondary endpoints	OS ORR CBR ECOG Safety QoL	Overall survival Overall response rate Clinical benefit rate Time to deterioration of performance (ECOG) status Safety and tolerability Quality of life
	Exploratory endpoints	Time to response, duration of response, exposure for ribociclib and letrozole, effects on estradiol suppression for combination vs. monotherapy, exposure-response relationship, hospital resource utilization, signaling pathway alterations, circulating DNA, mechanisms of resistance.	

Database lock	29 January 2016 (primary PFS analysis); 31 January 2017 (2nd interim OS analysis)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population		
Descriptive statistics and estimate variability	Treatment group	Ribociclib plus letrozole	Placebo plus letrozole
	Number of subjects	334	334
	PFS, investigator (median) [months]	NE	14.7
	95% CI of median PFS [months]	(19,3 – NE)	(13.0 – 16.5)
	PFS, BIRC (median) [months]	22.9	NE
	95% CI of median PFS [months]	(NE – NE)	(NE – NE)
	OR (OR rate) [%]	40.7	27.5
	95% CI of OR rate [%]	(35.4 – 46.0)	(22.8 – 32.3)
	OS (median) [months]	NE	NE
	95% CI of median PFS [months]	(NE – NE)	(NE – NE)
Effect estimate per comparison	**PFS investigator** (primary endpoint)	Comparison groups	Ribociclib + letrozole vs. placebo + letrozole
		Hazard ratio (HR)	0.556
		95% CI of HR	0.429 – 0.720
		P-value	0.00000329
	PFS, BIRC (supportive analysis)	Comparison groups	Ribociclib + letrozole vs. placebo + letrozole
		Hazard ratio (HR)	0.592
		95% CI of HR	0.412 – 0.852
		P-value	0.002
	OR (secondary endpoint)	Comparison groups	Ribociclib + letrozole vs. placebo + letrozole
		Difference (absolute %)	13.2
		95% CI of difference*	6.1 – 20.3
		P-value	0.000155

	OS (key secondary endpoint)	Comparison groups	Ribociclib + letrozole vs. placebo + letrozole
		Hazard ratio (HR)	1.128
		95% CI of HR	0.619 – 2.055
		P-value	0.653
Notes	NE= Not estimable * normal approximation		
Analysis description	**Other, Updated analysis with Data Cut-off Date of January 2, 2017**		
Analysis population and time point description	**Intent-to-Treat population**		
Descriptive statistics and estimate variability	Treatment group	Ribociclib plus letrozole	Placebo plus letrozole
	Number of subjects	334	334
	PFS, investigator (median) [months]	25.3	16.0
	95% CI of median PFS [months]	(23.0 – 30.3)	(13.4 – 18.2)
	OR (OR rate) [%]	42.5	28.7
	95% CI of OR rate [%]	(37.2– 47.8)	(23.9 – 33.6)
	OS (median) [months]	NE	33.0
	95% CI of median PFS [months]	(NE – NE)	(33.0 – NE)
Effect estimate per comparison	**PFS investigator** (primary endpoint)	Comparison groups	Ribociclib + letrozole vs. placebo + letrozole
		Hazard ratio (HR)	0.568
		95% CI of HR	0.457 – 0.704
		P-value	0.0000000963
	OR (secondary endpoint)	Comparison groups	Ribociclib + letrozole vs. placebo + letrozole
		P-value	0.0000918
	OS (key secondary endpoint)	Comparison groups	Ribociclib + letrozole vs. placebo + letrozole
		Hazard ratio (HR)	0.746
		95% CI of HR	0.517 – 1.078
		P-value	0.059
Notes	NE= Not estimable		

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)		Age 75-84 (Older subjects number /total number)		Age 85+ (Older subjects number /total number)	
Controlled Trials (A2301)	RIBO + LET 115/334	PBO + LET 111/334	RIBO + LET 32/334	PBO + LET 32/334	RIBO + LET 3/334	PBO + LET 2/334
	226/668		64/668		5/664	
Non Controlled Trials (X2107)	9/47		2/47		0/47	

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose-response studies

The ribociclib dose was escalated in studies CLEE011X1101 (400 mg and 600 mg) and CLEE011X2101 (50 mg to 1200 mg). The maximum tolerated dose (MTD) of ribociclib was 900 mg and the recommended dose was declared as 600 mg due to the acceptable safety profile, which included a lower risk for QTcF prolongation (as asymptomatic QTcF prolongation was seen more frequently at higher doses), adequate exposure, and preliminary evidence of clinical activity. In the expansion phase of Arm 1 of the CLEE011X2107 study in which ribociclib was administered in the 600 mg dose, one patient (3.6%) had a CR and 10 patients (35.7%) had a PR; overall response rate was 39.3%. It supports efficacy in the target population, similar to that of the pivotal study CLEE011A2301.

Main study

Evidence supporting efficacy for ribociclib largely derives from the pivotal CLEE011A2301 trial. This was a randomised double-blind, placebo-controlled phase 3 study of ribociclib (LEE011) in combination with letrozole intended for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease. Patients were randomly assigned in a 1:1 ratio to either ribociclib (600 mg once daily, days 1-21 in a 28-day cycle) plus letrozole (2.5 mg once daily) OR placebo (once daily, days 1-21 in a 28-day cycle) plus letrozole (2.5 mg once daily). Randomisation was stratified by the presence of liver and/or lung metastases (yes versus no). The trial design is considered acceptable.

Locally advanced or metastatic breast cancer patients derive benefit mainly from systemic treatments. For the targeted population, endocrine therapies such as letrozole, anastrozole, exemestane, fulvestrant and tamoxifen are used as 1st line options. The choice of an add-on therapy to letrozole is considered acceptable.

In scientific advice provided in November 2014 (EMEA/H/SA/2912/1/2014/II), PFS was accepted as a primary outcome measure. It was assumed that patients would be followed not only for survival, but also for PFS2 in line with the Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4).

The scientific advice was however received too late to be implemented in Study A2301; PFS2 data are therefore unavailable.

In the absence of PFS2 data, assessments of time to 1st and 2nd subsequent lines of anti-neoplastic therapy following treatment discontinuation were made, as well as time since treatment discontinuation to time to disease progression or death for patients discontinuing study treatment for reasons other than disease progression or death. This is considered acceptable.

Within a study protocol amendment the sample size was increased from initially planned 500 patients to 650 patients in order to better characterize the effect of ribociclib and letrozole on overall survival. The increased total sample size had an impact on the power and the timing of the analyses but there were no changes in any of the efficacy assumptions made. Statistical methods and planned analyses are overall acceptable.

In terms of baseline data, there were small imbalances in baseline demographic data, disease characteristics and prior therapy but these are not considered likely to affect the overall study results.

Efficacy data and additional analyses

In the pivotal CLEE011A2301 trial, the preplanned interim analysis for outstanding efficacy met the stopping boundary, with 243 (36%) investigator PFS events in 668 patients, a HR of 0.556, and a one-sided log-rank p-value of 0.00000329. The estimated placebo + letrozole median PFS was 14.7 months, whereas the median for ribociclib+letrozole was not reached (data cut off 29 Jan 2016).

The blinded independent review committee identified considerably fewer progression events than the investigators. In about 60% of cases, PD by investigator was not confirmed in BIRC review, a tendency that was balanced between treatment arms (60% experimental arm, 61% control arm). There was no indication of bias between arms in the investigators' review. This was further supported by the balanced early and late discordance rates. Also, the hazard ratio was unaffected despite considerably fewer PFS events; with 122 (18%) BIRC PFS events in 668 patients, the HR was 0.592, and the one-sided log-rank p-value 0.002.

Several sensitivity analyses were conducted, including a per protocol analysis, an 'actual event analysis' (date of progression was accepted even after two or more missing tumour assessments), a 'backdating' approach (date of next scheduled assessment was used as PFS event date whenever it occurred after missing tumour assessment), and a 'no censoring for antineoplastic therapy' approach (patients were not censored if next line therapy had been initiated prior to progression). These variations had limited effects on the number of events vs. censorings, and hazard ratios were unaffected.

In an updated PFS analysis, carried out at the time of the second interim analysis for overall survival (data cut-off of 02-Jan-2017), with an increase in PFS event rate to 42% (experimental arm) and 61% (control arm), there was no significant change in hazard ratio or medians (HR 0.57; median PFS placebo + letrozole 16 months; median PFS ribociclib + letrozole 25 months).

The previously very immature OS findings are still immature with 15% and 20% events in the experimental and control arms (data cut-off of 02-Jan-2017), with a trend towards benefit for the experimental arm (HR 0.75; 0.52 – 1.1). Accordingly, there is no indication of a detrimental effect of adding ribociclib to letrozole in poor prognosis patients in the target population. The final CSR for CLEE011A2301/MONALEESA-2 is expected by Q4 2021.

Considering time to progression and prolongation of PFS for first-line endocrine options ranging from 5 - 15 months, a 9 month increase in median PFS over letrozole is of important clinical relevance. This can be put in further perspective by comparing findings to those of the PALOMA-2 trial, targeting the same 1st line

hormone receptor positive, HER2-negative patient population, utilizing a CDK4/6 inhibitor (Study PALOMA 2: investigator PFS median 24.8 months for palbociclib+letrozole vs 14.5 months for letrozole+placebo; HR 0.567; see Ibrance EPAR).

In subgroup analyses, there was no convincing difference in effect on PFS in relation to potential CDK-signaling linked molecules (Cyclin D1, Rb, P16). Loss of Rb function and other perturbations of the cyclin-CDK-RB-E2F pathway may however be more relevant for ER negative breast cancer cells.

The applicant collected baseline (pre-treatment) FFPE (formalin-fixed, paraffin-embedded) tumor tissue and circulating tumor DNA, as well as end-of-treatment tumor biopsies (few; < 10) and ctDNA (about 70% collection rate) to find biomarkers predictive of ribociclib efficacy, and also to understand mechanisms of resistance. These data will be provided post-approval together with the CSR of study CLEE011A2301/MONALEESA-2 (see RMP).

A series of pre specified subgroup PFS analyses was performed based on prognostic factors and baseline characteristics to investigate the internal consistency of treatment effect. A reduction in the risk of disease progression or death in favour of the ribociclib plus letrozole arm was observed in all individual patient subgroups of age, race, prior adjuvant or neo adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone only metastatic disease. This was evident for patients with liver and/or lung metastases (HR of 0.561 [95% CI: 0.424, 0.743], median progression free survival [mPFS] 24.8 months for ribociclib plus letrozole versus 13.4 months for letrozole alone), or without liver and/or lung metastases (HR of 0.597 [95% CI: 0.426, 0.837], mPFS 27.6 months versus 18.2 months) (see SmPC section 5.1).

The efficacy and safety of ribociclib have not been studied in patients with critical visceral disease (see SmPC section 4.4)

The differential rate (ORR and CBR) between arms was consistent with a PFS gain. There was no difference in the analysis of time to definitive deterioration by ECOG performance status.

Results of the SAP-specified QoL analyses of change from baseline and time to definitive 10% deterioration in the global health status score indicated a slight benefit for letrozole control arm during treatment, whereas deterioration was somewhat faster in this arm, likely reflecting disease progression. Overall, the global health status/QoL data showed no relevant difference between the Kisqali plus letrozole arm and the placebo plus letrozole arm (see SmPC section 5.1).

With regards to exploratory objectives, the observed slightly larger proportion of values with estradiol suppression below the LLOQ in the ribociclib plus letrozole is deemed a non-significant confounder of the PFS gain in ribociclib plus letrozole patients.

At the time of (data) cut-off (29-Jan-2016) more patients were still on treatment in the ribociclib and letrozole arm, 195/334 (58.4%), compared to the placebo and letrozole arm, 154/334 (46.1%). The primary reason for “end of treatment” was progressive disease with more patients in the placebo arm discontinuing study treatment due to progression (Investigator decision). In the updated analysis (data cut-off 02-Jan-2017), a higher proportion of patients discontinued treatment; in the ribociclib arm 60.8% (203/334) and in the placebo arm 72.5% (242/334). The proportions of patients discontinuing due to progression were very similar to the previous analysis and as such seemingly continue to support the efficacy of ribociclib on disease progression.

In addition the Applicant was asked to present analyses (using Kaplan-Meier curves) of time to end of treatment per treatment group irrespective of reason and time to end of treatment per treatment group for reasons other than progressive disease and death. In the updated analysis (data cut-off 02-Jan-2017) there

was a difference between treatments in favour of ribociclib in time to end of treatment irrespective of reason due to the difference in patients diagnosed with progressive disease being the main reason for treatment discontinuation. Median time on treatment was 20.3 and 13.7 months in the ribociclib and placebo arm respectively. The median PFS in the updated analysis was 25.3 and 16.0 months in the ribociclib and placebo arm respectively. In considering treatment discontinuation (irrespective of reason) as treatment failure the true difference in treatment efficacy may hence be smaller. In the analysis of time to treatment discontinuation for reasons other than progressive disease or death, the difference was in favour of placebo and comparing the number of events corresponds to the difference in number of patents who discontinued due to an AE.

2.5.4. Conclusions on the clinical efficacy

The size of the PFS benefit, as demonstrated for ribocilib in the CLEE011A2301/MONALEESA-2 trial, is statistically significant and clinically relevant. The results appear robust as shown by the results from the BIRC data, and are supported by the sensitivity analyses as well as subgroup analyses. With a PFS event rate of 52%, the effect appears stable, and OS results are supportive with a 17% event rate. A trend towards OS benefit and analysis of time to 1st and 2nd subsequent lines of therapy give no indication of an accelerated disease course post progression in ribociclib-treated patients.

The final CSR for CLEE011A2301/MONALEESA-2 is expected by Q4 2021 to address long term use (see RMP). Biomarker results relevant for efficacy and mechanisms of resistance in CLEE011A2301/MONALEESA-2 will also be provided.

2.6. Clinical safety

Patient exposure

In Study A2301, exposure to ribociclib + letrozole was considered to be appropriate to allow for an informed assessment of the safety profile of ribociclib + letrozole. The overall safety evaluation of ribociclib is based on data from 898 patients. A total of 568 subjects have been exposed to ribociclib at the proposed dose i.e. 600 mg QD on Days 1-21 of a 28-day cycle. This number includes the in total 381 patients that have received ribociclib in combination with letrozole at 2.5 mg QD in the pivotal study A2301 (n=334) and the open-label, Phase Ib/II, dose-finding study X2107 study (n=47).

- In Study A2301, 334 patients received treatment with ribociclib + letrozole and 330 patients received placebo + letrozole. The median exposure to study treatment was 13.0 months in the ribociclib + letrozole group and 12.4 months in the placebo + letrozole group with the median exposure to ribociclib at 12.2 months and placebo at 12.4 months.

- In Study X2107, 47 were treated with ribociclib + letrozole and the overall median duration of exposure to ribociclib 600 mg was 7.3 months (3.6 months for the dose escalation phase and 8.3 months for the dose expansion phase).

- Contributing further to the safety evaluation of ribociclib 600 mg is the monotherapy pool (N=187) with three single-agent studies (Study X2101, Study XUS03, and Study X1101).

The median duration of exposure to ribociclib 600 mg was 1.6 months.

Table 34: Duration of exposure to study treatment - combination therapy (Safety set)

	Study A2301						Study X2107			Pooled combination therapy		
	Study treatment		RIBO/PBO		LET		Study treatment	RIBO	LET	Study treatment	RIBO	LET
	RIBO+ LET N=334	PBO+ LET N=330	RIBO+ LET N=334	PBO+ LET N=330	RIBO+ LET N=334	PBO+ LET N=330	RIBO+ LET N=47	RIBO+ LET N=47	RIBO+ LET N=47	RIBO+ LET N=381	RIBO+ LET N=381	RIBO+ LET N=381
Total number of patients received component-n (%)	**334 (100)**	**330 (100)**	**334 (100)**	**330 (100)**	**334 (100)**	**330 (100)**	**47(100)**	**47 (100)**	**47 (100)**	**381 (100)**	**381 (100)**	**381 (100)**
Exposure categories (months) – n (%)												
< 3	40 (12.0)	47 (14.2)	54 (16.2)	48 (14.5)	40 (12.0)	47 (14.2)	12 (25.5)	12 (25.5)	12 (25.5)	52 (13.6)	66 (17.3)	52 (13.6)
3 - < 6	33 (9.9)	28 (8.5)	41 (12.3)	28 (8.5)	33 (9.9)	28 (8.5)	7 (14.9)	8 (17.0)	7 (14.9)	40 (10.5)	49 (12.9)	40 (10.5)
6 - < 9	21 (6.3)	31 (9.4)	22 (6.6)	40 (12.1)	21 (6.3)	31 (9.4)	12 (25.5)	12 (25.5)	12 (25.5)	33 (8.7)	34 (8.9)	33 (8.7)
9 - < 12	46 (13.8)	49 (14.8)	45 (13.5)	41 (12.4)	46 (13.8)	49 (14.8)	9 (19.1)	8 (17.0)	9 (19.1)	55 (14.4)	53 (13.9)	55 (14.4)
12 - < 15	83 (24.9)	91 (27.6)	75 (22.5)	91 (27.6)	83 (24.9)	91 (27.6)	2 (4.3)	3 (6.4)	2 (4.3)	85 (22.3)	78 (20.5)	85 (22.3)
15 - < 18	67 (20.1)	56 (17.0)	58 (17.4)	54 (16.4)	67 (20.1)	56 (17.0)	5 (10.6)	4 (8.5)	5 (10.6)	72 (18.9)	62 (16.3)	72 (18.9)
≥ 18	44 (13.2)	28 (8.5)	39 (11.7)	28 (8.5)	44 (13.2)	28 (8.5)	0	0	0	44 (11.5)	39 (10.2)	44 (11.5)
Exposure (months)												
Mean (SD)	11.8 (5.71)	11.1 (5.48)	10.9 (6.09)	10.9 (5.53)	11.8 (5.71)	11.1 (5.49)	7.4 (4.56)	7.2 (4.61)	7.4 (4.55)	11.3 (5.76)	10.4 (6.05)	11.3 (5.76)
Median	13.0	12.4	12.2	12.4	13.0	12.4	7.3	7.1	7.3	12.3	11.6	12.3
Min, Max	0, 23	0, 22	0, 23	0, 22	0, 23	0, 22	2, 17	1, 17	2, 17	0, 23	0, 23	0, 23

A patient is counted in only one duration range, per treatment.
Study treatment refers to ribociclib 600 mg + letrozole 2.5 mg or placebo + letrozole.
LET=letrozole; Min, Max=Minimum, Maximum; PBO=placebo; RIBO=ribociclib
Source: [SCS-Appendix 1-Table 2-1a]

The overall mean and median duration of exposure of the combination of ribociclib + letrozole and letrozole alone in the main study A2301 is similar, about 12 months. Patients still on treatment ≥12 months are 58.1 % and 53.0 % in the experimental and control arm respectively.

In study A2301, the mean and median relative dose intensity for ribociclib in the experimental arm was 81 % and 88 % respectively. About a third of the patients in the combination arm had a relative dose intensity of less than 70 % (34 % of the patients) and only 48 % achieved a relative dose intensity of > 90 %.

The mean and median relative dose intensity for letrozole in the experimental arm were 99 % and 100 % respectively with 97 % of the patients achieving a relative dose intensity of > 90 %.

Adverse events

Table 35: Summary of deaths and AE categories - combination therapy (Safety set)

	Study A2301 RIBO+LET N=334			Study A2301 PBO+LET N=330			Study X2107 RIBO+LET N=47			Pooled combination therapy RIBO+LET N=381		
	All	G3	G4	All	G3	G4	All	G3	G4	All	G3	G4
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse events	329 (98.5)	221 (66.2)	50 (15.0)	320 (97.0)	105 (31.8)	3 (0.9)	47 (100)	31 (66.0)	3 (6.4)	376 (98.7)	252 (66.1)	53 (13.9)
Suspected to be drug-related	319 (95.5)	199 (59.6)	43 (12.9)	249 (75.5)	27 (8.2)	1 (0.3)	46 (97.9)	25 (53.2)	3 (6.4)	365 (95.8)	224 (58.8)	46 (12.1)
All deaths[1]	23 (6.9)	--	--	19 (5.8)		--	0	--	--	23 (6.0)	--	--
On-treatment deaths[2]	3 (0.9)	--	--	1 (0.3)		--	0	--	--	3 (0.8)	--	--
Serious adverse events	71 (21.3)	42 (12.6)	16 (4.8)	39 (11.8)	27 (8.2)	2 (0.6)	6 (12.8)	4 (8.5)	1 (2.1)	77 (20.2)	46 (12.1)	17 (4.5)
AEs leading to discontinuation[3]	50 (15.0)	27 (8.1)	11 (3.3)	10 (3.0)	6 (1.8)	0	3 (6.4)	2 (4.3)	1 (2.1)	53 (13.9)	29 (7.6)	12 (3.1)
Suspected to be drug-related	44 (13.2)	21 (6.3)	11 (3.3)	5 (1.5)	1 (0.3)	0	3 (6.4)	2 (4.3)	1 (2.1)	47 (12.3)	23 (6.0)	12 (3.1)
AEs requiring dose interruption and/or adjustment	244 (73.1)	182 (54.5)	32 (9.6)	52 (15.8)	20 (6.1)	0	18 (38.3)	9 (19.1)	2 (4.3)	262 (68.8)	191 (50.1)	34 (8.9)

[1] All deaths including those >30 days after end of treatment.
[2] Deaths occurring >30 days after end of treatment are not included.
[3] Discontinuation defined as discontinuation of ribociclib/placebo only or ribociclib, placebo, and letrozole.
AEs up to 30 days after the last study treatment will be included.
Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories
All=All grades; G3=Grade 3; G4=Grade 4; LET=letrozole; PBO=placebo; RIBO=ribociclib
Source: [SCS-Appendix 1-Table 3-1a]

Table 36: AES by primary SOC and severity irrespective of causality (with at least 2% incidence in 'All' - pooled combination therapy) - combination therapy (Safety set)

	Study A2301 RIBO+LET N=334			Study A2301 PBO+LET N=330			Study X2107 RIBO+LET N=47			Pooled combination therapy RIBO+LET N=381		
	All	G3	G4	All	G3	G4	All	G3	G4	All	G3	G4
Primary System Organ Class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	329 (98.5)	221 (66.2)	50 (15.0)	320 (97.0)	105 (31.8)	3 (0.9)	47 (100)	31 (66.0)	3 (6.4)	376 (98.7)	252 (66.1)	53 (13.9)
Gastrointestinal disorders	266 (79.6)	35 (10.5)	2 (0.6)	207 (62.7)	9 (2.7)	0	35 (74.5)	1 (2.1)	0	301 (79.0)	36 (9.4)	2 (0.5)
Blood and lymphatic system disorders	227 (68.0)	135 (40.4)	34 (10.2)	38 (11.5)	8 (2.4)	0	36 (76.6)	21 (44.7)	2 (4.3)	263 (69.0)	156 (40.9)	36 (9.4)
General disorders and administration site conditions	219 (65.6)	17 (5.1)	2 (0.6)	186 (56.4)	6 (1.8)	0	27 (57.4)	1 (2.1)	0	246 (64.6)	18 (4.7)	2 (0.5)
Skin and subcutaneous tissue disorders	202 (60.5)	6 1.8)	0	119 (36.1)	0	0	25 (53.2)	0	0	227 (59.6)	6 (1.6)	0
Musculoskeletal and connective tissue disorders	199 (59.6)	15 (4.5)	1 (0.3)	216 (65.5)	11 (3.3)	0	23 (48.9)	0	0	222 (58.3)	15 (3.9)	1 (0.3)
Investigations	189 (56.6)	105 (31.4)	11 (3.3)	77 (23.3)	22 (6.7)	0	27 (57.4)	13 (27.7)	0	216 (56.7)	118 (31.0)	11 (2.9)
Infections and infestations	168 (50.3)	12 (3.6)	2 (0.6)	140 (42.4)	7 (2.1)	1 (0.3)	25 (53.2)	3 (6.4)	0	193 (50.7)	15 (3.9)	2 (0.5)
Nervous system disorders	150 (44.9)	10 (3.0)	0	137 (41.5)	9 (2.7)	0	16 (34.0)	1 (2.1)	0	166 (43.6)	11 (2.9)	0
Respiratory, thoracic and mediastinal disorders	145 (43.4)	11 (3.3)	1 (0.3)	112 (33.9)	7 (2.1)	0	20 (42.6)	0	0	165 (43.3)	11 (2.9)	1 (0.3)
Vascular disorders	124 (37.1)	36 (10.8)	0	134 (40.6)	37 (11.2)	0	18 (38.3)	1 (2.1)	0	142 (37.3)	37 (9.7)	0
Metabolism and nutrition disorders	117 (35.0)	29 (8.7)	2 (0.6)	98 (29.7)	12 (3.6)	1 (0.3)	20 (42.6)	3 (6.4)	0	137 (36.0)	32 (8.4)	2 (0.5)

Psychiatric disorders	92 (27.5)	4 (1.2)	0	80 (24.2)	2 (0.6)	0	7 (14.9)	0	0	99 (26.0)	4 (1.0)	0
Eye disorders	75 (22.5)	2 (0.6)	0	36 (10.9)	1 (0.3)	0	10 (21.3)	0	0	85 (22.3)	2 (0.5)	0
Injury, poisoning and procedural complications	46 (13.8)	6 (1.8)	0	35 (10.6)	5 (1.5)	0	5 (10.6)	1 (2.1)	0	51 (13.4)	7 (1.8)	0
Reproductive system and breast disorders	42 (12.6)	1 (0.3)	0	50 (15.2)	0	0	4 (8.5)	0	0	46 (12.1)	1 (0.3)	0
Renal and urinary disorders	29 (8.7)	2 (0.6)	0	25 (7.6)	3 (0.9)	0	4 (8.5)	0	0	33 (8.7)	2 (0.5)	0
Cardiac disorders	28 (8.4)	4 (1.2)	0	21 (6.4)	1 (0.3)	1 (0.3)	1 (2.1)	0	0	29 (7.6)	4 (1.0)	0
Ear and labyrinth disorders	25 (7.5)	0	0	17 (5.2)	0	0	4 (8.5)	0	0	29 (7.6)	0	0
Hepatobiliary disorders	13 (3.9)	7 (2.1)	1 (0.3)	7 (2.1)	0	0	3 (6.4)	0	0	16 (4.2)	7 (1.8)	1 (0.3)
Immune system disorders	11 (3.3)	0	0	7 (2.1)	0	0	0	0	0	11 (2.9)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (2.4)	4 (1.2)	0	12 (3.6)	1 (0.3)	0	2 (4.3)	0	1 (2.1)	10 (2.6)	4 (1.0)	1 (0.3)

System organ classes and preferred terms within a primary system organ class are sorted in descending order of frequency of in 'All' grades 'Pooled monotherapy'.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events is counted only once in the total row.
AEs up to 30 days after the last study treatment will be included.
All=All Grades; G3=Grade 3; G4=Grade 4; RIBO=ribociclib
Source: [SCS-Appendix 1-Table 3-2a]

The SOC in which the most AEs were reported with the experimental arm in the A2301 study were 'GI disorders' (80 %) followed by 'blood and lymphatic system disorders' (68 %), 'general disorders and administration site conditions' (66 %); 'skin and subcutaneous tissue disorders' (61 %); 'musculoskeletal and connective tissue disorders' (60 %); 'investigations (57 %), and 'infections and infestations (50 %).

Table 37: AEs irrespective of relationship to treatment occurring more commonly (by 5% or more) with ribociclib therapy by grade - Study A2301 (Safety Set)

	Ribociclib plus letrozole N=334			Placebo plus letrozole N=330		
MedDRA preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any adverse event	329 (98.5)	221 (66.2)	50 (15.0)	320 (97.0)	105 (31.8)	3 (0.9)
Haematological adverse events						
Neutropenia[a]	249 (74.6)	166 (49.7)	33 (9.9)	17 (5.2)	3 (0.9)	0
White blood cell count decreased	63 (18.9)	41 (12.3)	2 (0.6)	5 (1.5)	1 (0.3)	0
Anaemia	61 (18.3)	3 (0.9)	1 (0.3)	15 (4.5)	4 (1.2)	0
Leukopenia	52 (15.6)	27 (8.1)	2 (0.6)	9 (2.7)	1 (0.3)	0
Lymphocyte count decreased	21 (6.3)	14 (4.2)	1 (0.3)	3 (0.9)	2 (0.6)	0
Thrombocytopenia	20 (6.0)	2 (0.6)	0	2 (0.6)	0	0
Non-haematological adverse events						
Nausea	172 (51.5)	8 (2.4)	0	94 (28.5)	2 (0.6)	0
Fatigue	122 (36.5)	7 (2.1)	1 (0.3)	99 (30.0)	3 (0.9)	0
Diarrhoea	117 (35.0)	4 (1.2)	0	73 (22.1)	3 (0.9)	0
Alopecia	111 (33.2)	0	0	51 (15.5)	0	0
Vomiting	98 (29.3)	12 (3.6)	0	51 (15.5)	3 (0.9)	0
Constipation	83 (24.9)	4 (1.2)	0	63 (19.1)	0	0
Rash	57 (17.1)	2 (0.6)	0	26 (7.9)	0	0
ALT increased	52 (15.6)	25 (7.5)	6 (1.8)	13 (3.9)	4 (1.2)	0
AST increased	50 (15.0)	16 (4.8)	3 (0.9)	12 (3.6)	4 (1.2)	0
Pruritus	45 (13.5)	2 (0.6)	0	19 (5.8)	0	0
Pyrexia	42 (12.6)	1 (0.3)	0	18 (5.5)	0	0
Stomatitis	41 (12.3)	1 (0.3)	0	22 (6.7)	0	0
Dry skin	27 (8.1)	0	0	10 (3.0)	0	0
Blood creatinine increased	23 (6.9)	2 (0.6)	0	3 (0.9)	0	0
Lacrimation increased	23 (6.9)	0	0	6 (1.8)	0	0

ALT - Alanine aminotransferase; AST - Aspartate aminotransferase; MedDRA - Medical Dictionary for Regulatory Activities

[a] AESI pooled event category includes granulocytopenia, neutropenia, and neutrophil count decreased

Source: [SCS-Table 2-6] and [Study A2301-Table 14.3.1-1.16]

When comparing the proportion of AE reports between the two arms in Study A2301, the highest differences were found in the SOCs of 'blood and lymphatic system disorders' (overall +57 % but essentially neutropenia); 'investigations' (overall +33 % with decreased neutrophil count 18 %, AST increased +11 %, ALT increased +12 %); 'skin and subcutaneous tissue disorders' (overall +24 % with alopecia 18 %); 'gastrointestinal disorders' (overall +17 % with nausea +23 %, vomiting + 14 %, diarrhoea + 13 %) and 'eye disorders' (overall +12 % with increased lacrimation +5 %).

The proportion of pneumonitis was fairly similar between the experimental and control arm (4 patients [1.2 %] and 2 patients [0.6 %] respectively).

Febrile neutropenia and sepsis were reported in a low proportion in the experimental arm (5 cases [1.5 % with 3 cases of Grade 3 and one case of Grade 4] and 3 [0.9 % with one Grade 3 and two Grade 4]. There were no reports in the control arm.

Pulmonary embolism was infrequently reported (4 cases [~1 % with 2 Grade 3 and one Grade 4). One Grade 3 case was reported in the control arm.

ECG QT prolonged reports were 15 (4.5 % with one Grade 3 and no Grade 4). Reports of syncope amounted to nine (2.7 % with six reports of Grade 3 and no Grade 4).

Adverse drug reactions

Screening strategy for ADR selection

The algorithm followed for study A2301 was:

1. Any AE (MedDRA preferred term) with ≥ 2% incidence in the ribociclib plus letrozole treatment group

2. Any AE (from standard MedDRA query [SMQ]) with >5% incidence in the ribociclib plus letrozole treatment group

3. Any AE (MedDRA preferred term) with ≥ 2% difference in incidence between ribociclib plus letrozole and placebo plus letrozole treatment groups

4. Any AE (from SMQ) with ≥ 5% difference in incidence between ribociclib plus letrozole and placebo plus letrozole treatment groups

5. Any grade 3/4 AE with incidence ≥ 0.5% or > than the placebo plus letrozole group

6. AEs and SAEs leading to discontinuation with an occurrence of ≥ 0.5%

In Study A2301, the most frequently reported drug-related 'haematological' AEs (with incidences of ≥ 20 %) in the experimental arm and consistent with AEs irrespective of causality, was neutropenia (60 %) whereas the drug-related 'nonhaematological' AEs were nausea (43 %), alopecia (28 %), fatigue (27.5%), and diarrhoea (22 %).

The most common ADRs and the most common grade 3/4 ADRs (reported at a frequency ≥20% and ≥2%, respectively) for which the frequency for Kisqali plus letrozole exceeds the frequency for placebo plus letrozole were neutropenia, leukopenia, headache, back pain, nausea, fatigue, diarrhoea, vomiting, constipation, alopecia and rash and neutropenia, leukopenia, abnormal liver function test, lymphopenia, hypophosphataemia, vomiting, nausea, fatigue and back pain, respectively.

Table 38: Adverse drug reactions observed in the phase III clinical study A2301

Adverse drug reactions	Kisqali plus letrozole N=334 n (%) All grades	Placebo plus letrozole N=330 n (%) All grades	Kisqali plus letrozole N=334 n (%) Grades 3/4	Placebo plus letrozole N=330 n (%) Grades 3/4	Frequency category All grades
Infections and infestations					
Urinary tract infection	44 (13.2)	28 (8.5)	2 (0.6)	0 (0.0)	Very common
Blood and lymphatic system disorders					
Neutropenia	248 (74.3)	17 (5.2)	198 (59.3)	3 (0.9)	Very common
Leukopenia	110 (32.9)	13 (3.9)	70 (21.0)	2 (0.6)	Very common
Anaemia	63 (18.9)	15 (4.5)	4 (1.2)	4 (1.2)	Very common
Lymphopenia	35 (10.5)	7 (2.1)	23 (6.9)	3 (0.9)	Very Common
Thrombocytopenia	30 (9.0)	2 (0.6)	2 (0.6)	0	Common
Febrile neutropenia	5 (1.5)	0	4 (1.2)	0	Common
Eye disorders					
Lacrimation increased	23 (6.9)	6 (1.8)	0	0	Common
Dry eye	19 (5.7)	7 (2.1)	0	0	Common
Metabolism and nutrition disorders					
Decreased appetite	62 (18.6)	50 (15.2)	5 (1.5)	1 (0.3)	Very common
Hypocalcaemia	18 (5.4)	6 (1.8)	5 (1.5)	0	Common
Hypokalaemia	15 (4.5)	10 (3.0)	4 (1.2)	3 (0.9)	Common
Hypophosphatemia	14 (4.2)	3 (0.9)	12 (3.6)	2 (0.6)	Common

Adverse drug reactions	Kisqali plus letrozole N=334 n (%) All grades	Placebo plus letrozole N=330 n (%) All grades	Kisqali plus letrozole N=334 n (%) Grades 3/4	Placebo plus letrozole N=330 n (%) Grades 3/4	Frequency category All grades
Nervous system disorders					
Headache	74 (22.2)	63 (19.1)	1 (0.3)	1 (0.3)	Very common
Insomnia	39 (11.7)	31 (9.4)	1 (0.3)	0	Very common
Cardiac disorders					
Syncope	9 (2.7)	3 (0.9)	6 (1.8)	2 (0.6)	Common
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	39 (11.7)	29 (8.8)	4 (1.2)	2 (0.6)	Very common
Epistaxis	15 (4.5)	6 (1.8)	0	0	Common
Musculoskeletal and connective tissue disorders					
Back pain	66 (19.8)	58 (17.6)	7 (2.1)	1 (0.3)	Very common
Gastrointestinal disorders					
Nausea	172 (51.5)	94 (28.5)	8 (2.4)	2 (0.6)	Very common
Diarrhoea	117 (35.0)	73 (22.1)	4 (1.2)	3 (0.9)	Very common
Vomiting	98 (29.3)	51 (15.5)	12 (3.6)	3 (0.9)	Very common
Constipation	83 (24.9)	63 (19.1)	4 (1.2)	0	Very common
Stomatitis	41 (12.3)	22 (6.7)	1 (0.3)	0	Very common
Abdominal pain	35 (10.5)	25 (7.6)	4 (1.2)	0	Very common
Dysgeusia	31 (9.3)	19 (5.8)	1 (0.3)	0	Common
Dyspepsia	22 (6.6)	14 (4.2)	0	0	Common
Hepatobiliary disorders					
Hepatotoxicity[1]	5 (1.5)	1 (0.3)	5 (1.5)	0	Common
Skin and subcutaneous tissue disorders					
Alopecia	111 (33.2)	51 (15.5)	0	0	Very common
Rash[2]	67 (20.1)	27 (8.2)	3 (0.9)	0	Very common
Pruritus	49 (14.7)	20 (6.1)	2 (0.6)	0	Very common
Erythema	17 (5.1)	4 (1.2)	0	0	Common
General disorders and administration site conditions					
Fatigue	122 (36.5)	99 (30.0)	8 (2.4)	3 (0.9)	Very common
Peripheral oedema	51 (15.3)	34 (10.3)	0	0	Very common
Asthenia	43 (12.9)	38 (11.5)	3 (0.9)	2 (0.6)	Very common
Pyrexia	42 (12.6)	18 (5.5)	1 (0.3)	0	Very common
Investigations					
Abnormal liver function tests[3]	60 (18.0)	18 (5.5)	32 (9.6)	8 (2.4)	Very common
Blood creatinine increased	23 (6.9)	3 (0.9)	2 (0.6)	0	Common
Weight decreased	20 (6.0)	11 (3.3)	1 (0.3)	0	Common
Electrocardiogram QT prolonged	15 (4.5)	4 (1.2)	1 (0.3)	0	Common

[1]Hepatotoxicity: hepatocellular injury, drug induced liver injury, hepatotoxicity, hepatic failure "1 non-fatal case", autoimmune hepatitis (single case).

[2]Rash: rash, rash maculopapular

[3]Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

AEs of special interest (AESI)

The following were identified as the main adverse reactions for ribociclib: neutropenia, anaemia, leukopenia, thrombocytopenia, nausea, emesis, infections, diarrhoea, hepatobiliary toxicity, renal toxicity, QTc interval prolongation, pulmonary embolism, reproductive toxicity.

Table 39: AESIs by grouping, irrespective of causality – combination therapy (Safety set)

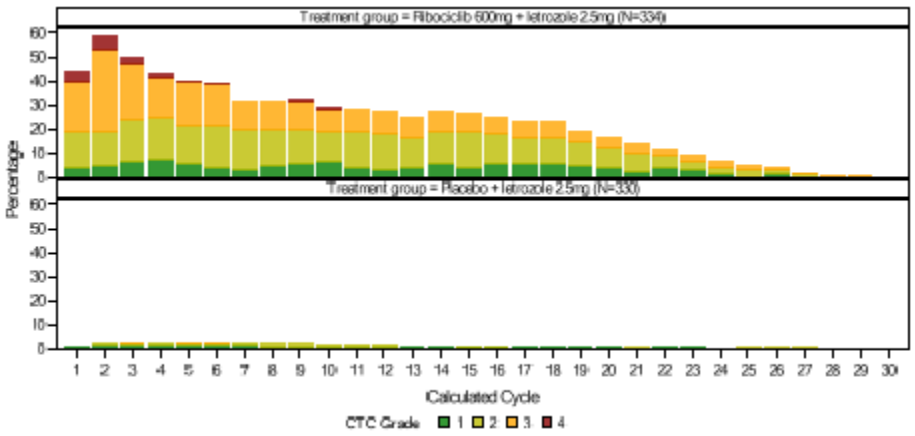
	Study A2301						Study X2107			Pooled combination therapy		
	RIBO+LET N=334			PBO+LET N=330			RIBO+LET N=47			RIBO+LET N=381		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
AESI Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hematological AESIs												
Neutropenia	249 (74.6)	166 (49.7)	33 (9.9)	17 (5.2)	3 (0.9)	0	39 (83.0)	24 (51.1)	2 (4.3)	288 (75.6)	190 (49.9)	35 (9.2)
Anemia	63 (18.9)	3 (0.9)	1 (0.3)	15 (4.5)	4 (1.2)	0	13 (27.7)	0	0	76 (19.9)	3 (0.8)	1 (0.3)
Leukopenia	55 (16.5)	27 (8.1)	5 (1.5)	12 (3.6)	2 (0.6)	0	9 (19.1)	4 (8.5)	0	64 (16.8)	31 (8.1)	5 (1.3)
Thrombocytopenia	30 (9.0)	2 (0.6)	0	2 (0.6)	0	0	6 (12.8)	0	0	36 (9.4)	2 (0.5)	0
Non-hematological AESIs												
Nausea, emesis	188 (56.3)	16 (4.8)	0	108 (32.7)	3 (0.9)	0	25 (53.2)	0	0	213 (55.9)	16 (4.2)	0
Infections	168 (50.3)	12 (3.6)	2 (0.6)	140 (42.4)	7 (2.1)	1 (0.3)	25 (53.2)	4 (8.5)	0	193 (50.7)	16 (4.2)	2 (0.5)
Diarrhea	117 (35.0)	4 (1.2)	0	74 (22.4)	3 (0.9)	0	16 (34.0)	0	0	133 (34.9)	4 (1.0)	0
Hepatobiliary toxicity	80 (24.0)	31 (9.3)	7 (2.1)	45 (13.6)	12 (3.6)	0	11 (23.4)	4 (8.5)	0	91 (23.9)	35 (9.2)	7 (1.8)
Renal impairment	28 (8.4)	3 (0.9)	0	7 (2.1)	3 (0.9)	0	4 (8.5)	0	0	32 (8.4)	3 (0.8)	0
QTc interval prolongation	25 (7.5)	7 (2.1)	1 (0.3)	8 (2.4)	2 (0.6)	0	2 (4.3)	0	0	27 (7.1)	7 (1.8)	1 (0.3)
Pulmonary embolism[1]	9 (2.7)	2 (0.6)	1 (0.3)	3 (0.9)	1 (0.3)	0	1 (2.1)	0	0	10 (2.6)	2 (0.5)	1 (0.3)
Reproductive toxicity	2 (0.6)	0	0	4 (1.2)	0	0	0	0	0	2 (0.5)	0	0

'Pulmonary embolism' grouped AEs includes thromboembolic preferred terms.
AESIs have been categorized as being hematological or non-hematological and are sorted into these respective categories in descending order of frequency in the pooled combination therapy 'All grades' column.
Patients with multiple events in the grouping are counted only once in the grouping. Patients with events in more than 1 category within a grouping are counted once in each of those categories. AEs up to 30 days after the last study treatment will be included.
AESI=Adverse event of special interest; LET=letrozole; PBO=placebo; RIBO=ribociclib
Source: [SCS-Appendix 1-Table 3-13a]

Neutropenia

In Study A2301, neutropenic events occurred in a substantially higher proportion of patients in the experimental arm compared to the control (74.3 % vs. 5.2 %, respectively). The majority of these events were Grade 3 (50 %) with Grade 4 about 10 %. A grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 59.6% of patients receiving Kisqali and letrozole.

Dose interruptions/adjustments were required for 52 % of the patients. Discontinuation due to neutropenic events occurred in less than 1 %.



Source: [Appendix 2-Figure 1-6]

Figure 12: Histogram of neutropenia events by treatment and cycle

Furthermore events of febrile neutropenia were reported in 1.5% of the patients (duration with a range of 1-8 days). GCS-F was administered to 8 % of patients in the combination therapy arm versus 0.3% in the control arm.

Among patients with grade ≥ 2 neutropenia (based upon laboratory findings) in the combination therapy pool, the median time-to-onset was 16 days in the combination arm. The median time to resolution i.e. to normalization or grade <2 (based on medians of patients with an event) was 32 days. The median time to resolution of grade ≥3 (to normalisation or grade <3) was 15 days in the ribociclib plus letrozole treatment group following treatment interruption and/or reduction and/or discontinuation.

Febrile neutropenia was reported in about 1.5% of patients exposed to Kisqali in the phase III study. Anaemia

In Study A2301, anaemia events occurred in a higher proportion of patients in the ribociclib + letrozole group (19 %), compared with the control (4.5%) with few Grade 3 /4 events (similar in both arms [1.2 %]). Few patients (1.2 %) required dose adjustments and there were no treatment discontinuations due to anaemia events. The event of anaemia in the ribociclib + letrozole group had a relative difference from the control arm of +14 %. In terms of erythropoietin requirements, a total of four patients received erythropoietin in studies A2301 and XUS03 whilst none in studies X2107, X2101, and X1101.

Leukopenia

As expected, also events of leukopenia occurred in a higher proportion of patients in the experimental arm (17 %) compared with the control (4 %) as did grade 3/4 AEs (~ 10 % and 0.6%, respectively). Dose adjustments/interruptions were required in 5 % of the patients in the experimental arm whilst none in the control arm. One patient had an SAE and one patient discontinued study treatment due to leukopenia. The relative difference was +13 between the two arms.

Thrombocytopenia

Thrombocytopenia occurred in 9 % in the experimental arm compared whilst 0.6 % in the control arm. Two patients experienced grade 3/4 AEs and one patient had an SAE of thrombocytopenia in the combination arm. About 1 % required dose adjustments/interruptions. There were no treatment discontinuations. The only bleeding event (associated with Grade 3 or 4 post baseline platelet count decrease) was epistaxis (n=1 event).

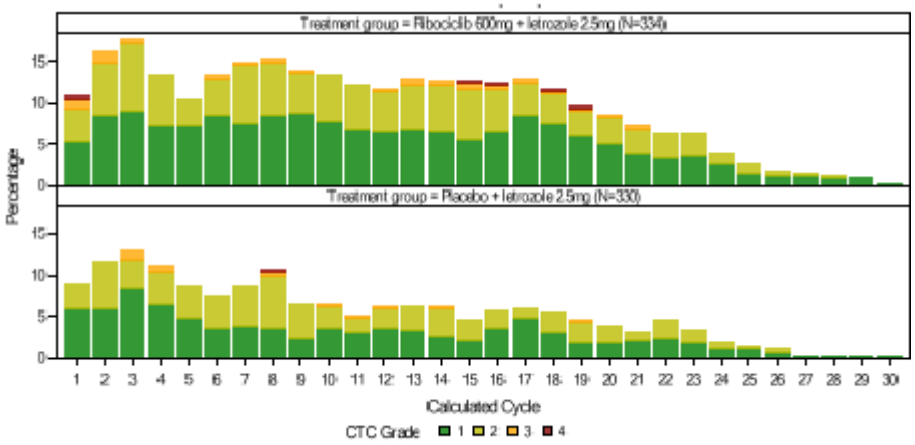
Nausea, emesis

Nausea/ emesis events were reported in 56 % of the patients in the experimental arm whereof 52 % events of nausea and 29 % of vomiting. A total of 5 % experienced a Grade 3 event mostly vomiting (4 %). SAEs were reported in 2.4 %. In the majority of nausea cases (91 %), no action was taken with the study drug. Ribociclib was temporarily interrupted in 10 % and discontinued in 1.7%. Similarly, for the majority of vomiting events (83 %), no action was taken with the study drug and ribociclib was temporarily interrupted in 20 % and discontinued in 8 %. No Grade 4 events of nausea or vomiting were reported.

Infections

A high proportion of infectious events were reported in the experimental arm (50 %) but also fairly high in the control arm (42 %). The similarity in terms of individual causes between the two arms is recognised save slightly more viral infections in the experimental arms (e.g. influenza, herpes). The vast majority were Grade 1/2 with about 4 % Grade 3/4 in the experimental arm compared to 2.4 % in the control arm. SAEs were

reported in 3 % mainly due to pneumonia (1 %), sepsis (1 %) and urinary tract infections (0.6 %). Few led to discontinuation of study drug (< 1%) and about 5 % led to dose adjustments/ interruption.



Source: [Appendix 2-Figure 1-6]

Figure 13: Histogram of infectious events by treatment and cycle

In terms of the proportion and distribution of infectious events according to neutropenia, no increased risk for `all grade´ infections was observed with increasing severity of neutropenia. However, the severity of the infectious events increased with increasing grade of neutropenia (more Grade 3 or 4 events).

Only one event in study A2301 was classified as being an opportunistic infection (pneumocystis jirovecii pneumonia) in the experimental arm.

Hepatobiliary toxicity

In Study A2301, hepatobiliary toxicity events occurred in a higher proportion of patients in the experimental arm compared with the control arm (24.0 % vs. 13.6 %, respectively), with more grade 3/4 AEs reported in the patients treated with ribociclib plus letrozole (11.4 % vs. 3.6 %, respectively). The main cause was ALT and AST elevations.

Increases in transaminases were observed; Grade 3 or 4 increases in ALT (10.2% versus 1.2%) and AST (6.9% versus 1.5%) were reported in the ribociclib and placebo arms respectively. Concurrent elevations in ALT or AST greater than three times the upper limit of normal and total bilirubin greater than two times the upper limit of normal, with normal alkaline phosphatase, in the absence of cholestasis occurred in 4 (1.2%) patients and all patients recovered to normal levels within 154 days after treatment with Kisqali was discontinued.

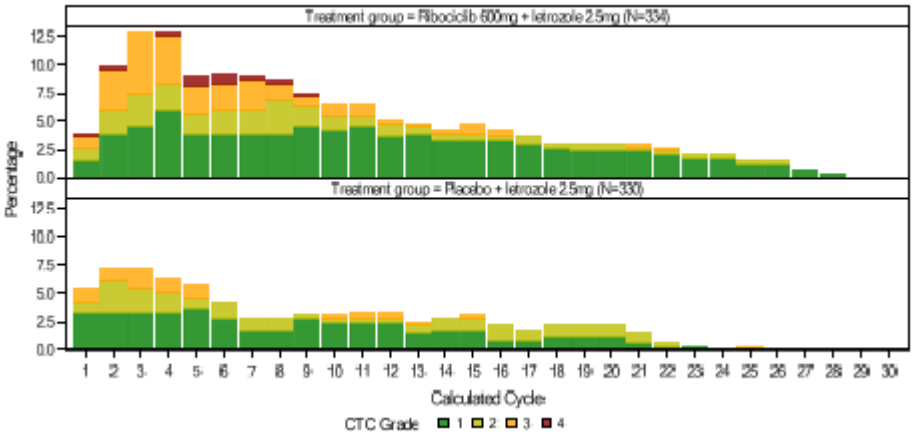
Dose interruptions and/or adjustments due to hepatotobiliary toxicity events were reported in 8.4% of ribociclib plus letrozole-treated patients, primarily due to ALT increased (5.7%) and/or AST increased (4.5%). Discontinuation of treatment with Kisqali plus letrozole due to abnormal liver function tests or hepatotoxicity occurred in 3.0% and 0.6% of patients respectively (see sections 4.2 and 4.4).

In the combination therapy pool the majority (83.8 %; 31/37) of the grade 3/4 ALT and AST increases occurred during the first 6 months of treatment. The median time-to-onset of grade ≥ 3 ALT/AST elevation was 57 days and 62 days (based upon medians of patients with events) for the experimental and control arm respectively. The median time to resolution i.e. to normalization or grade ≤2 (again based upon medians of patients with events) was 24 days and 19 days respectively.

As of 29-Jan-2016, four cases of liver injury (Hy's law cases with ALT or AST >3-times the upper limit of the normal range [ULN] and total bilirubin >2×ULN and alkaline phosphatase <2×ULN) were reported in patients treated with the experimental combination in Study A2301. Two of these four cases showed findings on biopsy suggestive of autoimmune hepatitis. None of them was fatal or associated with hepatic failure with permanent disability. Liver function tests for all four patients recovered to normal levels 98-154 days following the discontinuation of therapy. A further three Hy's law cases were reported in the broader development program.

Events of hepatobiliary toxicity were reported most frequently in Cycles 2, 3, and 4, and overall were reported more frequently in the ribociclib plus letrozole treatment group than in the control arm.

Figure 2-6 Histogram of hepatobiliary toxicity events by treatment and cycle



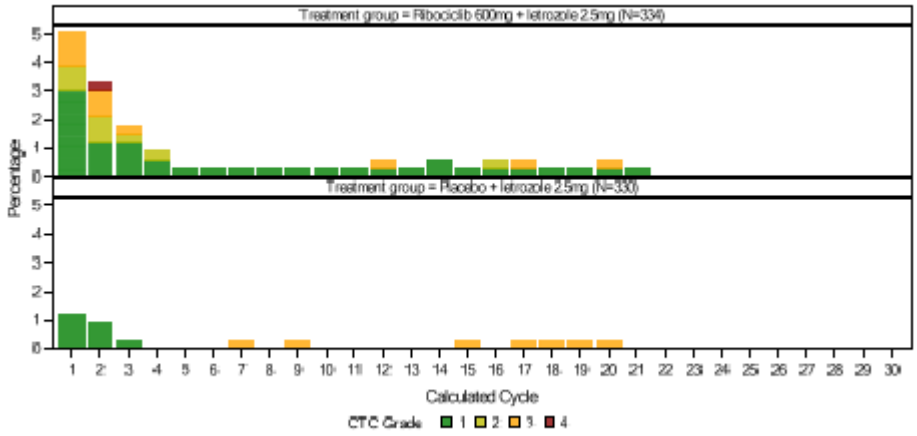
Source: [Appendix 2-Figure 1-6]

Figure 14: Histogram of hepatobiliary toxicity events by treatment and cycle

QTc interval prolongation

In Study A2301, 'QTc interval prolongation' events (including ECG QT prolonged and syncope) occurred in 7.5% of the patients in the experimental arm as compared to the control arm (2.4 %) with ECG QT prolonged being the most frequent AE (4.5 %) reported followed by syncope (3 %). There were also single cases of loss of consciousness, sudden death and ventricular tachycardia reported. SAEs, discontinuations and dose adjustments/interruptions occurred in 4 %, 0.3 % and ~1 % respectively in the experimental arm.

Figure 2-8 Histogram of events of QTc prolongation by treatment and cycle



Source: [Appendix 2-Figure 1-6]

Figure 15: Histogram of events of QTc prolongation by treatment and cycle

Review of ECG data (average of triplicate) showed 1 patient (0.3%) had >500 msec post-baseline QTcF value, and 9 patients (2.7%) had a >60 msec increase from baseline in QTcF intervals. There were no reported cases of torsade de pointes. Dose interruptions/adjustments were reported in 0.9% of ribociclib plus letrozole-treated patients due to electrocardiogram QT prolonged and syncope.

A central analysis of ECG data (average of triplicate) showed 11 patients (3.3%) and 1 patient (0.3%) with at least one >480 msec post-baseline QTcF for the ribociclib plus letrozole arm and the placebo plus letrozole arm respectively. Amongst the patients who had QTcF prolongation >480 msec, the median time to onset was 15 days and these changes were reversible with dose interruption and/or dose reduction.

Pulmonary embolism (including all thromboembolic preferred terms)

In Study A2301, thromboembolic events occurred in 9 patients (~3 %) in the combination arm compared with about 1 % in the control arm. All Grade 3/4 events (1 %) with ribociclib + letrozole pertained to pulmonary embolism. Dose adjustments/interruptions were required for 1 patient (0.3%) with pulmonary embolism in the ribociclib + letrozole arm. There were no treatment discontinuations.

Renal toxicity

Events of renal toxicity were reported in the main study in 28 patients [8 %] and 7 [2 %] in the experimental and control arm respectively. The main cause being elevated blood creatinine (7 %). The proportion of Grade 3/4 was ~1 %, SAEs ~1% and the need of dose adjustments/interruptions ~1 %. None led to discontinuation in the experimental arm.

Reproductive toxicity

In Study A2301, mastitis and omphalitis occurred in one patient (0.3%) each in the ribociclib + letrozole group whereas four patients (1.2%) in the control arm experienced mastitis. There were no grade 3/4 AEs, dose adjustments/interruptions, SAEs, or discontinuations from ribociclib + letrozole due to reproductive toxicity events.

Diarrhoea

A slightly higher proportion of diarrhoea events were reported in the experimental arm as compared to the control arm (35 % and 22 % respectively). In 22 % in the experimental arm it was considered by the

investigator to be related to the study treatment. The vast majority were of Grade 1/2 with rather few Grade 3/4 events (~1 %) and similar between the two arms.

Serious adverse event / deaths / other significant events

Table 40: Overview of serious or clinically significant AEs - Studies A2301 and X2107 and the combination and monotherapy pools (Safety Set)

	Study A2301		Study X2107	Combination pool	Monotherapy pool
	Ribociclib plus letrozole	Placebo plus letrozole	Ribociclib plus letrozole	Ribociclib plus letrozole	Ribociclib
	N=334	N=330	N=47	N=381	N=187
Category	n (%)	n (%)	n (%)	n (%)	n (%)
Serious adverse events (SAEs)	**71 (21.3)**	**39 (11.8)**	**6 (12.8)**	**77 (20.2)**	**65 (34.8)**
Suspected to be drug related	25 (7.5)	5 (1.5)	3 (6.4)	28 (7.3)	11 (5.9)
AEs leading to discontinuation	**50 (15.0)[b]**	**10 (3.0)**	**3 (6.4)**	**53 (13.9)**	**16 (8.6)**
Suspected to be drug related	44 (13.2)	5 (1.5)	3 (6.4)	47 (12.3)	8 (4.3)

AE Adverse event

[a] An additional patient, who did not take any study medication, died post-randomization (and was excluded from the Safety Set)

[b] Note: 7.5% of patients discontinued treatment with ribociclib plus letrozole as a consequence of an AE(s) and the remaining patients discontinued ribociclib but remained on letrozole [Study A2301-Table 14.1-1.3]

Source: [SCS-Table 2-1], [SCS-Table 2-2], [SCS-Table 2-12], [SCS-Table 2-14], [SCS-Table 2-17], [SCS-Table 2-18], [SCS-Appendix 1-Table 3-9a], [SCS-Appendix 2-Table 3-9b], and [Study X2107-Table 12-3]

In Study A2301, SAEs were reported in 21 % in the experimental arm compared to 12 % in the control arm. As regards Grade 3 and 4 events there were 13 % and 5 % in the former compared to 8 % and 0.6 % in the control arm.

The SOCs in which SAEs were most frequently reported occurred (irrespective of causality and with an incidence of at least 1 %) were 'GI disorders' (5 %) followed by `blood disorders´(4 %) and 'infections' (3 % mainly pneumonia ~ 1%) in the experimental arm. The most frequently reported SAEs were the non-haematological SAEs of abdominal pain and vomiting (each 1.5%), followed by constipation, dyspnoea, increased ALT, and nausea (each 1.2%), whereas the most frequently reported haematological SAEs were anaemia and febrile neutropenia (each 1.2%). In the control arm, pleural effusion (1.2%) was the most frequently reported SAE followed by nausea, spinal compression fracture, and vomiting (each 0.6%).

Table 41: Overview of deaths - Studies A2301 and X2107 and the combination and monotherapy pools (Safety Set)

	Study A2301		Study X2107	Combination pool	Monotherapy pool
	Ribociclib plus letrozole	Placebo plus letrozole	Ribociclib plus letrozole	Ribociclib plus letrozole	Ribociclib
	N=334	N=330	N=47	N=381	N=187
Category	n (%)	n (%)	n (%)	n (%)	n (%)
All deaths	**23 (6.9)**	**19 (5.8) [a]**	**0**	**23 (6.0)**	**49 (26.2)**
On-treatment deaths	**3 (0.9)**	**1 (0.3)**	**0**	**3 (0.8)**	**20 (10.7)**
Study indication	**1 (0.3)**	**1 (0.3)**	**0**	**1 (0.3)**	**15 (8.0)**
AE as primary cause	**2 (0.6)**	**0**	**0**	**2 (0.5)**	**5 (2.7)**
On-treatment death by preferred term					
Death (unknown cause)	1 (0.3)	0	0	1 (0.3)	0
Sudden death	1 (0.3)	0	0	1 (0.3)	0
Respiratory failure	0	0	0	0	2 (1.1)
Acute respiratory failure	0	0	0	0	1 (0.5)
Cardio-respiratory arrest	0	0	0	0	1 (0.5)
Dyspnoea	0	0	0	0	1 (0.5)

AE Adverse event

[a] An additional patient, who did not take any study medication, died post-randomization (and was excluded from the Safety Set)

[b] Note: 7.5% of patients discontinued treatment with ribociclib plus letrozole as a consequence of an AE(s) and the remaining patients discontinued ribociclib but remained on letrozole [Study A2301-Table 14.1-1.3]

Source: [SCS-Table 2-1], [SCS-Table 2-2], [SCS-Table 2-12], [SCS-Table 2-14], [SCS-Table 2-17], [SCS-Table 2-18], [SCS-Appendix 1-Table 3-9a], [SCS-Appendix 2-Table 3-9b], and [Study X2107-Table 12-3]

Overall deaths were reported for 23 patients (~ 7 %) in the experimental arm whereof 18 (~5 %) were attributed to underlying malignancy. Of the remaining five (1.5%) one was due to sudden death, cardiac arrest, acute respiratory failure, hepatic failure and death due to unknown reason.

Three on-treatment deaths regardless of causality (≤ 30 days after last dose of study drug) were reported in the experimental arm (0.9 %) versus one in the control arm (0.3%). The Applicant has provided brief narratives for the three patients that died while on study. Causes of death on Kisqali plus letrozole included one case of each of the following: study indication, death (cause unknown) and sudden death (in the setting of grade 3 hypokalaemia and grade 2 QT prolongation).

In the case of death due to unknown reason, ribociclib was permanently discontinued due to bone pain (D5). The patient died on D23 due to unknown reason and no autopsy was performed. This was deemed not attributable to the study treatment according to the investigator. The second case died due to sudden death on D39 of study treatment. This patient continued with methadone which was a prohibited concomitant medication due to potential of prolonging the QT interval. The last ECG was taken on D 29 that clearly showed a QT prolongation with worsening to Grade 2. No autopsy was performed. The investigator deemed it likely related to study drug. The third patient died due to progressive disease 11 days after last dose of study treatment (D177).

A total of 19 patients (~ 6 %) in the control arm died with the vast majority due to disease progression (17 patients [~ 5 %]).

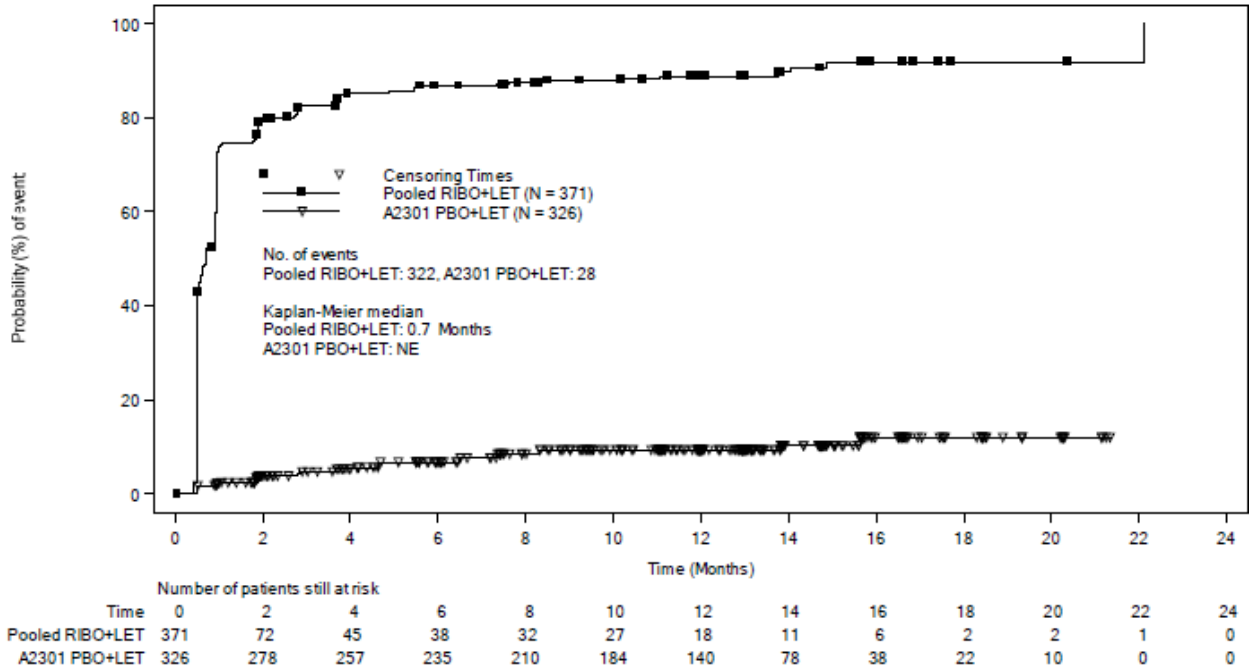
Laboratory findings

Haematology

Table 42: Select worst post-baseline haematology abnormalities based on CTCAE grade – combination therapy (Safety set)

	Study A2301						Study X2107			Pooled combination therapy		
	RIBO+LET N=334			PBO+LET N=330			RIBO+LET N=47			RIBO+LET N=381		
	G1-2	G3	G4	G1-2	G3	G4	G1-2	G3	G4	G1-2	G3	G4
Laboratory parameter	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hemoglobin - hypo	183 (54.8)	6 (1.8)	0	83 (25.2)	4 (1.2)	0	35 (74.5)	0	0	218 (57.2)	6 (1.6)	0
Leukocytes - hypo	196 (58.7)	105 (31.4)	10 (3.0)	92 (27.9)	4 (1.2)	1 (0.3)	27 (57.4)	19 (40.4)	0	223 (58.5)	124 (32.5)	10 (2.6)
Lymphocytes (absolute) - hypo	124 (37.1)	40 (12.0)	5 (1.5)	61 (18.5)	11 (3.3)	2 (0.6)	24 (51.1)	11 (23.4)	0	148 (38.8)	51 (13.4)	5 (1.3)
Neutrophils (absolute) - hypo	112 (33.5)	163 (48.8)	36 (10.8)	75 (22.7)	3 (0.9)	1 (0.3)	14 (29.8)	28 (59.6)	2 (4.3)	126 (33.1)	191 (50.1)	38 (10.0)
Platelets - hypo	94 (28.1)	2 (0.6)	1 (0.3)	20 (6.1)	0	1 (0.3)	22 (46.8)	0	0	116 (30.4)	2 (0.5)	1 (0.3)
Prothrombin INR - hyper	28 (8.4)	3 (0.9)	0	13 (3.9)	3 (0.9)	0	--	--	--	28 (8.4)[1]	3 (0.9)[1]	0
Total absolute neutrophil count - hypo	116 (34.7)	162 (48.5)	31 (9.3)	74 (22.4)	3 (0.9)	1 (0.3)	--	--	--	116 (34.7)[1]	162 (48.5)[1]	31 (9.3)[1]

[1] Based on N1=334
Baseline is defined as the last non-missing value prior to the first dose of study treatment.
Percent is based on N
G1-2= Grades 1-2; G3=Grade 3; G4=Grade 4; INR=international normalized ratio; LET=letrozole; PBO=placebo; RIBO=ribociclib
Source: [SCS-Appendix 1-Table 4-2a]



Source: [SCS-Appendix-1-Figure 1-3a]

Figure 16: K-M plot of time to grade 2-3-4 of neutropenia, by treatment – combination therapy (Safety set)

A treatment cycle encompasses 28 days (21 days on, 7 days off). The K-M curve above indicate that the risk of neutropenia Grade ≥ 2 rises steeply early on after initiation of treatment with ribociclib and start to level out after about 2 months (median time to neutropenia Grade 3-4 event 2.8 months and to Grade 2-4 events approximately 0.7 months).

Clinical chemistry

Table 43: Worst post-baseline clinical chemistry abnormalities based on CTCAE grade – combination therapy (Safety set)

	A2301 RIBO+LET N=334			A2301 PBO+LET N=330			X2107 RIBO+LET N=47			Pooled combotherapy RIBO+LET N=381		
	G1/2	G3	G4	G1/2	G3	G4	G1/2	G3	G4	G1/2	G3	G4
Parameter	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Alanine aminotransferase - hyper	121 (36.2)	27 (8.1)	7 (2.1)	115 (34.8)	4 (1.2)	0	20 (42.6)	2 (4.3)	0	141 (37.0)	29 (7.6)	7 (1.8)
Albumin - hypo	34 (10.2)	1 (0.3)	0	14 (4.2)	0	0	12 (25.5)	0	0	46 (12.1)	1 (0.3)	0
Alkaline phosphatase - hyper	125 (37.4)	5 (1.5)	0	126 (38.2)	4 (1.2)	0	21 (44.7)	0	0	146 (38.3)	5 (1.3)	0
Amylase - hyper	27 (8.1)	3 (0.9)	0	17 (5.2)	3 (0.9)	0	--	--	--	27 (8.1)[2]	3 (0.9)[2]	0
Aspartate aminotransferase - hyper	124 (37.1)	19 (5.7)	4 (1.2)	101 (30.6)	5 (1.5)	0	22 (46.8)	1 (2.1)	0	146 (38.3)	20 (5.2)	4 (1.0)
Bilirubin - hyper	13 (3.9)	3 (0.9)	1 (0.3)	8 (2.4)	1 (0.3)	0	3 (6.4)	0	0	16 (4.2)	3 (0.8)	1 (0.3)
Cholesterol - hyper	29 (8.7)	3 (0.9)	0	34 (10.3)	2 (0.6)	0	--	--	--	29 (8.7)[2]	3 (0.9)[2]	0
Corrected calcium - hyper	1 (0.3)	0	0	1 (0.3)	0	0	--	--	--	1 (0.3)[2]	0	0
Corrected calcium - hypo	1 (0.3)	0	0	0	0	0	--	--	--	1 (0.3)[2]	0	0
Creatine kinase - hyper	--	--	--	--	--	--	0	0	0	0	0	0
Creatinine - hyper	63 (18.9)	2 (0.6)	0	18 (5.5)	0	0	13 (27.7)	0	0	76 (19.9)	2 (0.5)	0
Glucose, plasma, fasting - hyper	--	--	--	--	--	--	2 (4.3)	0	0	2 (4.3)[1]	0	0
Glucose, serum, fasting - hyper	261 (78.1)	9 (2.7)	0	254 (77.0)	7 (2.1)	1 (0.3)	20 (42.6)	0	0	281 (73.8)	9 (2.4)	0
Glucose, serum, fasting - hypo	42 (12.6)	0	0	25 (7.6)	0	0	4 (8.5)	0	0	46 (12.1)	0	0
Magnesium - hyper	14 (4.2)	1 (0.3)	0	7 (2.1)	2 (0.6)	0	7 (14.9)	1 (2.1)	0	21 (5.5)	2 (0.5)	0
Magnesium - hypo	18 (5.4)	0	0	6 (1.8)	0	0	6 (12.8)	0	0	24 (6.3)	0	0
Phosphate - hypo	27 (8.1)	17 (5.1)	0	12 (3.6)	2 (0.6)	0	7 (14.9)	2 (4.3)	0	34 (8.9)	19 (5.0)	0
Potassium - hyper	15 (4.5)	3 (0.9)	0	17 (5.2)	2 (0.6)	1 (0.3)	9 (19.1)	1 (2.1)	0	24 (6.3)	4 (1.0)	0
Potassium - hypo	34 (10.2)	2 (0.6)	2 (0.6)	20 (6.1)	4 (1.2)	0	13 (27.7)	0	0	47 (12.3)	2 (0.5)	2 (0.5)
Sodium - hyper	19 (5.7)	0	0	17 (5.2)	1 (0.3)	0	3 (6.4)	0	0	22 (5.8)	0	0
Sodium - hypo	54 (16.2)	5 (1.5)	0	59 (17.9)	7 (2.1)	0	11 (23.4)	1 (2.1)	0	65 (17.1)	6 (1.6)	0
Triacylglycerol lipase - hyper	14 (4.2)	2 (0.6)	0	23 (7.0)	6 (1.8)	1 (0.3)				14 (4.2)[1]	2 (0.6)[1]	0
Triglycerides - hyper	205 (61.4)	5 (1.5)	0	198 (60.0)	7 (2.1)	1 (0.3)				205 (61.4)[1]	5 (1.5)[1]	0

Safety in special populations

Table 44: Adverse events by age group

MedDRA terms	Age <65 N=184 n (%)	Age 65-74 N=115 n (%)	Age 75-84 N=32 n (%)	Age 85+ N=3 n (%)
Total AEs	182 (98.9)	113 (98.3)	32 (100)	3 (100)
Serious AEs – Total **	37 (20.1)	27 (23.5)	15 (46.9)	1 (33.3)
- Fatal **	3 (1.6)	3 (2.6)	1 (3.1)	0
- Hospitalization **	2 (1.1)	3 (2.6)	1 (3.1)	0
- Life-threatening **	1 (0.5)	2 (1.7)	2 (6.3)	0
- Disability/incapacity **	31 (16.8)	20 (17.4)	10 (31.3)	1 (33.3)
- Other (medically significant) **	1 (1.1)	0	0	0
AE leading to drop-out [1]	22 (12.0)	17 (14.8)	11 (34.4)	2 (66.7)
Psychiatric disorders [2]	56 (30.4)	32 (27.8)	11 (34.4)	0
Nervous system disorders [3]	90 (48.9)	55 (47.8)	17 (53.1)	1 (33.3)
Accidents and injuries [4]	15 (8.2)	10 (8.7)	9 (28.1)	0
Cardiac disorders [5]	18 (9.8)	9 (7.8)	3 (9.4)	0
Vascular disorders [6]	77 (41.8)	43 (37.4)	11 (34.4)	1 (33.3)
Cerebrovascular disorders [7]	0	0	0	0
Infections and infestations [8]	100 (54.3)	63 (54.8)	16 (50.0)	1 (33.3)
Anticholinergic syndrome [9]	0	0	0	0
Quality of life decreased [10]	103 (56.0)	65 (56.5)	23 (71.9)	2 (66.7)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [11]	31 (16.8)	19 (16.5)	12 (37.5)	1 (33.3)

** Source: Novartis ARGUS Safety database.
[1] AEs leading to permanently discontinuation of Ribociclib with or without letrozole
[2] AEs in the SOC of psychiatric disorders
[3] AEs in the SOC of nervous system disorders
[4] AEs in the SMQ of accidents and injuries (Narrow)
[5] AEs in the SOC of cardiac disorders
[6] AEs in the SOC of vascular disorders
[7] AEs in the SMQ of central nervous system vascular disorders (Narrow)
[8] AEs in the SOC of infections and infestations
[9] AEs in the SMQ of anticholinergic syndrome (Narrow)
[10] Global quality of life decreased by at least 10% compared to baseline
[11] AEs with PTs of orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, ataxia, fracture
Sources: [Appendix 2-Table 1-10] and [Appendix 5-Novartis ARGUS Safety database outputs]

Age

The median age of patients treated with the combination with ribociclib and letrozole was 62 years in study A2301. There were no relevant findings and no consistent trends observed indicative of an increased risk for AEs by age categories.

Race

The vast majority of the enrolled patients were Caucasian. In the ribociclib + letrozole combination therapy pool 305 patients were Caucasian, 32 were Asian, 14 were Black and 17 were Others.

Safety related to drug-drug interactions and other interactions

See PK section.

Discontinuation due to adverse events

Table 45: AEs leading to discontinuation by primary SOC and PT irrespective of causality (with an incidence of at least 1.0% in 'All grades' - combination therapy pool) - (Safety set)

	Study A2301						Study X2107			Pooled combination therapy		
	RIBO+LET N=334			PBO+LET N=330			RIBO+LET N=47			RIBO+LET N=381		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Primary SOC Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any primary SOC - Total	**50 (15.0)**	**27 (8.1)**	**11 (3.3)**	**10 (3.0)**	**6 (1.8)**	**0**	**3 (6.4)**	**2 (4.3)**	**1 (2.1)**	**53 (13.9)**	**29 (7.6)**	**12 (3.1)**
Investigations-Total	**18 (5.4)**	**11 (3.3)**	**3 (0.9)**	**2 (0.6)**	**2 (0.6)**	**0**	**2 (4.3)**	**2 (4.3)**	**0**	**20 (5.2)**	**13 (3.4)**	**3 (0.8)**
Alanine aminotransferase increased	15 (4.5)	9 (2.7)	3 (0.9)	1 (0.3)	0	0	2 (4.3)	2 (4.3)	0	17 (4.5)	11 (2.9)	3 (0.8)
Aspartate aminotransferase increased	9 (2.7)	6 (1.8)	1 (0.3)	2 (0.6)	2 (0.6)	0	0	0	0	9 (2.4)	6 (1.6)	1 (0.3)
Gastrointestinal disorders - Total	**10 (3.0)**	**4 (1.2)**	**1 (0.3)**	**0**	**0**	**0**	**0**	**0**	**0**	**10 (2.6)**	**4 (1.0)**	**1 (0.3)**
Vomiting	8 (2.4)	4 (1.2)	0	0	0	0	0	0	0	8 (2.1)	4 (1.0)	0
Hepatobiliary disorders - Total	**4 (1.2)**	**3 (0.9)**	**1 (0.3)**	**1 (0.3)**	**0**	**0**	**0**	**0**	**0**	**4 (1.0)**	**3 (0.8)**	**1 (0.3)**

Discontinuation defined as discontinuation of ribociclib/placebo only or ribociclib, placebo, and letrozole.
System organ classes and preferred terms within a primary system organ class are sorted in descending order of frequency in 'All' grades 'Pooled monotherapy'.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events is counted only once in the total row.
AEs up to 30 days after the last study treatment will be included.
All=All Grades; G3=Grade 3; G4=Grade 4; LET=letrozole; RIBO=ribociclib; SOC=System Organ Class
Source: [SCS-Appendix 1-Table 3-10a]

Dose reduction due to adverse events, regardless of causality, occurred in 44.6% of patients receiving Kisqali plus letrozole and in 3.0% of patients receiving placebo plus letrozole. Permanent discontinuation due to adverse events was reported in 7.5% of patients receiving Kisqali plus letrozole and 2.1% in patients receiving placebo plus letrozole. The most common adverse drug reactions (ADRs) leading to treatment discontinuation in patients receiving Kisqali plus letrozole were ALT increased (2.7%), AST increased (2.4%) and vomiting (1.5%) (see SmPC section 4.8).

The AEs leading to discontinuation of study drug were reported more frequently in the ribociclib plus letrozole group compared to the placebo plus letrozole group (15 % and 3 %, respectively [all grades]).

The most commonly reported AEs in the experimental arm leading to discontinuation in the main study A2301 were ALT increased (4.5% with 2.7 % Grade 3 and 0.9 % Grade 4), AST increased (2.7% with 1.8 % Grade 3 and 0.3 % Grade 4), and vomiting (2.4% with 1.2 % Grade 3).

Interruption, delays and dose reductions were frequently required in the experimental arm. The proportions of patients that did not require any of these measures amounted to 23 %, 43 % and 46 % respectively. Dose interruptions were mainly caused by neutropenia (39 %), decreased neutrophil count (12 %), vomiting (6 %), nausea (5 %), increased ALT and increased AST (each 5 %). For dose reductions, most common cause was neutropenia (24 %) and decreased neutrophil count 8 %.

Hospital resource utilization

Overall, 113 patients were hospitalized during the course of study treatment: 64/334 (19.2%) patients in the ribociclib plus letrozole arm and 49/334 (14.7%) patients in the placebo plus letrozole arm; most of the hospitalizations were associated with utilization of the acute care facility (19.2% vs 14.4%, respectively). The median total duration of hospitalization stay was 6.0 days for both treatment arms.

Updated analysis of Study A2301 (data cut-off date of 22-Jun-2016)

As of this new data cut-off date with an additional 5 months of follow up, the median duration of exposure in the ribociclib plus letrozole arm exceeded ~ 17 months, with 137 patients (41 %) exposed to combination therapy with ribociclib for ≥ 18 months. The median duration of exposure to ribociclib and letrozole increased from 12 and 13 months, respectively, in the original submission to 16 and ~ 17 months in this updated analysis.

Disease progression remains the primary reason for treatment discontinuation from both treatment arms (33 % in the the ribociclib plus letrozole arm as compared to 53 % in the control arm). Discontinuations attributable to AEs were 8 % and 2.4%, respectively, similar to those reported in the original submission (8 % and 2 %).

Table 46: Relative differences in the frequency of the most frequently reported AEs at the respective data cut-offs (safety set)

	Original submission: 29-Jan-2016 data cut-off	Updated analysis: 22-Jun-2016 data cut-off
Hematologic AEs		
Neutropenia	+56.6%	+58.7%
Decreased neutrophil count	+18.0%	+18.9%
Decreased white blood cell count	+17.4%	+16.8%
Anemia	+13.8%	+13.1%
Leukopenia	+12.9%	+12.9%
Non-hematologic AEs		
Nausea	+23.0%	+23.6%
Alopecia	+17.7%	+17.7%
Vomiting	+13.8%	+15.0%
Diarrhea	+12.9%	+12.6%
Aspartate aminotransferase increased	+11.4%	+10.8%
Alanine aminotransferase increased	+11.7%	+11.4%
Rash	+9.2%	+10.4%

AEs presented are those where there is a ≥ 10% relative difference between treatment groups

Adverse events of special interest

Table 47: Adverse events of special interest (safety set)

	Original submission: 29-Jan-2016 data cut-off						Updated analysis: 22-Jun-2016 data cut-off					
	Ribociclib plus letrozole N=334			Placebo plus letrozole N=330			Ribociclib plus letrozole N=334			Placebo plus letrozole N=330		
AESI category	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematologic-related AESIs												
Neutropenia	249 (74.6)	166 (49.7)	33 (9.9)	17 (5.2)	3 (0.9)	0	254 (76.0)	172 (51.5)	33 (9.9)	18 (5.5)	3 (0.9)	0
Anemia	63 (18.9)	3 (0.9)	1 (0.3)	15 (4.5)	4 (1.2)	0	64 (19.2)	4 (1.2)	1 (0.3)	18 (5.5)	4 (1.2)	0
Leukopenia	55 (16.5)	27 (8.1)	5 (1.5)	12 (3.6)	2 (0.6)	0	55 (16.5)	27 (8.1)	5 (1.5)	13 (3.9)	2 (0.6)	0
Thrombocytopenia	30 (9.0)	2 (0.6)	0	2 (0.6)	0	0	30 (9.0)	2 (0.6)	0	2 (0.6)	0	0
Non-hematologic-related AESIs												
Nausea, emesis	188 (56.3)	16 (4.8)	0	108 (32.7)	3 (0.9)	0	197 (59.0)	16 (4.8)	0	112 (33.9)	3 (0.9)	0
Infections	168 (50.3)	12 (3.6)	2 (0.6)	140 (42.4)	7 (2.1)	1 (0.3)	180 (53.9)	17 (5.1)	3 (0.9)	150 (45.5)	8 (2.4)	1 (0.3)
Diarrhea	117 (35.0)	4 (1.2)	0	74 (22.4)	3 (0.9)	0	122 (36.5)	6 (1.8)	0	80 (24.2)	3 (0.9)	0
Hepatobiliary toxicity	80 (24.0)	31 (9.3)	7 (2.1)	45 (13.6)	12 (3.6)	0	84 (25.1)	33 (9.9)	7 (2.1)	48 (14.5)	13 (3.9)	0
Renal impairment	28 (8.4)	3 (0.9)	0	7 (2.1)	3 (0.9)	0	31 (9.3)	3 (0.9)	0	8 (2.4)	3 (0.9)	0
QTc interval prolongation	25 (7.5)	7 (2.1)	1 (0.3)	8 (2.4)	2 (0.6)	0	25 (7.5)	8 (2.4)	1 (0.3)	11 (3.3)	6 (1.8)	0
Pulmonary embolism	9 (2.7)	2 (0.6)	1 (0.3)	3 (0.9)	1 (0.3)	0	10 (3.0)	2 (0.6)	2 (0.6)	3 (0.9)	1 (0.3)	0
Reproductive toxicity	2 (0.6)	0	0	4 (1.2)	0	0	2 (0.6)	0	0	5 (1.5)	0	0

AESIs in patients receiving treatment for >12 months

Evaluation of the subgroup of patients who received treatment for a minimum of 12 months is based upon data from the 211 patients who were exposed to ribociclib at the recommended dose, and using the proposed treatment regimen (administered in combination with letrozole), and the 190 patients from the placebo plus letrozole control group.

The table below depicts AESIs (irrespective of relationship to treatment as requested) for patients receiving treatment for more than 12 months.

Table 48: AESIs irrespective of relationship to treatment for patients receiving treatment for more than 12 months: 22-Jun-2016 cut-off (safety set)

	Ribociclib plus letrozole						Placebo plus letrozole					
	0-12 months N=211		>12-18 months N=211		>18 months N=137 [1]		0-12 months N=190		>12-18 months N=190		>18 months N=105 [1]	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
AESI category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hematologic-related AESIs												
Neutropenia	162 (76.8)	127 (60.2)	86 (40.8)	49 (23.2)	45 (32.8)	23 (16.8)	9 (4.7)	1 (0.5)	4 (2.1)	0	2 (1.9)	0
Anemia	42 (19.9)	2 (0.9)	12 (5.7)	1 (0.5)	5 (3.6)	0	5 (2.6)	1 (0.5)	1 (0.5)	0	2 (1.9)	0
Leukopenia	34 (16.1)	16 (7.6)	10 (4.7)	2 (0.9)	4 (2.9)	0	6 (3.2)	0	1 (0.5)	0	2 (1.9)	0
Thrombocytopenia	17 (8.1)	1 (0.5)	2 (0.9)	0	2 (1.5)	0	1 (0.5)	0	0	0	0	0
Non-hematologic-related AESIs												
Infections	121 (57.3)	9 (4.3)	59 (28.0)	7 (3.3)	24 (17.5)	1 (0.7)	84 (44.2)	2 (1.1)	41 (21.6)	2 (1.1)	15 (14.3)	0
Nausea/emesis	117 (55.5)	7 (3.3)	26 (12.3)	2 (0.9)	4 (2.9)	0	56 (29.5)	1 (0.5)	12 (6.3)	1 (0.5)	5 (4.8)	0
Diarrhea	69 (32.7)	2 (0.9)	18 (8.5)	2 (0.9)	8 (5.8)	0	46 (24.2)	3 (1.6)	15 (7.9)	0	4 (3.8)	0
Hepatobiliary toxicity	45 (21.3)	16 (7.6)	10 (4.7)	3 (1.4)	5 (3.6)	1 (0.7)	18 (9.5)	6 (3.2)	8 (4.2)	1 (0.5)	3 (2.9)	1 (1.0)
Renal impairment	21 (10.0)	2 (0.9)	7 (3.3)	1 (0.5)	3 (2.2)	0	3 (1.6)	1 (0.5)	2 (1.1)	0	0	0
QTc interval prolongation	9 (4.3)	1 (0.5)	4 (1.9)	2 (0.9)	0	0	4 (2.1)	1 (0.5)	4 (2.1)	4 (2.1)	0	0
Pulmonary embolism [2]	6 (2.8)	2 (0.9)	1 (0.5)	0	1 (0.7)	1 (0.7)	3 (1.6)	1 (0.5)	0	0	0	0
Reproductive toxicity	2 (0.9)	0	0	0	0	0	1 (0.5)	0	1 (0.5)	0	0	0

AESI Adverse event of special interest
[1] Denominator=number of patients treated for >18 months
[2] Includes all thromboembolic preferred terms
Source: [Appendix 2-Table 1-1]

Neutropenia

Table 49: Clinical impact of neutropenia in patients receiving treatment for more than 12 months: 22-Jun-2016 data cut-off (safety set)

	Ribociclib plus letrozole			Placebo plus letrozole		
	0-12 months N=211	>12-18 months N=211	>18 months N=137 [1]	0-12 months N=190	>12-18 months N=190	>18 months N=105 [1]
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse event (AE)	162 (76.8)	86 (40.8)	45 (32.8)	9 (4.7)	4 (2.1)	2 (1.9)
Grade ¾	127 (60.2)	49 (23.2)	23 (16.8)	1 (0.5)	0	0
Suspected to be related	159 (75.4)	82 (38.9)	43 (31.4)	9 (4.7)	4 (2.1)	2 (1.9)
Serious adverse event	4 (1.9)	0	0	0	0	0
AE leading to discontinuation	2 (0.9)	0	0	0	0	0
AE leading to permanent dose reduction	73 (34.6)	3 (1.4)	2 (1.5)	0	0	0
AE requiring dose interruption	107 (50.7)	39 (18.5)	25 (18.2)	1 (0.5)	1 (0.5)	0

[1] Denominator=number of patients treated for >18 months
Source: [Appendix 2-Table 1-1]

Hepatobiliary toxicity

Table 50: Clinical impact of Hepatobiliary toxicity in patients receiving treatment for more than 12 months: 22-Jun-2016 data cut-off (safety set)

	Ribociclib plus letrozole			Placebo plus letrozole		
	0-12 months N=211 n (%)	>12-18 months N=211 n (%)	>18 months N=137 [1] n (%)	0-12 months N=190 n (%)	>12-18 months N=190 n (%)	>18 months N=105 [1] n (%)
Adverse event (AE)	45 (21.3)	10 (4.7)	5 (3.6)	18 (9.5)	8 (4.2)	3 (2.9)
Grade ¾	16 (7.6)	3 (1.4)	1 (0.7)	6 (3.2)	1 (0.5)	1 (1.0)
Suspected to be related	33 (15.6)	5 (2.4)	2 (1.5)	8 (4.2)	4 (2.1)	2 (1.9)
Serious adverse event	3 (1.4)	0	0	0	0	0
AE leading to discontinuation	7 (3.3)	1 (0.5)	0	0	2 (1.1)	0
AE leading to permanent dose reduction	9 (4.3)	1 (0.5)	0	2 (1.1)	1 (0.5)	0
AE requiring dose interruption	14 (6.6)	3 (1.4)	0	4 (2.1)	3 (1.6)	0

[1] Denominator=number of patients treated for >18 months

Source: [Appendix 2-Table 1-1]

QTc interval prolongation

Table 51: Clinical impact of QTc interval prolongation in patients receiving treatment for more than 12 months: 22-Jun-2016 data cut-off (safety set)

	Ribociclib plus letrozole N=211			Placebo plus letrozole N=190		
	0-12 months N=211 n (%)	>12-18 months N=211 n (%)	>18 months N=137 [1] n (%)	0-12 months N=190 n (%)	>12-18 months N=190 n (%)	>18 months N=105 [1] n (%)
Adverse event (AE)	9 (4.3)	4 (1.9)	0	4 (2.1)	4 (2.1)	0
Grade ¾	1 (0.5)	2 (0.9)	0	1 (0.5)	4 (2.1)	0
Suspected to be related	7 (3.3)	0	0	1 (0.5)	0	0
Serious adverse event	0	0	0	0	2 (1.1)	0
AE leading to discontinuation	0	0	0	0	0	0
AE leading to permanent dose reduction	0	0	0	0	0	0
AE requiring dose interruption	2 (0.9)	0	0	0	1 (0.5)	0

[1] Denominator=number of patients treated for >18 months

Source: [Appendix 2-Table 1-1]

AEs leading to discontinuation

Table 52: AEs leading to discontinuation irrespective of relationship to treatment by preferred terms for patients receiving treatment for more than 12 months: 22-Jun-2016 data cut-off (safety set)

	Ribociclib plus letrozole			Placebo plus letrozole		
	0-12 months N=211 n (%)	>12-18 months N=211 n (%)	>18 months N=137 [1] n (%)	0-12 months N=190 n (%)	>12-18 months N=190 n (%)	>18 months N=105 [1] n (%)
Any AE leading to discontinuation	**18 (8.5)**	**3 (1.4)**	**1 (0.7)**	**1 (0.5)**	**3 (1.6)**	**0**
ALT increased	5 (2.4)	0	0	0	0	0
Neutropenia	2 (0.9)	0	0	0	0	0
Vomiting	2 (0.9)	0	0	0	0	0
Autoimmune hepatitis	1 (0.5)	0	0	0	0	0
Duodenal perforation	1 (0.5)	0	0	0	0	0
Dyspnoea	1 (0.5)	0	0	0	0	0
Fatigue	1 (0.5)	0	0	0	0	0
Headache	1 (0.5)	0	0	0	0	0
Hepatocellular injury	1 (0.5)	0	0	0	0	0
Interstitial ling disease	1 (0.5)	0	0	0	0	0
Lung infiltration	1 (0.5)	0	0	0	0	0
Pericardial effusion	1 (0.5)	0	0	0	0	0
Pruritus	1 (0.5)	0	0	0	0	0
Sinus headache	1 (0.5)	0	0	0	0	0
Weight decreased	1 (0.5)	0	0	0	0	0
Hypertension	0	1 (0.5)	0	1 (0.5)	0	0
AST increased	0	1 (0.5)	0	0	0	0
Pneumonia	0	1 (0.5)	0	0	0	0
Acute respiratory failure	0	0	1 (0.7)	0	0	0
Pulmonary embolism	0	0	1 (0.7)	0	0	0
Blood bilirubin increased	0	0	0	0	1 (0.5)	0
Hyperbilirubinaemia	0	0	0	0	1 (0.5)	0
Musculoskeletal pain	0	0	0	0	1 (0.5)	0

ALT Alanine aminotransferase increased; AST Aspartate aminotransferase increased

[1] Denominator=number of patients treated for >18 months

Source: [Appendix 2-Table 1-1a]

AEs leading to permanent dose reductions

Table 53: AEs leading to permanent dose reductions irrespective of relationship to treatment by preferred terms for patients receiving treatment for more than 12 months: 22-Jun-2016 data cut-off (safety set)

	Ribociclib plus letrozole			Placebo plus letrozole		
	0-12 months N=211 n (%)	>12-18 months N=211 n (%)	>18 months N=137 [1] n (%)	0-12 months N=190 n (%)	>12-18 months N=190 n (%)	>18 months N=105 [1] n (%)
Any AE leading to permanent dose reduction	**100 (47.4)**	**8 (3.8)**	**3 (2.2)**	**5 (2.6)**	**4 (2.1)**	**0**
Neutropenia	54 (25.6)	3 (1.4)	1 (0.7)	0	0	0
Neutrophil count decreased	19 (9.0)	0	1 (0.7)	0	0	0
ALT increased	8 (3.8)	1 (0.5)	0	1 (0.5)	0	0
Nausea	5 (2.4)	0	0	0	0	0
Diarrhoea	4 (1.9)	0	0	1 (0.5)	0	0
Leukopenia	4 (1.9)	0	0	0	0	0
Vomiting	3 (1.4)	0	0	0	0	0
Fatigue	2 (0.9)	1 (0.5)	0	1 (0.5)	1 (0.5)	0
AST increased	2 (0.9)	1 (0.5)	0	1 (0.5)	0	0
Asthenia	2 (0.9)	0	0	0	0	0
Blood creatinine increased	1 (0.5)	1 (0.5)	0	0	0	0
Constipation	1 (0.5)	0	0	0	0	0
Febrile neutropenia	1 (0.5)	0	0	0	0	0

ALT Alanine aminotransferase increased; AST Aspartate aminotransferase increased; PCJ Pneumocystis jirovecii

[1] Denominator=number of patients treated for >18 months

Source: [Appendix 2-Table 1-1b]

2.6.1. Discussion on clinical safety

The overall safety evaluation of Kisqali is based on data from 898 patients. Among these, a total of 568 subjects had been exposed to ribociclib at the proposed dose i.e. 600 mg QD on Days 1-21 of a 28-day cycle (data cut-off date of 29 January 2016). 381 patients had received ribociclib in combination with letrozole at 2.5 mg QD in the pivotal study A2301 (n=334) and the open-label, Phase Ib/II, dose-finding study X2107 study (n=47). The safety data base is considered of an acceptable magnitude at least for identifying the safety profile of ribociclib in combination with letrozole in the short-term perspective.

It is noted that about a third of the patients in the combination arm had a relative dose intensity for ribociclib of less than 70 % (34 % of the patients) and only 48 % achieved a relative dose intensity of > 90 %. The add-on of ribociclib to letrozole appears not to have a negative effect in upholding the dose intensity of the latter (mean and median of 99 % and 100 % respectively with 97 % of the patients achieving a relative dose intensity of > 90 %).

Although the overall proportion of AE reports between the two arms in the A2301 study, was similar (99 % and 97 %) there were overall higher proportions of Grade 3 (66 %), Grade 4 (15 %), SAEs (21 %), AEs leading to discontinuation (15 %) and dose interruptions/ adjustments (73 %) reported in the ribociclib

containing arm compared to the control arm (32 %; 1 %; 12 %; 3 %; 16 % respectively). As expected the vast majority in the combination arm was suspected to be drug-related (96 %). The high rate of AEs that required dose interruptions and/or adjustments of ribociclib could be subject to concern but in comparison rather few patients discontinued study treatment due to AEs. Hence it is considered that the main tolerability issues are well managed with adequate monitoring and minimizing measures taken. Furthermore, a discontinuation rate of 15 % is considered acceptable as this is commonly observed in oncology studies.

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption, reduction or discontinuation of Kisqali which are detailed in section 4.2 of the SmPC. The clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment (see SmPC sections 4.2 and 4.4).

Overall deaths were similar between the two arms and the majority was due to progressive disease (23 patients [~ 7 %] in the experimental arm whereof 18 (~5 %) were attributed to underlying malignancy versus 19 patients [~ 6 %] with 17 patients [~ 5 %] due to progressive disease).

There was no major difference in hospitalizations between the two arms (19 % in the combination arm versus about 15 % in the control arm).

Although neutropenic events occurred in a substantially higher proportion of patients in the experimental arm compared to the control (75 % vs. 5 %, respectively) including Grade 3/4 events with dose interruptions/adjustments required in more than 50 % of the patients, neutropenia appears to be well manageable with adequate monitoring and appropriate measures considering the low rate of discontinuations (0.9%), SAEs, and events of febrile neutropenia (1.5 %) into context. G-CSF was administered to 8 % of the patients in the ribociclib + letrozole arm (primarily filgrastim in 5 % patients) and 0.3% of patients in placebo + letrozole group. Based on its severity, neutropenia was managed by laboratory monitoring, dose interruption and/or dose modification. The monitoring and risk minimisation measures (guidance on dose reduction/interruption/ discontinuation) as proposed in section 4.2 in the SmPC are considered adequate for a safe management of neutropenic events in the out-patient setting. Complete blood counts (CBC) should be performed before initiating treatment with Kisqali. After initiating treatment CBC should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated. Patients should also be instructed to report any fever promptly (see SmPC section 4.4). Myelosuppression is also included as an important identified risk in the RMP.

Anaemia, leukopenia and thrombocytopenia are not considered to be of any major concern. Very few required erythropoetin treatment (four patients in total in studies A2301 and XUS03 whilst none in studies X2107, X2101, and X1101). Neither is there any concern in regard to the risk of bleeding associated with thrombocytopenia (one patient with epistaxis). Epistaxis is listed as an ADR in the SmPC. Review of data from the Clinical Database did not show an increased risk of hemorrhage (regardless of severity) secondary to thrombocytopenia in ribociclib-treated patients relative to the control arm.

The number of thromboembolic events as observed in the A2301 study may be considered within the expected range for a population of metastatic breast cancer already at risk and receiving concomitant endocrine therapy. Pulmonary embolism and thrombophlebitis including DVT are listed in section 4.8 of the letrozole SmPC. No conclusive link between ribociclib and thromboembolic events (VTE/PE) has been established and neither VTE nor PE is listed as ADRs. As these events are usually reported as serious, routine post marketing signal detection methods will be applied and any new signal will be followed up and subsequently reported in the PSURs.

Rather limited proportion of events of renal toxicity was reported in the main study. The event of 'blood creatinine increased' has been identified as an ADR subsequently included in the SmPC, Section 4.8. There were however four reports of renal failure and three of acute kidney injury (AKI) in the combination arm as compared to one each of these items in the control arm. No evidence for a causal relationship with ribociclib could be established in regard to these cases according to the Applicant. Based on the available data on blood creatinine increases however, 'renal toxicity' is included in the RMP as an important potential risk. Safety and pharmacokinetics in patients with severe renal impairment has been included as missing information in the RMP. The Applicant will provide the results of study CLEE011A2116 which evaluates the pharmacokinetics and safety of ribociclib in patients with varying degrees of impaired renal function compared to matched healthy volunteers with normal renal function (see RMP).

Diarrhoea appears to be manageable based on the fact that the vast majority were of Grade 1/2 with rather few Grade 3/4 events (~1 %) and similar rates were reported between the two arms. Moreover, the proportion of SAEs/ discontinuations/dose adjustment/interruptions due to diarrhoea does not evoke any major concern. There is no evidence of any cumulative toxicity.

A high proportion of infectious events were reported in the experimental arm (50 %) but also fairly high in the control arm (42 %). The similarity in terms of individual causes between the two arms is recognised although slightly more viral infections in the experimental arms (e.g. influenza, herpes). This appears non-problematic when considering that the vast majority were Grade 1/2, rather few SAEs and discontinuations. In regard to identified infectious ADRs, only urinary tract infections (UTI) are listed in Section 4.8. It is agreed that for specific individual reported infectious events other than UTI, the reported rates were too low to draw relevant conclusions as ADRs for ribociclib. Furthermore, only one event in study A2301 was classified as being an opportunistic infection (pneumocystis jirovecii pneumonia) in the experimental arm.

Four cases of liver injury (Hy's law cases) were reported in the experimental arm in the pivotal study albeit that none were fatal and liver function tests for all four patients recovered. Liver function tests should be performed before initiating treatment with Kisqali. After initiating treatment LFTs should be performed every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated. If grade ≥2 abnormalities are noted, more frequent monitoring is recommended (see sections 4.2, 4.4 and 4.8). Based on the severity of the transaminase elevations, treatment with Kisqali may have to be interrupted, reduced or discontinued as described in the SmPC (see sections 4.2 and 4.8). Recommendations for patients who have elevated AST/ALT grade ≥ 3 at baseline have not been established. Hepatobiliary toxicity is an important identified risk in the RMP.

The risk QTc interval prolongation appeared to be highest primarily within the first cycle(s) of ribiciclib treatment to thereafter slowly subsiding. There is no evidence for cumulative toxicity. This could be interpreted as the risk minimisation measurements as proposed in the SmPC are adhered to by the treating physician and thus adequate. Based on the observed QT prolongation during treatment, treatment with Kisqali may have to be interrupted, reduced or discontinued as described in the SmPC (see sections 4.2, 4.8 and 5.2). QT interval is an important identified risk in the RMP.

ECG should be assessed before initiating treatment. Treatment with Kisqali should be initiated only in patients with QTcF values less than 450 msec. ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated (see sections 4.2 and 4.8). Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed before initiating treatment, at the beginning of the first 6 cycles and then as clinically indicated. Any abnormality should be corrected before initiating treatment with Kisqali. The use of Kisqali should be avoided in patients who already have or who are at significant risk of developing QTc prolongation. This includes patients: with long QT syndrome; with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias; with electrolyte abnormalities.

The use of Kisqali with medicinal products known to prolong QTc interval and/or strong CYP3A inhibitors should be avoided as this may lead to clinically meaningful prolongation of the QTcF interval (see sections 4.2, 4.5 and 5.1). If treatment with a strong CYP3A4 inhibitor cannot be avoided, the dose should be reduced to 400 mg once daily (see sections 4.2 and 4.5). QT prolongation has been included as an important identified risk in the RMP.

From the safety update with a data cut-off date of 26 June 2016 (i.e. an additional 5 months), the safety profile and tolerability of ribociclib appears to remain consistent with the previous profile identified. There was no evidence of any cumulative toxicity and no new concerns have been evoked in regard to discontinuation or fatal cases. Overall, no new safety concerns or tolerability issues have been raised based on this update. The ribociclib associated toxicity appears manageable with the proposed risk minimization as laid out in the proposed SmPC.

In regard to gender and race, no conclusion can be drawn as only females were eligible in the A2301 study and the study population were in the vast majority Caucasian. Therefore, safety in male patients with breast cancer and safety in Japanese patients are included in the RMP as missing information. In terms of age groups, there was no major concern identified. Of interest is that there appears not to be any obvious differences in AE events by age group in terms of cardiac disorders, vascular disorders or infections/ infestations.

There are limited long term data with the use of ribociclib. Therefore long-term use has been included as missing information in the RMP. The Applicant continues to follow all surviving patients in the ongoing CLEE011A2301 study and safety data is being collected on an ongoing basis (see RMP). In addition, there are currently two large pivotal studies ongoing (CLEE011E2301 [MONALEESA-7] and CLEE011F2301 [MONALEESA-3]) which are still blinded. Patients are expected to be on-treatment on average for 13 months. In these studies ~ 1300 patients have been enrolled and randomized, with ~ 800 patients exposed to ribociclib; these study populations are similar to that of Study CLEE011A2301. Both phase 3 studies are expected to provide significant amount of safety data contributing to the safety profile of ribociclib (see RMP).

Safety data from two other ongoing studies (study CLEE011XDE01 (RIBECCA) and Study CLEE011A2404 (CompLEEment-1) will be provided as part of the PSURs.

The safety and efficacy of Kisqali in children and adolescents aged below 18 years have not been established. No data are available.

There were no known cases of overdosage with ribociclib. In the event of an overdose, symptoms such as nausea and vomiting may occur. In addition, haematological (e.g. neutropenia, thrombocytopenia) toxicity and possible QTc prolongation may occur. General supportive care should be initiated in all cases of overdosage as necessary (see SmPC section 4.9).

Kisqali may have minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines in case they experience fatigue during treatment with Kisqali (see section 4.8).

Kisqali contains soya lecithin. Patients who are hypersensitive to peanut or soya should not take Kisqali (see SmPC sections 4.3 and 4.4).Kisqali is contraindicated in case of hypersensitivity to the active substance or to peanut, soya or any of the excipients listed in SmPC section 6.1.

2.6.2. Conclusions on the clinical safety

The combination of ribociclib and letrozole is associated with a substantial increase in toxicity relative to letrozole, particularly in terms of myelosuppression (neutropenia). This is consistent with the safety profile of other products within the same class (e.g. palbociclib).

Therefore, the safety and tolerability of ribociclib in considered acceptable and appears manageable with the proposed risk minimization activities as laid out in the proposed SmPC.

2.7. Risk Management Plan

Safety concerns

Table: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Myelosuppression Hepatobiliary toxicity QT interval prolongation
Important potential risks	Renal toxicity
Missing information	Safety in Japanese patients Safety in male patients with breast cancer Long-term use Safety and pharmacokinetics in patients with severe renal impairment

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final Reports** (planned or actual)
CLEE011A2116: A phase I, open label, multicenter, parallel-group, single dose two-staged study to evaluate the pharmacokinetics and safety of a single 400 mg oral dose of LEE011 in	To characterize the PK and safety profile of LEE011 following a single oral dose in adult subjects with various degrees of renal impairment compared to a	Safety and pharmacokinetics in patients with severe renal impairment	Ongoing	Q1-2019

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final Reports** (planned or actual)
subjects with varying degrees of impaired renal function compared to matched healthy volunteers with normal renal function, category 3	matched group of healthy subjects with normal renal function.			
CLEE011F2301 (MONALEESA-3): A randomized double-blind, placebo controlled study of ribociclib in combination with fulvestrant for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment (Category 3).	To compare PFS between ribociclib in combination with fulvestrant to placebo in combination with fulvestrant among postmenopausal women with HR+, HER2-negative advanced breast cancer who received no or only one prior endocrine treatment for advanced disease.	Long term use	Ongoing	PFS Q3 2018
CLEE011E2301 (MONALEESA-7): A Phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer (Category 3).	To determine whether treatment with tamoxifen or a NSAI + goserelin + LEE011 prolongs PFS compared to treatment with tamoxifen or a NSAI + goserelin + placebo in premenopausal women with HR+, HER2- advanced breast cancer who received no prior hormonal therapy for advanced breast cancer.	Long term use	Ongoing	PFS Q3 2018
Study CLEE011A2301 (Monaleesa-2) [1] is an ongoing randomized double-blind, placebo-controlled Phase III study of ribociclib in combination with letrozole for the treatment of postmenopausal women with HR+, HER2-negative advanced breast cancer who received no prior therapy for advanced disease. (Category 3)	To compare PFS between ribociclib in combination with letrozole to placebo plus letrozole among postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior therapy for their advanced breast cancer.	Long term use	Ongoing	OS Q4 2021

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks		
Myelosuppression	SmPC Sections 4.2, 4.4, 4.8	None
Hepatobiliary toxicity	SmPC Sections 4.2, 4.8	None
QT interval prolongation	SmPC Section 4.2, 4.4, 4.5, 4.8	None
Important potential risks		
Renal toxicity	SmPC Section 4.8	None
Missing information		
Safety in Japanese patients	Currently available data are limited and do not support the need for risk minimization. Prescription only medicine, treatment with ribociclib should be initiated by a physician experienced in the use of anticancer therapies and to be used in the approved indication.	None
Safety in male patients with breast cancer	Currently available data are limited and do not support the need for risk minimization. Prescription only medicine, treatment with ribociclib should be initiated by a physician experienced in the use of anticancer therapies and to be used in the approved indication.	None
Long-term use	Currently available data are limited and do not support the need for risk minimization. Prescription only medicine, treatment with ribociclib should be initiated by a physician experienced in the use of anticancer therapies and to be used in the approved indication.	None
Safety and pharmacokinetics in patients with severe renal impairment	SmPC Section 4.2, 5.2	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 dated 22 June 2017 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 13.03.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of ribociclib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers ribociclib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kisqali (ribociclib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indication is for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer.

3.1.2. Available therapies and unmet medical need

Locally advanced or metastatic breast cancer patients derive benefit mainly from systemic treatments. For the targeted population, a variety of endocrine therapies such as letrozole, anastrozole, exemestane, fulvestrant and tamoxifen are valid 1st line options. TTP/PFS in the range of 5- 15 (20) months is typical in endocrine therapy trials in the postmenopausal population (Kümler ESMO Open 2016). Prolonging overall survival is an unmet need in the targeted population. The first in class CDK4/6 inhibitor palbociclib was recently approved for an indication including that presently sought for ribociclib (EPAR Ibrance).

According to treatment guidelines, chemotherapy should be reserved for cases of rapidly progressive disease or proven endocrine resistance.

3.1.3. Main clinical studies

The pivotal trial CLEE011A2301 was an international, multi-centre, randomized, double-blinded, placebo-controlled Phase III study. Patients were randomly assigned in a 1:1 ratio to either ribociclib (600 mg once daily, days 1-21 in a 28-day cycle) plus letrozole (2.5 mg once daily) or placebo (once daily, days 1-21 in a 28-day cycle) plus letrozole (2.5 mg once daily). Randomization was stratified by the presence of liver and/or lung metastases (yes versus no). Patients received study treatment until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason. Treatment crossover from placebo to ribociclib was not permitted in this study.

3.2. Favourable effects

The pivotal trial CLEE011A2301/MONALEESA-2 showed a PFS benefit of combined ribociclib and letrozole compared to letrozole of 9 months where the median PFS for the ribociclib and letrozole combination was 25 months whereas, the median PFS for letrozole was 16 months with a HR 0.568 (0.457 – 0.704). OS data was immature with 17 % events revealed a trend towards benefit for ribociclib. The median for the experimental arm was not reached, the median for the control arm was 33 months, and the HR 0.746 (0.517 – 1.078). ORR was 42.5 % and 28.7 % in the combination arm and letrozole arm respectively.

A reduction in the risk of disease progression or death in favour of the ribociclib plus letrozole arm was also observed in all individual patient subgroups of age, race, prior adjuvant or neo adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone only metastatic disease. For patients with liver and/or lung metastases median progression free survival [mPFS] was 24.8 months for ribociclib plus letrozole versus 13.4 months for letrozole alone (HR of 0.561 [95% CI: 0.424, 0.743]). For patients without liver and/or lung metastases mPFS was 27.6 months versus 18.2 months respectively (HR of 0.597 [95% CI: 0.426, 0.837].

Preclinical data indicate heterogeneity in sensitivity to CDK4/6 inhibitors. In CLEE011A2301/MONALEESA-2 there was no compelling evidence of differential effects in subgroups defined by Cyclin D1, RB or P16 mRNA or protein expression. As the investigated biomarkers may be more relevant for ER negative breast cancer cells, the possibility that there is a group of patients with distinct molecular signature and tumour characteristics that would benefit the most from this therapy should be further investigated. The results from the biomarker assessment in study CLEE011A2301/MONALEESA-2 will be submitted together with the CSR (see RMP).

3.3. Uncertainties and limitations about favourable effects

The efficacy and safety of ribociclib have not been studied in patients with critical visceral disease (see SmPC section 4.4).

3.4. Unfavourable effects

There were overall higher proportions of Grade 3 (66 %), Grade 4 (15 %), SAEs (21 %), AEs leading to discontinuation (15 %) and dose interruptions/ adjustments (73 %) reported in the ribociclib containing arm compared to the control arm (corresponding rates: 32 %; 1 %; 12 %; 3 %; 16 % respectively). The discontinuations due to AEs (at least within the range often observed and accepted in oncology studies [15 %]) and likewise, the proportion of deaths (7 %, primarily due to progressive disease and not AE related) in the combination arm in study A2301 were fairly low. In addition, there was no major difference in hospitalizations (due to any cause) between the two arms (19 % in the combination arm versus about 15 % in the control arm).

The most common adverse reactions for ribociclib were neutropenia, leukopenia, headache, back pain, nausea, fatigue, diarrhoea, vomiting, constipation, alopecia. The most common grade 3/4 ADRs were rash and neutropenia, leukopenia, abnormal liver function test, lymphopenia, hypophosphataemia, vomiting, nausea, fatigue and back pain.

In terms of anaemia, leukopenia, thrombocytopenia, reproductive toxicity and pulmonary embolism none of them appears be of major concern. Although, neutropenia is frequently reported, it appears manageable with adequate monitoring and appropriate minimisation measures (febrile neutropenia and sepsis were reported in a low proportion [1.5 % and ~ 1 % respectively]). In addition, in regard to nausea, vomiting, diarrhoea and infections it is believed that also these risks can be appropriately handled in clinical practice.

It appears that renal toxicity was reported in the pivotal study (mainly 'blood creatinine increased' which has been identified as an ADR and subsequently included in the SmPC, Section 4.8). There were however four reports of renal failure and three of acute kidney injury (AKI) in the combination arm as compared to one each of these items in the control arm. Thus, renal toxicity is included as an important potential risk in the RMP.

Hepatobiliary toxicity is supported by non-clinical observations. The precise aetiology has not been elucidated but available evidence suggests an underlying immune mechanism triggering the hepatic effects (possibly through the formation of protein adducts). Thus, hepatobiliary toxicity is included as an important identified risk in the RMP.

In Study A2301, 'QTc interval prolongation' events occurred more frequently in the combination arm compared to the letrozole arm with ECG QT prolonged being the most frequent AE (4.5 %) reported followed by syncope (3 %). It is recognised that the risk QTc interval prolongation appear to be highest primarily

within the first cycle(s) of ribociclib treatment to thereafter slowly subsiding. This could be a consequence of better patient management and implementation of the risk minimisation measurements as proposed in the SmPC by the treating physician as a function of time spent on treatment. Thus, QT prolongation is included as an important identified risk in the RMP.

3.5. Uncertainties and limitations about unfavourable effects

Long-term safety data is lacking but is addressed in the safety specification as missing information. Studies CLEE011A2301,CLEE011E2301 [MONALEESA-7] and CLEE011F2301 [MONALEESA-3]) will provide significant amount of safety data contributing to the safety profile of ribociclib (see RMP).

3.6. Effects Table

Table 54: Effects Table for ribociclib in combination with an aromatase inhibitor 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 (Database lock: 29 January 2016 (primary PFS analysis); 31 January 2017 (2nd interim OS analysis))

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Study A2301 (MONALEESA-2)						
Favourable Effects						
PFS	Progression-free survival (investigator)	Hazard ratio	0.568	1	0.457 - 0.704 p= 9.63 x 10^{-8}	Clinical efficacy section
		Months; median	25.3	16.0	Difference of 9.3 months	
ORR	Overall response rate	Proportion (%)	42.5	28.7	13.8 % absolute difference p= 0.0000918	
OS	Overall survival	Hazard ratio	0.746	1	0.517 – 1.078 p= 0.059	
		Months; median	Not reached	33.0	Not assessed	
Study A2301 (MONALEESA-2)						
Unfavourable Effects						
Discontinuations due to AEs – All SOCs	Incidence of discontinuation due to AEs	%	15.0	3.0	Fairly similar exposure between arms In terms of tolerability a substantial proportion of dose adjustments and dose reductions occurred, however rather few did discontinue study treatment which is reassuring.	Clinical Safety section
AEs requiring dose interruption and/or adjustments	Incidence	%	73.1	15.8		
AE All	Incidence of AE %	%	98.5	97.0	Discontinuation due to	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Study A2301 (MONALEESA-2)						
Neutropenia Nausea Diarrhoea Vomiting Rash Anaemia ALT ↗ AST ↗ Stomatitis Thrombocytopenia			74.6 51.5 30.5 29.3 17.1 18.3 15.6 15.0 12.3 6.0	5.2 28.5 22.1 15.5 7.9 4.5 3.9 3.6 6.7 0.6	neutropenia was very low. Majority of interruptions were due to AEs for ribociclib (68% mainly neutropenia [39 %]) but dosing errors accounted for 22%.	
AE Grade 3 AE Grade 4	Incidence	%	66.2 15.0	31.8 0.9		
SAE All GI disorder Infections - pneumonia Blood SOC - febrile neutropenia Respiratory total Hep disorder total Cardiac disorder total	Incidence of SAEs	%	 21.3 5.1 3.3 0.9 3.6 1.2 3.6 2.4 1.2	 11.8 2.4 2.1 0.3 0.3 0 1.2 0 0.3		

[a]Number of patients with at least one dose delay by reason (AEs)

[b]Dose delays are the subset of interruptions that occur at the beginning of a new cycle after a rest period

Note:n/a: not applicable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The current guidelines recommend endocrine therapy as a first choice of therapy in HR positive, HER2 negative advanced or metastatic breast cancer. TTP/PFS in the range of 5- 15 (20) months is typical in endocrine therapy trials in the postmenopausal population (Kümler ESMO Open 2016). The apparent acceptance for using combination therapy instead of endocrine-therapy in monotherapy is understood as a consequence of the benign tolerability profile of CDK 4/6 inhibitors, further underscored by the clinical acceptance of palbociclib as add-on to an aromatase inhibitor in ER positive/HER-2 negative advanced breast cancer (Cardoso Ann Oncol 2016). The efficacy presented in the pivotal trial showed a PFS gain of 9 months

for the combination therapy of ribociclib with letrozole compared to letrozole alone. This magnitude of the effect is considered clinically relevant. A delay in disease progression is further supported by a trend towards OS benefit and postponement of 1st and 2nd subsequent lines of therapy.

The combination of ribociclib to letrozole is associated with an increase in toxicity relative to letrozole alone. The most common ADR is myelosuppression (neutropenia). This is however not regarded as a major concern since it is manageable with the measures proposed in the SmPC. The safety risks observed in the pivotal trial are similar to those that are expected from the class of CDK4/6 inhibitors. There is also no evidence of any cumulative toxicity. Therefore, the safety of ribociclib appears acceptable and manageable with the proposed risk minimization as laid out in the proposed SmPC.

3.7.2. Balance of benefits and risks

A clinically relevant effect in PFS has been demonstrated for the combination therapy of ribociclib with letrozole 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 initial endocrine based therapy. The OS findings are still immature with 15% and 20% events in the experimental and control arms, but with a reassuring trend towards benefit for the ribociclib arm. Accordingly, there is no evidence of an accelerated resistance or progression in ribociclib-treated patients that have received subsequent therapies; neither does time to 1st and 2nd subsequent line of therapy indicate such an effect.

The safety of ribociclib in the short term is considered acceptable and fairly well characterised. The additional 5 months of safety update not revealed no new safety concerns or tolerability issues. The ribociclib associated toxicity appears manageable and the measures and risk minimizations as proposed in Section 4.2 of the SmPC are considered appropriate.

Based on the above the benefit/risk balance of ribociclib in combination with an aromatase inhibitor 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 is considered positive.

The indication has included the class of “aromatase inhibitors” instead of “letrozole” since it is reasonable to extrapolate from letrozole to aromatase inhibitors based on the similarity of the mechanism of action of aromatase inhibitors in general, where inhibiting the aromatase enzyme will block the conversion of androgens to oestrogens. There are no DDI/PK issues between exemestane or anastrozole and ribociclib that preclude the extrapolation (See PK section).

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Kisqali in combination with an aromatase inhibitor 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 is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Kisqali is favourable in 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 growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer as initial endocrine based therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that ribociclib is considered to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.