

NEW ZEALAND DATA SHEET

KISQALI® 200 mg film coated tablet

1. NAME OF THE MEDICINAL PRODUCT

KISQALI® 200 mg film coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each immediate release film-coated tablet contains ribociclib succinate equivalent to 200 mg of ribociclib free base.

Excipients with known effect

Each film-coated tablet contains 0.344 mg soya lecithin.

For the full list of KISQALI tablet excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Light greyish violet that is also unscored, round (approx. diameter: 11.1 mm), curved film-coated tablet with bevelled edges; debossed with "RIC" on one side and "NVR" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KISQALI is indicated for the treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, in combination with an aromatase inhibitor or fulvestrant, as an initial endocrine-based therapy or following prior endocrine therapy.

In pre- or peri-menopausal women or men, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

4.2 Dose and method of administration

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

Monitoring for adverse drug reactions (ADRs) is required, including complete blood counts, LFTs, serum electrolytes, and ECG; dose modification (delay, reduction) or cessation may be required (see Tables 1-6).

Dose

KISQALI

The recommended dose of KISQALI is 600 mg (three 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days, followed by 7 days off treatment, resulting in a complete cycle of 28 days. KISQALI may be taken with or without food (see section 4.5 Interaction with other medicines and other forms of interaction).

Treatment should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

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Aromatase inhibitor

When co-administered with KISQALI, the aromatase inhibitor is taken daily throughout the 28-day cycle. Please refer to the full New Zealand data sheet for the aromatase inhibitor dosing regimen.

Patients should be encouraged to take their dose of KISQALI and aromatase inhibitor at approximately the same time each day, preferably in the morning.

Fulvestrant

When co-administered with KISQALI, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, 29, and once monthly thereafter. Please refer to the full fulvestrant data sheet.

Luteinising hormone-releasing hormone (LHRH) agonist

In pre- or peri-menopausal women or men, the endocrine therapy should be co-administered with a luteinising hormone-releasing hormone (LHRH) agonist, according to current local clinical practice standards.

Dose Modifications

Management of severe or intolerable ADRs may require temporary dose interruption, dose reduction, or permanent discontinuation of KISQALI. If dose reduction is required, the recommended dose reduction guidelines are listed in Table 1.

Refer to the data sheet for any co-administered medicines (aromatase inhibitor, fulvestrant or LHRH agonist) for dose modification guidelines and other relevant safety information in the event of toxicity.

Table 1 Recommended dose modification guidelines

| | Dose | Number of Tablets |
|-----------------------|-------------|--------------------------|
| Starting dose | 600 mg/day | 3 × 200 mg tablets |
| First dose reduction | 400 mg/day | 2 × 200 mg tablets |
| Second dose reduction | 200 mg*/day | 1 × 200 mg tablets |

*If further dose reduction below 200 mg/day is required, discontinue the treatment.

Tables 2 to 6 provide recommendations for dose interruption, reduction, or discontinuation of KISQALI in the management of specific ADRs. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment (see section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects).

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Table 2 Dose modification and management for QT prolongation

| On treatment ECGs with QTcF value of: | Recommendations |
|--|---|
| > 480 ms | <ol style="list-style-type: none"> 1. The dose should be interrupted 2. If QTcF prolongation resolves to < 481 ms, resume treatment at the next lower dose level; 3. If QTcF \geq 481 ms recurs, dose interrupt until QTcF < 481 ms, and then resume KISQALI at next lower dose level |
| > 500 ms on at least 2 separate ECGs (on the same visit) | Interrupt KISQALI until QTcF < 481 ms then resume KISQALI at next lower dose level |
| > 500 ms or > 60 ms change from baseline With either: <ul style="list-style-type: none"> • Torsade de Pointes <li style="text-align: center;">or • polymorphic ventricular tachycardia <li style="text-align: center;">or • unexplained syncope <li style="text-align: center;">or • signs/symptoms of serious arrhythmia | Permanently discontinue KISQALI. |
| ECG should be performed prior to initiation, repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, and as clinically indicated. In patients with higher risk of QTcF prolongation or ventricular arrhythmias, more frequent ECG monitoring is recommended. | |
| Serum electrolytes (including potassium, calcium, phosphorous and magnesium) should be performed prior to initiation of treatment and at the beginning of the next 5 cycles, with abnormalities corrected prior to commencement/ resumption of treatment. Cycle commencement must be accompanied by active review of all concomitantly administered medicines. | |
| In case of QTcF prolongation at any given time during treatment: <ul style="list-style-type: none"> • Perform analysis of serum electrolytes (K^+, Ca^{2+}, PO_4^{3-}, Mg^{2+}). If outside the normal range, interrupt ribociclib treatment, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. • Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval • More frequent ECG monitoring is recommended, e.g. 7 and 14 days after resumption of KISQALI | |

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Table 3 Dose modification and management for neutropenia and febrile neutropenia

| Grade 1 or 2 (ANC 1000/mm ³ – < LLN) | Grade 3 (ANC 500 - < 1000/mm ³) | Grade 3 febrile* neutropenia | Grade 4 (ANC < 500/mm ³) |
|---|---|---|--|
| No dose adjustment is required. | Dose interruption until recovery to grade ≤ 2. Resume KISQALI at the same dose level. If toxicity recurs at grade 3, dose interruption until recovery to grade ≤ 2, then resume KISQALI at the next lower dose level. | Dose interruption until recovery of neutropenia to grade ≤ 2. Resume KISQALI at the next lower dose level. | Dose interruption until recovery to grade ≤ 2. Resume KISQALI at the next lower dose level. |

Perform Full blood counts (FBC) before initiating treatment with KISQALI.

After initiating treatment with KISQALI, monitor FBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, then as clinically indicated.

*Grade 3 neutropenia with a single episode of fever >38.3°C (or) above 38°C for more than one hour and/or concurrent infection

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

ANC = absolute neutrophil count; LLN = lower limit of normal

Table 4 Dose modification and management for hepatobiliary toxicity

| | Grade 1 (> ULN – 3 x ULN) | Grade 2 (>3 to 5 x ULN) | Grade 3 (>5 to 20 x ULN) | Grade 4 (>20 x ULN) |
|--|---------------------------------|--|--|------------------------|
| AST and/or ALT elevations from baseline*, without increase in total bilirubin above 2 x ULN | No dose adjustment is required. | Baseline at Grade ≤2: Dose interruption until recovery to ≤ baseline grade, then resume KISQALI at same dose level. If grade 2 recurs, resume KISQALI at next lower dose level. Baseline Grade = 2: No dose interruption. | Dose interruption until recovery to ≤ baseline grade, then resume at next lower dose level. If grade 3 recurs, discontinue KISQALI. | Discontinue KISQALI |

Combined elevations in AST and/or ALT together with total bilirubin increase, in the absence of cholestasis

If patients develop ALT and/or AST > 3 x ULN along with total bilirubin > 2 x ULN irrespective of baseline grade, discontinue KISQALI.

Liver Function Tests (LFTs) should be performed before initiating treatment with KISQALI.

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| Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|--|-----------------|------------------|-------------|
| (> ULN – 3 x ULN) | (>3 to 5 x ULN) | (>5 to 20 x ULN) | (>20 x ULN) |
| <p>After initiating treatment with KISQALI, LFTs should be monitored every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.</p> <p>If Grade 2, 3 or 4 abnormalities are noted, more frequent monitoring is recommended</p> <p>ULN = upper limit of normal</p> <p>*Baseline = prior to treatment initiation. Grading according to CTCAE Version 4.0. CTCAE=Common Terminology Criteria for Adverse Events</p> | | | |

Table 5 Dose modification and management for Interstitial Lung Disease (ILD)/Pneumonitis

| Grade 1 (asymptomatic) | Grade 2 (symptomatic) | Grade 3 or 4 (severe) |
|---|---|----------------------------|
| <p>No dose adjustment is required.</p> <p>Initiate appropriate medical therapy and monitor as clinically indicated.</p> | <p>Interrupt KISQALI until recovery to Grade ≤1, then resume KISQALI at the next lower dose level*.</p> | <p>Discontinue KISQALI</p> |

Grading according to CTCAE Version 4.03.

* An individualized benefit-risk assessment should be performed when considering resuming KISQALI

Table 6 Dose modification and management for other toxicities*

| Grade 1 or 2 | Grade 3 | Grade 4 |
|--|---|-----------------------------|
| <p>Other toxicities</p> <p>No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.</p> | <p>Dose interruption until recovery to grade ≤1 resume KISQALI at same dose level.</p> <p>If grade 3 recurs, resume KISQALI at the next lower dose level.</p> | <p>Discontinue KISQALI.</p> |

*excluding neutropenia, febrile neutropenia, hepatobiliary toxicity, and QT interval prolongation.

Grading according to CTCAE Version 4.03. CTCAE=Common Terminology Criteria for Adverse Events.

Dose modification for use of KISQALI with strong CYP3A inhibitors

Avoid concomitant use of KISQALI with strong CYP3A inhibitors and consider an alternative concomitant medication with less potential for CYP3A inhibition. If a strong CYP3A inhibitor must be co-administered, reduce the KISQALI dose to 200 mg once daily.

Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients, therefore close monitoring of signs of toxicity is recommended. If the strong inhibitor is discontinued, the KISQALI dose should be changed (after 5 elimination half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor (see section 4.4 Special warnings and precautions for use, section 4.5

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Interaction with other medicines and other forms of interaction and section 5.2 Pharmacokinetic (PK) Properties).

Special Populations

Renal Impairment

Based on a population pharmacokinetic analyses and data from cancer patients in clinical trials, no dose adjustment is necessary in patients with mild or moderate renal impairment (see section 5.2 Pharmacokinetic (PK) Properties).

There is limited experience in patients with moderate renal impairment and no experience in patients with severe renal failure or who require haemodialysis with the use of KISQALI.

KISQALI has not been studied in breast cancer patients with severe renal impairment. Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment, a KISQALI starting dose of 200 mg once daily is recommended (see section 5.2 Pharmacokinetic (PK) Properties).

Hepatic Impairment

A pharmacokinetic study in healthy subjects and non-cancer subjects with impaired hepatic function found that no dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). A dose adjustment is required in patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) can have increased (less than two-fold) exposure to ribociclib, and the starting dose of KISQALI 400 mg once daily is recommended. Ribociclib has not been studied in breast cancer patients with moderate and severe hepatic impairment (see section 5.2 Pharmacokinetic (PK) Properties).

Refer to the New Zealand data sheet for the co administered medicines (aromatase inhibitor, fulvestrant, or LHRH agonist) for dose modification related to hepatic impairment.

Paediatric population

The safety and efficacy of KISQALI in children and adolescents aged below 18 years have not been established.

Elderly

No dose adjustment is necessary in patients over 65 years of age (see section 5.2 Pharmacokinetic (PK) Properties).

Method of administration

KISQALI should be administered orally once daily at the same time every day, preferably in the morning, with or without food. 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.

KISQALI tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

4.3 Contraindications

KISQALI is contraindicated in patients with corrected QT interval (QTcF) > 450 milliseconds (ms) prior to treatment or who have long QT syndrome or who are at

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significant risk of developing QTc prolongation (see section 4.4 Special warnings and precautions for use).

KISQALI is contraindicated in patients with hypersensitivity to ribociclib succinate or to any of the excipients, which include soya lecithin (see section 6.1 List of excipients).

4.4 Special warnings and precautions for use

QT interval prolongation

KISQALI causes QT interval prolongation in a concentration-dependent manner (see Section 5.1 Pharmacodynamic_properties).

Increased QT prolongation occurs with co-administration of KISQALI and tamoxifen. Use of KISQALI with tamoxifen is not recommended (see sections 4.8 Undesirable effects and 5.1 Pharmacodynamic properties).

In phase III clinical studies (MONALEESA-2, MONALEESA-7 and MONALEESA-3), excluded patients with certain conditions known to increase QT prolongation risk, such as heart failure, cardiomyopathy, or recent coronary disease. Across these studies in patients with advanced or metastatic breast cancer who received the combination of KISQALI plus an aromatase inhibitor or fulvestrant, 15 out of 1054 patients (1%) had >500 ms post-baseline QTcF value, and 61 out of 1054 patients (6%) had a >60 ms increase from baseline in QTcF intervals. These ECG changes were reversible with dose interruption and the majority (63%) occurred within the first four weeks of treatment. There were no reported cases of *Torsade de Pointes*.

In MONALEESA-2, in the KISQALI plus letrozole treatment arm, there was one (0.3%) sudden death in a patient with Grade 3 hypokalaemia and Grade 2 QT prolongation that improved to Grade 1 on the same day, reported 10 days before the event. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3 (see section 4.8 Undesirable effects).

An ECG should be assessed before initiating treatment. Treatment with KISQALI should be initiated only in patients with QTcF interval values < 450 ms (see section 4.3 Contraindications). ECG should be repeated at approximately Day 14 of the first cycle, at the beginning of the second cycle, then as clinically indicated. More intensive ECGs should be considered based on a patient's individual risk factors, if there are any symptoms that may be related to QT prolongation (e.g. palpitations or syncope), or if there is any increase in the risk of QT prolongation (e.g. new medication, or condition that may increase the likely exposure to ribociclib).

Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorous and magnesium) should be performed before initiating treatment, at the beginning of first 6 cycles and as clinically indicated. Treatment should be interrupted for any abnormalities to be corrected before commencing or continuing KISQALI therapy.

KISQALI should be avoided in patients who already have or who are at significant risk of developing QTc prolongation. This includes patients with:

- QTcF >450 ms prior to treatment (see section 4.3 Contraindications)
- a history of ventricular arrhythmias
- long QT syndrome

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- significant risk of developing QTc prolongation including:
 - uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
 - electrolyte abnormalities.

KISQALI should be avoided in patients taking medicinal products that are known to prolong the QTc interval (see section 4.5 Interaction with other medicines and other forms of interaction) and/or strong CYP3A inhibitors as this may lead to clinically meaningful prolongation of the QTcF (see section 4.2 Dose and method of administration, section 4.5 Interaction with other medicines and other forms of interaction and section 5.1 Pharmacodynamic properties). If treatment with a strong CYP3A4 inhibitor cannot be avoided, the dose should be reduced to 200 mg once daily (see sections 4.2 Dose and method of administration, 4.5 Interaction with other medicines and other forms of interaction and 5.2 Pharmacokinetic (PK) Properties). Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 2 (see sections 4.2 Dose and method of administration, section 4.8 Undesirable effects), and section 5.2 Pharmacokinetic (PK) Properties).

Hepatobiliary toxicity

Ribociclib commonly causes reversible elevations in transaminase levels, including uncommonly causes life-threatening hepatotoxicity.

In the phase III clinical studies, increases in transaminases were observed. Grade 3 or Grade 4 increases in ALT (11% vs. 2%) and AST (8% vs. 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had Grade 3 or Grade 4 ALT/AST elevation, the median time to onset was 92 days for patients treated with KISQALI plus an aromatase inhibitor or fulvestrant. The median time to resolution (to normalisation or \leq Grade 2) was 21 days in patients treated with KISQALI plus an aromatase inhibitor or fulvestrant.

The majority of increases in ALT and AST were reported without concurrent elevations of bilirubin. In MONALEESA-2 and MONALEESA-3, concurrent elevations of ALT or AST greater than three times the upper limit of normal (ULN) and of total bilirubin greater than two times the ULN, with normal alkaline phosphatase levels, in the absence of cholestasis occurred in 6 patients (1%), and all patients recovered after discontinuation of KISQALI. There were no such cases in MONALEESA-7.

Liver function tests (LFTs) should be performed before initiating therapy with KISQALI. The LFTs should be monitored every 2 weeks for first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated.

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation as described in Table 4 (see section 4.2 Dose and method of administration). Recommendations for patients who have elevated AST/ALT $>$ Grade 3 at baseline have not been established.

Neutropenia

In the phase III clinical studies MONALEESA-2, MONALEESA-7 and MONALEESA-3, neutropenia was the most frequently reported adverse reaction (75%) and a Grade 3 or

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Grade 4 decrease in neutrophil counts (based on laboratory findings) was reported in 62% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Among the patients who had Grades 2, 3, or 4 neutropenia, the median time to onset 17 days. The median time to resolution of Grade ≥ 3 neutropenia (to normalisation or $<$ Grade 3) was 12 days in patients treated with KISQALI plus an aromatase inhibitor or fulvestrant. Febrile neutropenia was reported in 2% of patients exposed to KISQALI plus an aromatase inhibitor or fulvestrant. Patients should be instructed to report any fever promptly (see section 4.8 Undesirable effects).

A Full blood count (FBC) should be performed before initiating therapy with KISQALI. FBC should be monitored every 2 weeks for the first 2 cycles, and at the beginning of each subsequent 4 cycles, then as clinically indicated.

Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction or discontinuation as described in Table 3 (see section 4.2 Dose and method of administration).

Severe cutaneous reactions

Toxic epidermal necrolysis (TEN) has been reported with KISQALI treatment. If signs and symptoms suggestive of severe cutaneous reactions (e.g., progressive widespread skin rash often with blisters or mucosal lesions) appear, KISQALI should be immediately and permanently discontinued.

Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis has been reported with CDK4/6 inhibitors including reports of fatal cases. In the three phase III clinical studies (MONALEESA-2 (A2301), MONALEESA-7 (E2301-NSAI) and MONALEESA-3 (F2301)), ILD (any grade 0.3%, including 0.1% grade 3) was reported in the KISQALI treated group, with no cases in the placebo treated group. Pneumonitis (any grade 0.6% vs 0.4%) was reported in the KISQALI and placebo treated groups, respectively, with no grade 3/4 events in either treatment group. Additional cases of ILD/pneumonitis have been observed with Kisqali in the post-marketing setting (see section 4.8 Undesirable Effects).

Based on the severity of the ILD/pneumonitis, patients may require treatment interruption, dose reduction or permanent discontinuation as described in Table 5 (see section 4.2 Dose and method of administration).

Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough, and dyspnea.

Reproductive toxicity and fertility

Women of reproductive potential should be advised to use an effective method of contraception while taking Kisqali and for at least 21 days after the last dose (see section 4.6 Fertility, pregnancy and lactation).

4.5 Interaction with other medicines and other forms of interaction

Drugs that may increase the QT interval

Co-administration of KISQALI with medicinal products with a known potential to prolong the QT interval may have an additive effect with ribociclib and increase the risk of QT prolongation.

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Avoid co-administration of KISQALI with medicinal products with a known potential to prolong the QT interval, including, but not limited to: amiodarone, disopyramide, procainamide, quinidine, sotalol, ciprofloxacin, levofloxacin, azithromycin, moxifloxacin, erythromycin, clarithromycin, fluconazole, pentamidine, citalopram, escitalopram, lithium, clomipramine, desipramine, imipramine, trimipramine, chlorpromazine, haloperidol, ziprasidone, cisapride, ondansetron, dolasetron, chloroquine, halofantrine, methadone, bepridil, and pimozide). If co-administration cannot be avoided, consider reducing the dose of ribociclib and monitor by ECG for QT prolongation. KISQALI is not recommended for use in combination with tamoxifen (see section 4.4 Special warnings and precautions for use).

Interactions with co-administered anticancer medicines

Ribociclib and letrozole

Comparison of data from a clinical trial in patients with breast cancer to historical controls, and a population PK analysis indicated no clinically important drug-drug interaction between ribociclib and letrozole following their co-administration.

Ribociclib and exemestane

Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and exemestane following their co-administration.

Ribociclib and anastrozole

Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug-drug interaction between ribociclib and anastrozole following their co-administration.

Ribociclib and fulvestrant

Data from a clinical trial in patients with breast cancer indicated no clinically relevant effect of fulvestrant on ribociclib exposure following co-administration of the drugs.

Ribociclib and tamoxifen

KISQALI is not indicated for concomitant use with tamoxifen. Data from a clinical trial in patients with breast cancer indicated that tamoxifen exposure (C_{max} and AUC) approximately doubled following co-administration of ribociclib and tamoxifen.

In vitro interaction data

Effect of ribociclib on cytochrome P450 enzymes

In vitro, ribociclib is 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 ribociclib has no potential to inhibit the activities of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 at clinically relevant concentrations. Ribociclib has no potential for time-dependent inhibition of CYP1A2, CYP2C9, and CYP2D6.

In vitro data indicate that ribociclib has no potential to induce UGT enzymes or the CYP enzymes CYP2B6, CYP2C9, CYP2C19 and CYP3A4 via CAR or PXR. Therefore, KISQALI is unlikely to affect substrates of these enzymes.

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Effect of transporters on ribociclib

Based on *in vitro* data, ribociclib is a substrate of P-gp but not a substrate of BCRP. However, P-gp mediated transport is unlikely to affect the extent of oral absorption of ribociclib at therapeutic doses because of moderate passive permeability. Ribociclib is not a substrate for hepatic uptake transporters OATP1B1/1B3 or OCT-1 *in vitro*.

Effect of ribociclib on transporters

In vitro evaluations indicated that ribociclib has a potential to inhibit the activities of drug transporters Pgp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1, MATE2K and BSEP. 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. Ribociclib did not inhibit OAT1, OAT3 or MRP2 at clinically relevant concentrations *in vitro*.

Drugs that may increase ribociclib plasma concentrations

CYP3A4 inhibitors

Ribociclib is primarily metabolized by CYP3A4 and is a time-dependent inhibitor of CYP3A4 *in vitro* (see section 5.2 Pharmacokinetic (PK) Properties). Therefore, medicinal products which can influence CYP3A4 enzyme activity may alter the PK of ribociclib. No dose adjustments are required for mild and moderate CYP3A4 inhibitors, however, if treatment with a moderate CYP3A4 inhibitor is initiated, close monitoring for ribociclib-related AEs is recommended.

Concomitant use of strong CYP3A inhibitors including, but not limited to, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir (see below), nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole should be avoided (see section 4.4 Special warnings and precautions for use). Alternative concomitant medications with less potential to inhibit CYP3A should be considered and patients should be monitored for adverse drug reactions (ADRs) (see sections 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic (PK) Properties).

If co-administration of ribociclib with a strong CYP3A inhibitor cannot be avoided, reduce KISQALI dose to 200 mg. However, there are no clinical data with this dose adjustment (see section 4.2 Dose and method of administration). If the strong inhibitor is discontinued, resume the KISQALI dose (after at least 5 elimination half-lives of the CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Due to inter-patient variability, the recommended dose adjustments may not be optimal in all individual patients, therefore close monitoring for ribociclib related AEs is recommended. In case of ribociclib related toxicity, dose should be modified or treatment should be interrupted until toxicity is resolved (see section 4.2 Dose and method of administration and 5.2 Pharmacokinetic (PK) Properties).

Ritonavir

A drug interaction trial in healthy subjects was conducted with ritonavir (strong CYP3A inhibitor). Compared to ribociclib alone, ritonavir (100 mg bid for 14 days) increased ribociclib C_{max} and AUC_{inf} by 1.7-fold and 3.2-fold, respectively, following a single 400 mg ribociclib dose. C_{max} and AUC_{last} for LEQ803 (a prominent metabolite of LEE011, accounting for < 10 % of parent exposure) decreased by 96 % and 98 %, respectively.

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Erythromycin

Simulations using physiologically-based pharmacokinetic modelling (PBPK) suggested that erythromycin, a moderate CYP3A4 inhibitor, may increase ribociclib C_{max} and AUC by 1.3-fold and 1.9-fold, respectively.

Drugs that may decrease ribociclib plasma concentrations

CYP3A4 inducers

Avoid concomitant use of strong CYP3A inducers, including, but not limited to, phenytoin, rifampin, carbamazepine, and St John's Wort (*Hypericum perforatum*). Consider an alternate concomitant medication with no or minimal potential to induce CYP3A (see section 4.4 Special warnings and precautions for use).

Rifampicin

A drug interaction trial in healthy subjects was conducted with rifampicin, a strong CYP3A4 inducer. Compared to ribociclib alone, co-administration with rifampicin (600 mg daily for 14 days) decreased ribociclib C_{max} and AUC_{inf} by 81% and 89%, respectively, following a single 600 mg ribociclib dose. LEQ803 C_{max} increased 1.7-fold and AUC_{inf} decreased by 27%, respectively.

Efavirenz

Simulations using PBPK suggested that efavirenz, a moderate CYP3A inducer, may decrease ribociclib C_{max} and AUC by 37% and 60%, respectively.

Effect of ribociclib on other drugs

Ribociclib is a moderate to strong CYP3A4 inhibitor and may interact with medicinal substrates that are metabolised via CYP3A4, which can lead to increased serum concentrations of the concomitantly used medicinal product.

Caution is recommended in case of concomitant use with sensitive CYP3A substrates with a narrow therapeutic index (see section 4.4 Special warnings and precautions for use).

The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozone, quinidine, sirolimus and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

Midazolam

Simulations using PBPK suggested that at a 600 mg ribociclib dose, midazolam C_{max} and AUC may increase 2.4-fold and 5.2-fold, respectively.

Co-administration of midazolam (CYP3A4 substrate) with multiple doses of ribociclib (400 mg) increased the midazolam exposure by 3.8-fold in healthy subjects, compared with administration of midazolam alone. Simulations using physiologically-based PK (PBPK) models suggested that ribociclib given at the clinically relevant dose of 600 mg is expected to increase the midazolam AUC by 5.2-fold.

Caffeine

Simulations using PBPK suggested only weak inhibitory effects on CYP1A2 substrates at a 600 mg ribociclib dose.

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Co-administration of caffeine (CYP1A2 substrate) with multiple doses of ribociclib (400 mg) decreased C_{max} by 10 % and increased the caffeine AUC_{inf} by 20% (1.2-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 (less than 2-fold increase in AUC).

Drug-food interactions

Patients should be instructed to avoid fruits (including fruit juices) that are known to be strong inducers or inhibitors of cytochrome CYP3A enzymes and may therefore increase exposure to ribociclib. These include grapefruit, grapefruit hybrids, pummelos, star fruit, and Seville oranges.

KISQALI can be administered with or without food (see sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic (PK) Properties).

Gastric pH elevating medicines

Ribociclib exhibits high solubility at or below pH 4.5 and in bio-relevant media (at pH 5.0 and 6.5). Co-administration of ribociclib with medicinal products that elevate the gastric pH was not evaluated in a clinical trial; however, altered ribociclib absorption with proton pump inhibitors was not observed in population pharmacokinetic analysis, non-compartmental pharmacokinetic analyses nor in simulations using PBPK models.

4.6 Fertility, pregnancy and lactation

Effects on fertility

There are no clinical data available regarding effects of KISQALI on human fertility. Based on animal studies, KISQALI may impair fertility in males of reproductive potential.

Use in pregnancy (Category D)

There are no adequate and well-controlled studies in pregnant women. Based on findings in animals, KISQALI can cause foetal harm (including foetal developmental abnormalities and foetal loss) when administered to a pregnant woman (see section 5.3 Preclinical Safety Data).

KISQALI is not recommended during pregnancy and in females of reproductive potential not using highly effective contraception.

Pregnancy testing

The pregnancy status for females of reproductive potential should be verified prior to initiating treatment with KISQALI.

Contraception in females

Females of reproductive potential who are receiving KISQALI should use effective contraception (methods that result in less than 1 % pregnancy rates) during therapy and for at least 21 days after stopping treatment with KISQALI.

Breastfeeding

It is not known if KISQALI is present in human milk. There are no data on the effects of KISQALI on the breastfed child or the effects of KISQALI on milk production. Ribociclib

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and its metabolites readily passed into the milk of lactating rats (see section 5.3 Preclinical Safety Data).

Patients receiving KISQALI should not breastfeed for at least 21 days after the last dose.

4.7 Effects on ability to drive and use machines

No studies on the effects of ribociclib on the ability to drive or operate machinery have been conducted. Patients experiencing fatigue, dizziness, or vertigo while taking ribociclib should exercise caution when driving or operating machinery (see section 4.8 Undesirable effects).

4.8 Undesirable Effects

Clinical trial data

MONALEESA 2: KISQALI in combination with letrozole

Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy

The safety data reported below are based on a clinical study of 668 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole. The median duration of exposure to KISQALI plus letrozole was 20 months with 63% patients exposed for ≥ 12 months. Dose reductions due to adverse reactions (ARs) occurred in 49% of patients receiving KISQALI plus letrozole and in 3% of patients receiving placebo plus letrozole. Among patients receiving KISQALI plus letrozole, 11% were reported to have permanently discontinued both KISQALI and letrozole, and 9% were reported to have permanently discontinued KISQALI alone due to ARs. Among patients receiving placebo plus letrozole, 3% were reported to have permanently discontinued both and 2% were reported to have permanently discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation of KISQALI in patients receiving KISQALI plus letrozole were ALT increased (5%), AST increased (3%) and vomiting (2%). Antiemetics and antidiarrhoea medications were used to manage symptoms as clinically indicated.

On-treatment deaths, regardless of causality, were reported in 8 cases (2%) of KISQALI plus letrozole treated patients vs 3 cases (0.9%) in placebo plus letrozole treated patients. Causes of death in KISQALI plus letrozole included progressive disease in 2 cases (0.6%), 2 cases of acute respiratory failure (0.6%), and one case each (0.1%) of the following: sudden death (in a patient who had Grade 3 hypokalemia and Grade 2 QT prolongation that improved to Grade 1 on the same day, both reported 10 days before the event), death due to unknown cause, acute myocardial infarction, and pneumonia. Causes of death in placebo plus letrozole included 2 (0.6%) cases of progressive disease and 1 (0.3%) case of subdural hematoma (not related to study treatment).

The most common ARs (reported at an incidence $\geq 20\%$ in the KISQALI arm and $\geq 2\%$ higher than placebo) were neutropenia, nausea, infections, fatigue, diarrhoea, alopecia, leukopenia, vomiting, constipation, headache, back pain, cough, anaemia, rash, abnormal liver function tests, decreased appetite and abdominal pain.

The most common Grade 3/4 ARs (reported at a frequency $\geq 5\%$) were neutropenia, infections, leukopenia, abnormal liver function tests, and lymphopenia. Syncope occurred in 15 patients (5%) in the KISQALI plus letrozole arm versus 9 (3%) in the placebo plus letrozole arm.

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ARs and laboratory abnormalities occurring in patients in MONALEESA-2 are listed in Table 7 and Table 8, respectively.

Table 7 Adverse reactions occurring in $\geq 10\%$ and $\geq 2\%$ higher than placebo arm in MONALEESA-2 (all grades)

| | KISQALI + letrozole | | | Placebo + letrozole | | |
|--|---------------------|---------|---------|---------------------|---------|---------|
| | | N = 334 | | N = 330 | | |
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| Adverse drug reactions | % | % | % | % | % | % |
| Infections and Infestations | | | | | | |
| Infections ¹ | 49 | 4 | <1 | 36 | <1 | <1 |
| Blood and lymphatic system disorders | | | | | | |
| Neutropenia | 77 | 54 | 10 | 6 | 1 | 0 |
| Leukopenia | 35 | 21 | 1 | 5 | < 1 | 0 |
| Anaemia | 24 | 3 | < 1 | 8 | 2 | 0 |
| Lymphopenia | 13 | 7 | 1 | 3 | 1 | 0 |
| Thrombocytopenia | 11 | <1 | 0 | <1 | <1 | 0 |
| Metabolism and nutrition disorders | | | | | | |
| Decreased appetite | 22 | 1 | 0 | 18 | < 1 | 0 |
| Nervous system disorders | | | | | | |
| Headache | 29 | < 1 | 0 | 23 | < 1 | 0 |
| Insomnia | 16 | 0 | 0 | 14 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | | | | |
| Dyspnoea | 16 | 2 | 0 | 13 | < 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | | | | |
| Back pain | 27 | 3 | 0 | 23 | 1 | 0 |
| Eye disorders | | | | | | |
| Lacrimation increased | 12 | 0 | 0 | 2 | 0 | 0 |
| Gastrointestinal disorders | | | | | | |
| Nausea | 55 | 3 | 0 | 32 | < 1 | 0 |
| Diarrhoea | 41 | 2 | 0 | 26 | < 1 | 0 |
| Vomiting | 35 | 4 | 0 | 19 | < 1 | 0 |
| Constipation | 30 | 1 | 0 | 22 | 0 | 0 |
| Abdominal pain | 21 | 1 | 0 | 14 | < 1 | 0 |
| Stomatitis | 12 | < 1 | 0 | 7 | 0 | 0 |
| Dry mouth | 14 | <1 | 0 | 11 | <1 | 0 |
| Dyspepsia | 11 | <1 | 0 | 8 | 0 | 0 |

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| | KISQALI + letrozole | | | Placebo + letrozole | | |
|---|---------------------|---------|---------|---------------------|---------|---------|
| | N = 334 | | | N = 330 | | |
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| Adverse drug reactions | % | % | % | % | % | % |
| Dysgeusia | 10 | <1 | 0 | 7 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | | | | |
| Alopecia | 35 | 0 | 0 | 17 | 0 | 0 |
| Rash ³ | 24 | 1 | 0 | 11 | < 1 | 0 |
| Pruritus | 18 | < 1 | 0 | 8 | 0 | 0 |
| Dry skin | 10 | 0 | 0 | 4 | 0 | 0 |
| General disorders and administration site conditions | | | | | | |
| Fatigue | 43 | 3 | < 1 | 35 | < 1 | 0 |
| Abnormal liver function tests ⁴ | 23 | 10 | 2 | 9 | 2 | 0 |
| Oedema peripheral | 19 | < 1 | 0 | 13 | 0 | 0 |
| Pyrexia | 15 | < 1 | 0 | 7 | 0 | 0 |
| Investigations | | | | | | |
| Blood creatinine increased | 11 | <1 | 0 | 3 | 0 | 0 |

Grading according to CTCAE 4.03 (Common Terminology Criteria for Adverse Events)

¹Infections: urinary tract infections; respiratory tract infections, gastroenteritis, sepsis (<1%).

²Abdominal pain: abdominal pain; abdominal pain upper.

³Rash: rash, rash maculo-papular and rash pruritic.

⁴abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased

Table 8 Laboratory abnormalities occurring ≥ 10 % of patients in MONALEESA-2

| | KISQALI + letrozole | | | Placebo + letrozole | | |
|------------------------------|---------------------|---------|---------|---------------------|---------|---------|
| | N = 334 | | | N = 330 | | |
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| Laboratory parameters | % | % | % | % | % | % |
| Haematology | | | | | | |
| Leukocyte count decreased | 95 | 37 | 3 | 34 | 1 | < 1 |
| Neutrophil count decreased | 94 | 53 | 11 | 28 | 1 | < 1 |
| Haemoglobin decreased | 63 | 5 | 0 | 33 | 2 | 0 |
| Lymphocyte count decreased | 58 | 16 | 2 | 26 | 4 | < 1 |
| Platelet count decreased | 35 | < 1 | 0 | 9 | < 1 | < 1 |

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| | KISQALI + letrozole | | | Placebo + letrozole | | |
|--------------------------------------|---------------------|---------|---------|---------------------|---------|---------|
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| Laboratory parameters | % | % | % | % | % | % |
| Chemistry | | | | | | |
| Alanine aminotransferase increased | 59 | 11 | 2 | 42 | 1 | 0 |
| Aspartate aminotransferase increased | 57 | 7 | 1 | 39 | 2 | 0 |
| Creatinine increased | 27 | < 1 | < 1 | 8 | < 1 | 0 |
| Phosphorous decreased | 15 | 6 | 0 | 6 | 1 | 0 |
| Potassium decreased | 16 | 2 | 2 | 8 | 2 | 0 |

MONALEESA-7: KISQALI in combination with an aromatase inhibitor

Pre- or perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine-based therapy

MONALEESA-7 was conducted in 672 pre- or perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KISQALI plus endocrine therapy (goserelin plus either a non-steroidal aromatase inhibitor (NSAI) or tamoxifen) or placebo plus endocrine therapy (goserelin plus either a NSAI or tamoxifen). The median duration of exposure on the KISQALI plus an NSAI arm was 24.6 months with 67.3% of patients exposed for ≥ 12 months.

KISQALI is not recommended for use in combination with tamoxifen due to the risk of QTc prolongation (see Section 4.4 Special warnings and precautions for use).

The safety data reported below are based on 495 NSAI-treated patients, which included 248 patients who received KISQALI plus goserelin plus NSAI (the KISQALI arm) and 247 patients who received placebo plus goserelin plus NSAI (the placebo arm). Dose reductions due to adverse reactions (ARs) occurred in 36% of patients receiving KISQALI plus NSAI plus goserelin and in 5% of patients receiving placebo plus NSAI plus goserelin. In the KISQALI arm, 4% were reported to have permanently discontinued both KISQALI and NSAI and 6% were reported to have permanently discontinued KISQALI alone due to ARs. In the placebo arm, 3% were reported to have permanently discontinued both and 1% were reported to have permanently discontinued placebo alone due to ARs. Adverse reactions leading to KISQALI or placebo treatment discontinuation in the KISQALI arm versus the placebo arm were ALT increased (3% vs 0.8%), AST increased (2% vs 1%) and neutropenia (2% vs 0%). One patient (0.4%) died while on treatment with KISQALI plus NSAI plus goserelin due to the underlying malignancy.

The most common ARs (reported at a frequency $\geq 20\%$ in the KISQALI arm and $\geq 2\%$ higher than placebo) were neutropenia, infections, nausea, leukopenia, headache, fatigue, back pain, diarrhoea, abnormal liver function tests, vomiting, alopecia and anaemia. The most common Grade 3/4 ARs (reported at a frequency $\geq 5\%$) were neutropenia, leukopenia, abnormal liver function tests and lymphopenia.

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Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-7 are listed in Table 9 and Table 10, respectively.

Table 9 Adverse reactions occurring in $\geq 10\%$ and $\geq 2\%$ higher than placebo arm in MONALEESA-7 (NSAI-treated patients only) (all grades)

| | KISQALI + NSAI + goserelin | | | Placebo + NSAI + goserelin | | |
|---|----------------------------|---------|---------|----------------------------|---------|---------|
| | | N = 248 | | | N = 247 | |
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| Adverse drug reactions | % | % | % | % | % | % |
| Infections and Infestations | | | | | | |
| Infections ¹ | 43 | 2 | 0 | 32 | < 1 | 0 |
| Blood and lymphatic system disorders | | | | | | |
| Neutropenia | 80 | 57 | 12 | 10 | 4 | < 1 |
| Leukopenia | 33 | 15 | < 1 | 4 | < 1 | 0 |
| Anaemia | 20 | 4 | 0 | 9 | 2 | 0 |
| Lymphopenia | 13 | 5 | <1 | 3 | 1 | <1 |
| Thrombocytopenia | 10 | 0 | <1 | 2 | 0 | <1 |
| Nervous system disorders | | | | | | |
| Headache | 29 | 0 | 0 | 26 | <1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | | | | |
| Cough | 20 | 0 | 0 | 11 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | | | | |
| Arthralgia | 43 | < 1 | 0 | 38 | 1 | 0 |
| Back pain | 24 | <1 | 0 | 21 | 2 | 0 |
| Gastrointestinal disorders | | | | | | |
| Nausea | 33 | 0 | 0 | 25 | 0 | 0 |
| Diarrhoea | 23 | 2 | 0 | 21 | 2 | 0 |
| Vomiting | 21 | <1 | 0 | 19 | 0 | 0 |
| Abdominal pain ² | 19 | 1 | 0 | 16 | <1 | 0 |
| Constipation | 18 | 0 | 0 | 14 | 0 | 0 |
| Stomatitis | 14 | 0 | 0 | 9 | < 1 | 0 |
| Skin and subcutaneous tissue disorders | | | | | | |
| Alopecia | 21 | 0 | 0 | 14 | 0 | 0 |
| Rash ³ | 20 | < 1 | 0 | 10 | 0 | 0 |
| Pruritus | 12 | 0 | 0 | 6 | 0 | 0 |
| General disorders and administration site conditions | | | | | | |
| Abnormal liver function tests ⁴ | 21 | 7 | 0 | 15 | 3 | 0 |

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| | | | | | | |
|-----------------------------|-------|-----|---|----|-----|---|
| Pyrexia | 17 | < 1 | 0 | 8 | < 1 | 0 |
| Pain in extremity | 17 | 0 | 0 | 11 | 1 | 0 |
| Asthenia | 15 | < 1 | 0 | 11 | 0 | 0 |
| Oedema peripheral | 11 | 0 | 0 | 8 | 0 | 0 |
| Oropharyngeal pain | 10 | 0 | 0 | 4 | 0 | 0 |
| Investigations | | | | | | |
| Electrocardiogram prolonged | QT 10 | 1 | 0 | 2 | 0 | 0 |

Grading according to CTCAE 4.03 (Common Terminology Criteria for Adverse Events)

¹Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (< 1%).

²Abdominal pain: abdominal pain; abdominal pain upper.

³Rash: rash, rash maculo-papular, and rash pruritic.

⁴Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

Table 10 Laboratory abnormalities occurring in ≥10% of patients in MONALEESA-7

| Laboratory parameters | KISQALI + NSAI + goserelin N = 248 | | | Placebo + NSAI + goserelin N = 247 | | |
|--------------------------------------|---------------------------------------|--------------|--------------|---------------------------------------|--------------|--------------|
| | All Grades % | Grade 3 % | Grade 4 % | All Grades % | Grade 3 % | Grade 4 % |
| Haematology | | | | | | |
| Leukocyte count decreased | 94 | 38 | 3 | 35 | 1 | < 1 |
| Neutrophil count decreased | 93 | 56 | 12 | 32 | 4 | < 1 |
| Haemoglobin decreased | 85 | 3 | 0 | 55 | < 1 | 0 |
| Lymphocyte count decreased | 60 | 17 | 3 | 21 | 3 | < 1 |
| Platelet count decreased | 31 | < 1 | 1 | 11 | < 1 | < 1 |
| Chemistry | | | | | | |
| Aspartate aminotransferase increased | 48 | 7 | 0 | 41 | 1 | < 1 |
| Gamma-glutamyl transferase increased | 46 | 7 | 2 | 44 | 9 | 1 |
| Alanine aminotransferase increased | 45 | 6 | < 1 | 34 | 2 | < 1 |
| Phosphorous decreased | 17 | 2 | 0 | 15 | < 1 | < 1 |
| Potassium decreased | 17 | < 1 | < 1 | 15 | < 1 | < 1 |
| Glucose serum decreased | 15 | < 1 | < 1 | 11 | < 1 | < 1 |
| Creatinine increased | 21 | 2 | < 1 | 20 | < 1 | < 1 |

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MONALEESA-3: KISQALI in combination with fulvestrant

Postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine-based therapy or after disease progression on endocrine therapy

The safety data reported below are based on a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months with 58% of patients exposed for ≥ 12 months. Dose reductions due to adverse reactions (ARs) occurred in 35% of patients receiving KISQALI plus fulvestrant and in 5% of patients receiving placebo plus fulvestrant. Among patients receiving KISQALI plus fulvestrant, 10% were reported to have permanently discontinued both KISQALI and fulvestrant and 9% were reported to have discontinued KISQALI alone due to ARs. Among patients receiving placebo plus fulvestrant, 4% were reported to have permanently discontinued both and 3% were reported to have discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation of KISQALI in patients receiving KISQALI plus fulvestrant (as compared to the placebo arm) were ALT increased (5% vs 0%), AST increased (3% vs 0.6%), and vomiting (1% vs 0%).

On-treatment deaths, regardless of causality, were reported in seven patients (1.4%) due to the underlying malignancy and six patients (1.2%) due to other causes while on treatment with KISQALI plus fulvestrant. Causes of death included one pulmonary embolism, one acute respiratory distress syndrome, one cardiac failure, one pneumonia, one haemorrhagic shock, and one ventricular arrhythmia. Seven patients (2.9%) died due to the underlying malignancy and 1 patient (0.4%) died due to pulmonary embolism while on placebo plus fulvestrant.

The most common ARs (reported at a frequency $\geq 20\%$ in the KISQALI arm and $\geq 2\%$ higher than placebo) were neutropenia, infections, nausea, diarrhoea, vomiting, constipation, rash, cough, headache, pruritis, alopecia and anaemia. The most common Grade 3/4 ARs (reported at a frequency $\geq 5\%$) were neutropenia, infections, leukopenia, lymphopenia and abnormal liver function tests.

Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-3 are listed in Table 11 and Table 12 respectively.

Table 11 Adverse reactions occurring in $\geq 10\%$ and $\geq 2\%$ higher than placebo arm in MONALEESA-3 (all grades)

| | KISQALI + fulvestrant | | | Placebo + fulvestrant | | |
|---|-----------------------|---------|---------|-----------------------|---------|---------|
| | All Grades | N = 483 | | All Grades | N = 241 | |
| Adverse drug reactions | % | Grade 3 | Grade 4 | % | Grade 3 | Grade 4 |
| | | % | % | | % | % |
| Infections and Infestations | | | | | | |
| Infections ¹ | 48 | 6 | 0 | 35 | 3 | 0 |
| Blood and lymphatic system disorders | | | | | | |
| Neutropenia | 72 | 50 | 7 | 4 | < 1 | 0 |
| Leukopenia | 31 | 14 | < 1 | < 1 | 0 | 0 |
| Anaemia | 20 | 4 | 0 | 9 | 3 | 0 |

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| | | | | | | |
|---|----|-----|-----|----|-----|---|
| Lymphopenia | 10 | 5 | < 1 | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | | | | |
| Decreased appetite | 18 | < 1 | 0 | 13 | 0 | 0 |
| Nervous system disorders | | | | | | |
| Headache | 25 | 1 | 0 | 21 | < 1 | 0 |
| Dizziness | 15 | < 1 | 0 | 8 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | | | | |
| Cough | 25 | 0 | 0 | 17 | 0 | 0 |
| Dyspnoea | 18 | 2 | < 1 | 14 | 2 | 0 |
| Gastrointestinal disorders | | | | | | |
| Nausea | 47 | 2 | 0 | 31 | < 1 | 0 |
| Diarrhoea | 33 | 1 | 0 | 22 | 1 | 0 |
| Vomiting | 29 | 2 | 0 | 14 | 0 | 0 |
| Constipation | 26 | 1 | 0 | 13 | 0 | 0 |
| Abdominal pain ² | 19 | 2 | 0 | 15 | 1 | 0 |
| Stomatitis | 12 | < 1 | 0 | 5 | 0 | 0 |
| Dyspepsia | 11 | 0 | 0 | 6 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | | | | |
| Rash ³ | 26 | < 1 | 0 | 9 | 0 | 0 |
| Alopecia | 20 | 0 | 0 | 5 | 0 | 0 |
| Pruritus | 22 | < 1 | 0 | 7 | 0 | 0 |
| General disorders and administration site conditions | | | | | | |
| Abnormal liver function tests ⁴ | 18 | 8 | 2 | 10 | < 1 | 0 |
| Oedema peripheral | 17 | 0 | 0 | 9 | 0 | 0 |
| Asthenia | 16 | < 1 | 0 | 13 | < 1 | 0 |
| Pyrexia | 15 | < 1 | 0 | 7 | 0 | 0 |

Grading according to CTCAE 4.03 (Common Terminology Criteria for Adverse Events)

¹Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (1%).

²Abdominal pain: abdominal pain; abdominal pain upper.

³Rash: rash, rash maculo-papular, and rash pruritic.

⁴Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

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Table 12 Laboratory abnormalities occurring in ≥10% of patients in MONALEESA-3

| Laboratory parameters | KISQALI + fulvestrant N = 483 | | | Placebo + fulvestrant N = 241 | | |
|--------------------------------------|----------------------------------|--------------|--------------|----------------------------------|--------------|--------------|
| | All Grades % | Grade 3 % | Grade 4 % | All Grades % | Grade 3 % | Grade 4 % |
| Haematology | | | | | | |
| Leukocyte count decreased | 95 | 29 | 1 | 29 | < 1 | 0 |
| Neutrophil count decreased | 93 | 49 | 8 | 23 | 1 | 0 |
| Lymphocyte count decreased | 75 | 19 | 2 | 38 | 4 | < 1 |
| Haemoglobin decreased | 64 | 6 | 0 | 38 | 4 | 0 |
| Platelet count decreased | 35 | 1 | 1 | 12 | 0 | 0 |
| Chemistry | | | | | | |
| Creatinine increased | 68 | 1 | < 1 | 35 | < 1 | 0 |
| Gamma-glutamyl transferase increased | 57 | 8 | 1 | 50 | 9 | 2 |
| Aspartate aminotransferase increased | 56 | 6 | 2 | 47 | 3 | 0 |
| Alanine aminotransferase increased | 50 | 8 | 3 | 39 | 2 | 0 |
| Glucose serum decreased | 25 | 0 | 0 | 21 | 0 | 0 |
| Phosphorous decreased | 20 | 5 | 0 | 9 | < 1 | 0 |
| Albumin decreased | 12 | 0 | 0 | 9 | 0 | 0 |

COMPLEEMENT-1: KISQALI in combination with Letrozole and Goserelin or Leuprolide

Men with HR-positive, HER2-negative Advanced Breast Cancer for Initial Endocrine-Based Therapy

The safety of KISQALI in combination with letrozole was evaluated in men (n=39) in an open-label, multicentre clinical study for the treatment of adult patients with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease (COMPLEEMENT-1) (see section 5.1 Clinical Studies).

The median duration of exposure to KISQALI was 20.8 months (range: 0.5 to 30.6 months).

Other adverse reactions occurring in men treated with KISQALI plus letrozole and goserelin or leuprolide were similar to those occurring in women treated with KISQALI plus endocrine therapy.

Description of selected adverse drug reactions

QT prolongation

In the phase III clinical studies, 9% of ribociclib-treated patients and 4% of placebo-treated patients had at least one event of QT interval prolongation or syncope. Dose interruptions/

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adjustments were reported in 3% of the KISQALI-treated patients due to QT interval prolongation or syncope.

A central analysis of ECG data (average of triplicate) showed at least one post-baseline QTcF of > 480 ms occurred in 5% ribociclib-treated patients and 2% of placebo-treated patients. Among the ribociclib-treated patients who had QTcF prolongation of >480 ms, the median time to onset is 15 days regardless of what treatment ribociclib was combined with, and these changes were reversible with dose interruption and/or dose reduction (see sections 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic (PK) Properties).

In MONALEESA-7, the observed mean QTcF increase from baseline was >10 ms higher in the tamoxifen plus placebo subgroup compared with NSAID plus placebo subgroup, suggesting that tamoxifen contributed to the QTcF prolongation observed in the ribociclib plus tamoxifen group (see section 5.1 Pharmacodynamic properties). A QTcF increase of >60 ms from baseline occurred in zero patients who received placebo plus NSAID, 7% of patients who received placebo plus tamoxifen, 7% of patients who received ribociclib plus NSAID, and 16% of patients who received ribociclib plus tamoxifen. Co-administration of KISQALI and tamoxifen is not recommended (see section 4.4 Special warnings and precautions for use).

Hepatobiliary toxicity

Across the phase III clinical studies, hepatobiliary toxicity events occurred in a higher proportion of ribociclib-treated patients compared with the placebo-treated patients (27% and 20%), and more Grade 3/4 adverse events were reported in the ribociclib-treated patients than placebo-treated patients (13% versus 6%). Dose interruptions and/or adjustments due to hepatobiliary toxicity events were reported in 12% of ribociclib-treated patients, primarily due to ALT increased (8%) and/or AST increased (7%). Discontinuation of treatment with KISQALI due to abnormal liver function tests, and hepatotoxicity occurred at rates of 2% and 0.3 % respectively (see sections 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties).

Neutropenia

Neutropenia was most frequently reported by laboratory findings in the phase III studies. Based on its severity, neutropenia was managed by laboratory monitoring, dose interruption and/or dose modification. Permanent treatment discontinuation due to neutropenia was low in patients receiving KISQALI (0.8%), however, dose interruptions and/or modifications were required in around half of ribociclib-treated patients (see sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

Post marketing experience

The following adverse reactions ~~s areis~~ derived from post-marketing experience with KISQALI via spontaneous case reports and literature cases. As ~~theseis~~ reactions ~~areis~~ reported voluntarily from a population of uncertain size, it is not possible to reliably estimate ~~theiirts~~ frequency which is therefore categorized as not known.

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Table 13 Adverse reactions from spontaneous reports and literature

| Adverse reaction | Frequency |
|--|-----------|
| <i>Respiratory, thoracic and mediastinal disorders</i> Interstitial lung disease (ILD)/pneumonitis | Unknown |
| <i>Skin and subcutaneous tissue disorders</i> Toxic epidermal necrolysis (TEN) | Unknown |

Reporting of suspected adverse reactions

The reporting suspected adverse reactions after the authorisation of the medicine is important. It allows for continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to Medsafe via the following web site: <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdosage

Symptoms and Signs

Limited experience in humans suggests that in the event of KISQALI overdose, nausea, vomiting, neutropenia and thrombocytopenia could occur. QTc prolongation may also occur, as it is known to be concentration-dependent.

Treatment

The treatment of overdose should consist of general symptomatic and supportive measures. For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - protein- kinase inhibitors.

Anatomical Therapeutic Chemical (ATC) code: L01EF02.

Mechanism of action

Ribociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6. 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).

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 in a rat xenograft model with human tumour cells lead to decreased tumour volumes, which correlated with inhibition of pRb phosphorylation.

In studies using a patient-derived oestrogen receptor-positive breast cancer xenograft models, combination of ribociclib and antioestrogen (e.g. letrozole) resulted in increased

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tumour growth inhibition compared to each drug alone. Additionally, the combination of ribociclib and fulvestrant resulted in tumour growth inhibition in an oestrogen receptor positive breast cancer xenograft model.

Pharmacodynamic effects

Ribociclib inhibits the CDK4/cyclin-D1 and CDK6/cyclin-D3 enzyme complexes with concentration resulting in 50% inhibition (IC₅₀) values of 0.01 micromolar (µM) (4.3 ng/mL) and 0.039 µM (16.9 ng/mL) in biochemical assays, respectively.

In cell based assays with pRb positive cancer cell lines, ribociclib inhibits CDK4/6-dependent pRb phosphorylation with an IC₅₀ of 0.06 µM (26 ng/mL). Ribociclib halts G1 to S phase cell cycle progression measured by flow cytometry with IC₅₀ of 0.11 µM (47.8 ng/mL). Ribociclib also inhibits cellular proliferation measured by bromodeoxyuridine uptake with IC₅₀ of 0.08µM (34.8ng/mL). When tested in a panel of breast cancer cell lines with known ER status, ER-positive cell lines were more sensitive than ER-negative cell lines to the anti-proliferation effects of ribociclib. Ribociclib had no inhibitory activity against pRb-negative breast cancer cell lines. In the preclinical models tested so far, intact pRb was required for ribociclib activity.

Cardiac electrophysiology

Serial, triplicate electrocardiograms (ECGs) were collected following a single dose and at steady-state to evaluate the effect of ribociclib on the QTc interval in patients with advanced cancer. *In vitro* studies have shown that both ribociclib and its major metabolite, LEQ803, interact with hERG channels. A pharmacokinetic-pharmacodynamic analysis included a total of 997 patients treated with ribociclib at doses ranging from 50 mg to 1,200 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval. The estimated mean change from baseline in QTcF for KISQALI 600 mg in combination with aromatase inhibitors or fulvestrant was 22.0 ms (90 % CI: 20.6, 23.0) and 23.7 ms (90% CI: 22.3, 25.1), respectively, and was 34.7 ms (90% CI: 31.6, 37.8) in combination with tamoxifen at the geometric mean C_{max} at steady-state (see section 4.4 Special warnings and precautions for use).

Clinical Trials

MONALEESA 2 (Study CLEE011A2301)

MONALEESA-2 was a randomised, double-blind, placebo-controlled, multicentre phase III clinical study of KISQALI plus letrozole versus placebo plus letrozole conducted in postmenopausal women with HR positive, HER2-negative, advanced breast cancer who had received no prior therapy for advanced disease.

A total of 668 patients were randomized to receive either KISQALI plus letrozole (n= 334) or placebo and letrozole (n=334), stratified according to the presence of liver and/or lung metastases. Demographics and baseline disease characteristics were balanced and comparable between study arms. Letrozole 2.5 mg was given orally once daily for 28 days, with either KISQALI 600 mg or placebo once daily for 21 consecutive days followed by 7 days off treatment until progression or unacceptable toxicity. Patients who had prior (neo-) adjuvant or adjuvant therapy with anastrozole or letrozole must have completed at least 12 months before randomisation, and patients were not allowed to cross over from placebo to KISQALI during the study or after disease progression. The primary efficacy endpoint for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

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Patients enrolled in MONALEESA-2 had a median age of 62 years (range 23 to 91). The majority of patients were Caucasian (82%), Asian (8%), or Black (3%), and all patients had an ECOG performance status of 0 or 1. Almost all patients had metastatic breast cancer (99.6 %) at study entry. A total of 47% of patients had received chemotherapy and 51% had received antihormonal therapy in the neoadjuvant or adjuvant setting. At study entry, 34% of patients had *de novo* metastatic disease, 22% had bone only disease and 59% had visceral disease.

Primary analysis

The efficacy findings are summarised in Table 14 and Figure 1. The results shown are from the pre-planned primary interim efficacy analysis of PFS and from an updated analysis performed at the time of the second interim analysis of overall survival (OS). Results were consistent across patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastatic disease. The PFS assessment based on a blinded independent central radiological review was consistent with investigator assessment.

Table 14 Efficacy results from MONALEESA 2 (investigator-assessed, intent-to-treat (ITT) population)

| | First interim analysis (29 Jan 2016 cut off) ^a | | Second interim analysis (2 Jan 2017 cut off) ^b | |
|--|--|---------------------------|--|---------------------------|
| | KISQALI plus letrozole | Placebo plus letrozole | KISQALI plus letrozole | Placebo plus letrozole |
| Progression-free survival (PFS) | | | | |
| Number of events, n (%) | 93 (27.8) | 150 (44.9) | 140 (41.9) | 205 (61.4) |
| Median PFS [months] (95 % CI) | NE (19.3 – NE) | 14.7 (13.0 – 16.5) | 25.3 (23.0 – 30.3) | 16.0 (13.4 – 18.2) |
| Hazard ratio, HR (95 % CI) | 0.556 (0.429 to 0.720) | | 0.568 (0.457 to 0.704) | |
| p-value ^c | 0.00000329 | | 0.0000000963 | |
| Patients with measurable disease | n=256 | n=245 | n=257 | n=245 |
| Overall Response Rate (ORR) (95 % CI) | 52.7 (46.6, 58.9) | 37.1 (31.1, 43.2) | 54.5 (48.4, 60.6) | 38.8 (32.7, 44.9) |

CI=confidence interval; N=number of patients; NE = Not estimable

^a Median duration of study follow up = 15.3 months

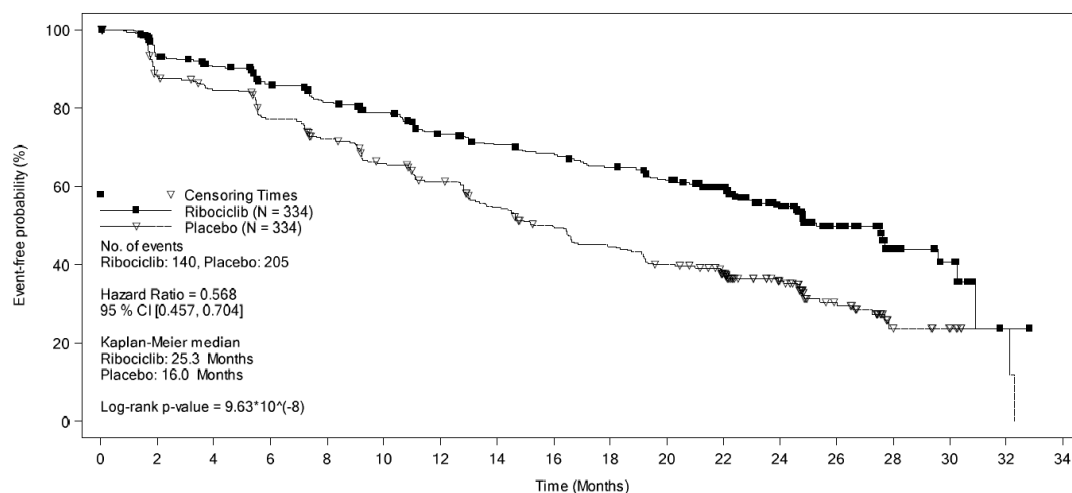
^b Median duration of study follow up = 26.4 months

^c p-value is obtained from the one-sided stratified log-rank test

ORR: Overall Response Rate = proportion of patients with complete response + partial response

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Figure 1 Kaplan-Meier plot for PFS (investigator-assessed, ITT population, 2 Jan 2017 data cut-off)



| Number of patients still at risk | | | | | | | | | | | | | | | | | | |
|----------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|
| Time | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 |
| Ribociclib | 334 | 294 | 277 | 257 | 240 | 227 | 207 | 196 | 188 | 176 | 164 | 132 | 97 | 46 | 17 | 11 | 1 | 0 |
| Placebo | 334 | 279 | 265 | 239 | 219 | 196 | 179 | 156 | 138 | 124 | 110 | 93 | 63 | 34 | 10 | 7 | 2 | 0 |

CI Confidence interval; PFS Progression-free survival

Final OS analysis

At the time of the final overall survival (OS) analysis (10-Jun-2021 cut-off), the study met its key secondary endpoint demonstrating a statistically significant and clinically meaningful improvement in OS with a 24% relative reduction in risk of death (HR: 0.765, 95% CI: 0.628, 0.932; p-value=0.004).

OS benefit increased over time, with a 6-year survival rate of 44% (38.5, 49.8) for Kisqali vs. 32% (26.8, 37.3) for placebo. The median OS was 63.9 months (95% CI: 52.4, 71.0) for the Kisqali arm and 51.4 months (95% CI: 47.2, 59.7) for the placebo arm, with a 12.5-months improvement in median OS for the Kisqali arm.

The exploratory OS results from subgroup analyses demonstrated that the OS benefit was generally consistent across the patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastatic. This was evident for patients with liver and/or lung disease (HR: 0.806 [95% CI: 0.621, 1.045]; a similar benefit was observed for those patients without liver and/or lung disease (HR: 0.711 [95% CI: 0.526, 0.962]).

The OS results from this final analysis are summarized in Table 15 and Figure 2.

Table 15 Efficacy results from MONALEESA 2 (OS 10 Jun 2021 cut-off)

| Overall survival, overall study population | KISQALI plus letrozole n=334 | Placebo plus letrozole n=334 |
|--|---------------------------------|---------------------------------|
| Number of events, n (%) | 181 (54.2%) | 219 (65.6%) |
| Median OS [months] (95% CI) | 63.9 (52.4, 71.0) | 51.4 (47.2, 59.7) |
| Hazard ratio ^a (95% CI) | 0.765 (0.628, 0.932) | |
| p-value ^b | 0.004 | |
| OS event-free rate, (%) (95% CI) | | |

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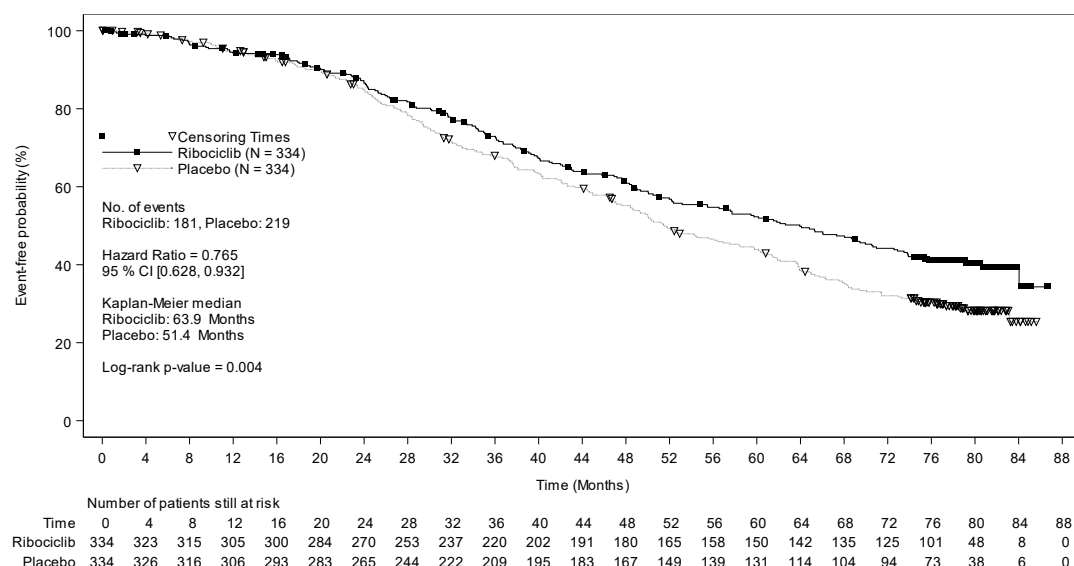
| Overall survival, overall study population | KISQALI plus letrozole n=334 | Placebo plus letrozole n=334 |
|--|---------------------------------|---------------------------------|
| 24 months | 86.6 (82.3, 89.9) | 85.0 (80.5, 88.4) |
| 60 months | 52.3 (46.5, 57.7) | 43.9 (38.3, 49.4) |
| 72 months | 44.2 (38.5, 49.8) | 32.0 (26.8, 37.3) |

CI=confidence interval;

^aHazard ratio is obtained from stratified Cox PH model;

^bp-value is obtained from the one-sided log-rank test. Stratification performed by lung and/or liver metastases status as per IRT.

Figure 2 Kaplan-Meier curve for OS (FAS)(10 Jun 2021 cut-off)



Log-rank test and Cox PH model are stratified by liver and/or lung metastasis as per IRT.

One sided P-value is obtained from stratified log rank test.

Additionally, the median time to first subsequent chemotherapy was prolonged by 11.7 months in the Kisqali arm compared to the placebo arm (50.6 months, 95% CI: 38.9, 60.0 months vs 38.9 months, 95% CI: 31.4, 45.4). The probability of chemotherapy usage was reduced by 26% in the Kisqali arm compared to the placebo arm (HR: 0.742; 95% CI: 0.606, 0.909).

MONALEESA-7 (Study CLEE011E2301)

MONALEESA-7 was a randomised, double-blind, placebo-controlled, multicentre clinical study of KISQALI plus endocrine therapy (goserelin plus either a non-steroidal aromatase inhibitor (NSAI) or tamoxifen) versus placebo plus endocrine therapy (goserelin plus either a NSAI or tamoxifen) for the treatment of pre- and peri-menopausal women with HR-positive, HER2-negative, advanced breast cancer who had received no prior endocrine therapy for advanced disease.

A total of 672 patients were randomised to receive either KISQALI plus goserelin plus NSAI/tamoxifen (n=335) or placebo plus goserelin plus NSAI/tamoxifen (n=337), stratified

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according to the presence of liver and/or lung metastases, prior chemotherapy for advanced disease and endocrine combination partners (NSAI and goserelin [n=493] versus tamoxifen and goserelin [n=179]). KISQALI is not recommended for use in combination with tamoxifen due to the risk of QTc prolongation (see section 4.4 Special warnings and precautions for use).

In the NSAI-treated patients, NSAI (letrozole 2.5 mg or anastrozole 1 mg) was given orally once daily on a continuous schedule, and goserelin (3.6 mg) was administered subcutaneously on day 1 of each 28 day cycle, with either KISQALI 600 mg or placebo orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. Patients were not allowed to cross over from placebo to KISQALI during the study or after disease progression, or to switch between endocrine combination partners. The primary efficacy endpoint for the study was investigator-assessed PFS using RECIST v1.1.

Patients enrolled in MONALEESA-7 had a median age of 44 years (range 25 to 58) and 28% were younger than 40. The majority of patients were Caucasian (58%), Asian (29%) or Black (3%), and nearly all patients (99%) had an ECOG performance status of 0 or 1. Of the 672 patients, 33% had received chemotherapy in the adjuvant setting, 18% had received chemotherapy in the neoadjuvant setting, 40% had received endocrine therapy in the adjuvant setting, and 0.7% had received endocrine therapy in the neoadjuvant setting. At study entry, 40% of patients had de novo metastatic disease, 24% had bone only disease, and 57% had visceral disease. Demographics and baseline disease characteristics were balanced and comparable between study arms, including in endocrine combination partner subgroups.

The efficacy results from a pre-specified subgroup analysis of 495 patients who had received KISQALI or placebo in combination with NSAI plus goserelin are summarised in Table 16 and Figure 3. In the NSAI subgroups, there was no significant difference demonstrated between the treatment arms for the Time to response (TTR) or Duration of response (DoR) – responders. Consistent results were observed in stratification subgroups of disease site and prior chemotherapy for advanced disease. At the time of the PFS analysis, 13% of patients had died, and overall survival data were immature.

Table 16 Efficacy results from MONALEESA-7 (investigator-assessed, NSAI subgroup)

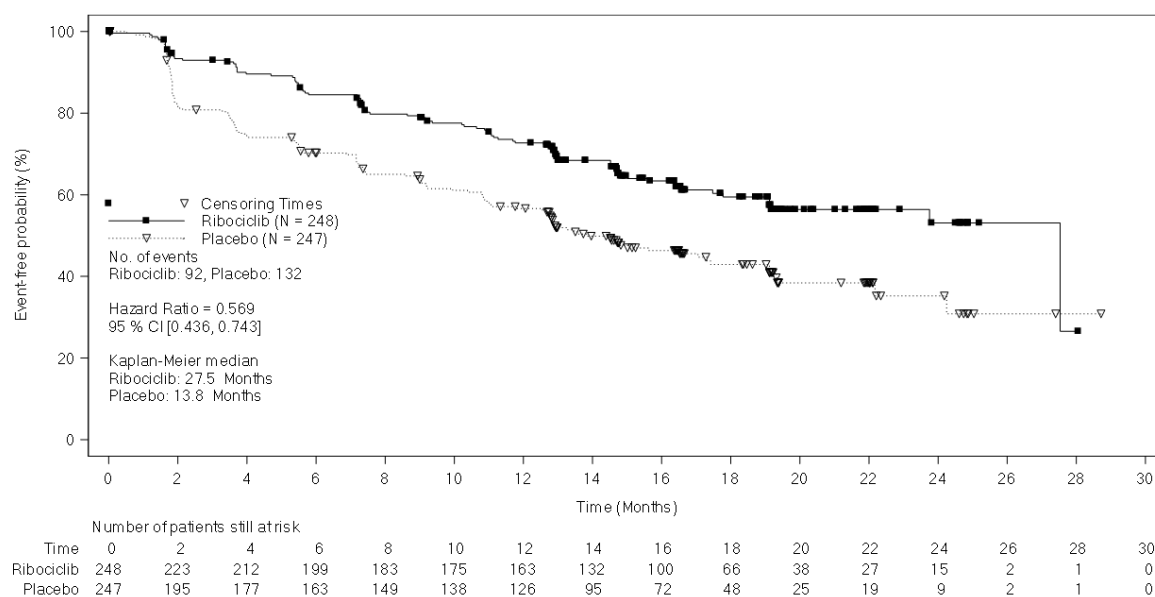
| | KISQALI + NSAI + goserelin | Placebo + NSAI + goserelin |
|--|----------------------------|----------------------------|
| Progression free survival (PFS) | N=248 | N=247 |
| Median PFS [months] (95% CI) | 27.5 (19.1, NE) | 13.8 (12.6, 17.4) |
| Hazard ratio (95% CI) | 0.569 (0.436, 0.743) | |
| Patients with measurable disease | N=192 | N=199 |
| Overall response rate (ORR)^a 95% CI | 50.5 (43.4, 57.6) | 36.2 (29.5, 42.9) |

CI = confidence interval; N = number of patients; NE = not estimable.

^a Based on confirmed responses ORR: Overall Response Rate = proportion of patients with complete response + partial response,

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Figure 3 Kaplan-Meier curve for PFS from MONALEESA-7 (investigator-assessed, NSAI subgroup)



Final Overall Survival (OS) Analysis

At the time of the second OS analysis (30-Nov-2018 cut-off), the study met its key secondary endpoint demonstrating a statistically significant improvement in OS.

The demonstrated OS benefit was consistent across exploratory subgroups and the safety profile of both treatment arms remained consistent with the results from the primary analysis.

A more mature update of overall survival data (30-Nov-2018 cut-off) is provided in Table 17 as well as in Figures 4 and 5.

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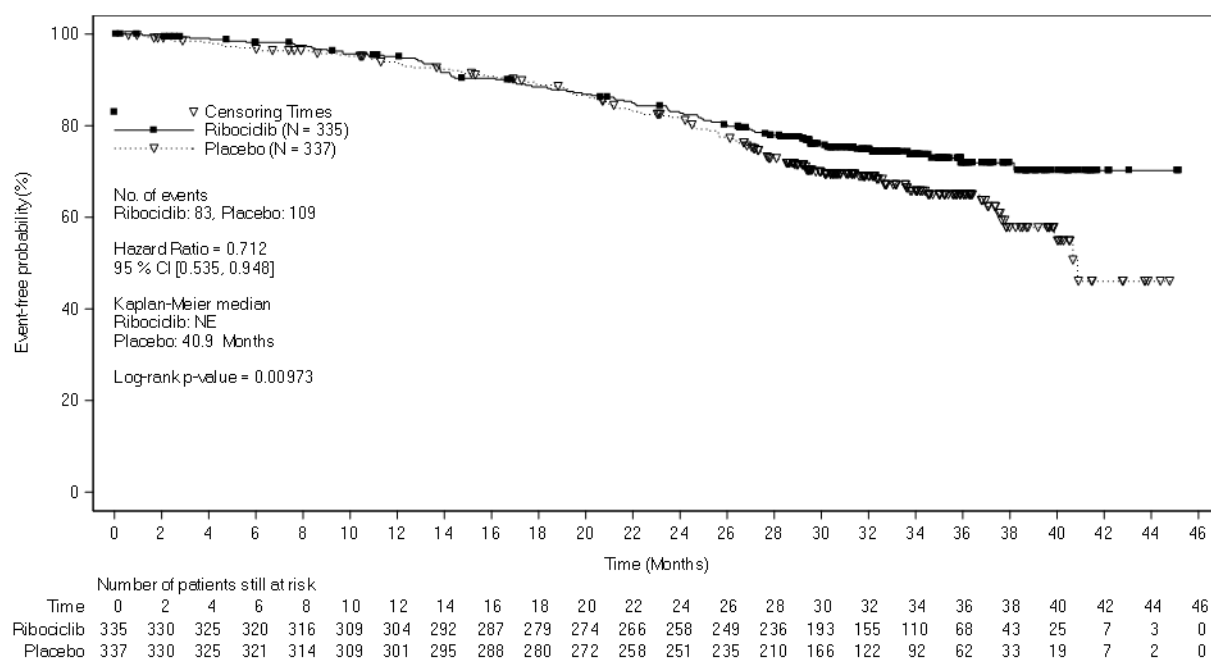
Table 17 MONALEESA-7 (E2301) efficacy results (OS) (30-Nov-18 cut-off)

| | | |
|--|----------------------------|------------------|
| Overall survival, overall study population | Ribociclib 600 mg N=335 | Placebo N=337 |
| Number of events – n [%] | 83 (24.8) | 109 (32.3) |
| Median OS [months] (95% CI) | NE (NE, NE) | 40.9 (37.8, NE) |
| Hazard ratio (95% CI) | 0.712 (0.535, 0.948) | |
| p-value ^a | 0.00973 | |
| Overall survival, NSAI subgroup | Ribociclib 600 mg N=248 | Placebo N=247 |
| Number of events – n [%] | 61 (24.6) | 80 (32.4) |
| Median OS [months] (95% CI) | NE (NE, NE) | 40.7 (37.4, NE) |
| Hazard ratio (95% CI) | 0.699 (0.501, 0.976) | |

CI=confidence interval, NE=not estimable, N=number of patients, NSAI = non-steroidal aromatase inhibitor;

^ap-value is obtained from the one-sided log-rank test stratified by lung and/or liver metastases, prior chemotherapy for advanced disease, and endocrine partner per IRT

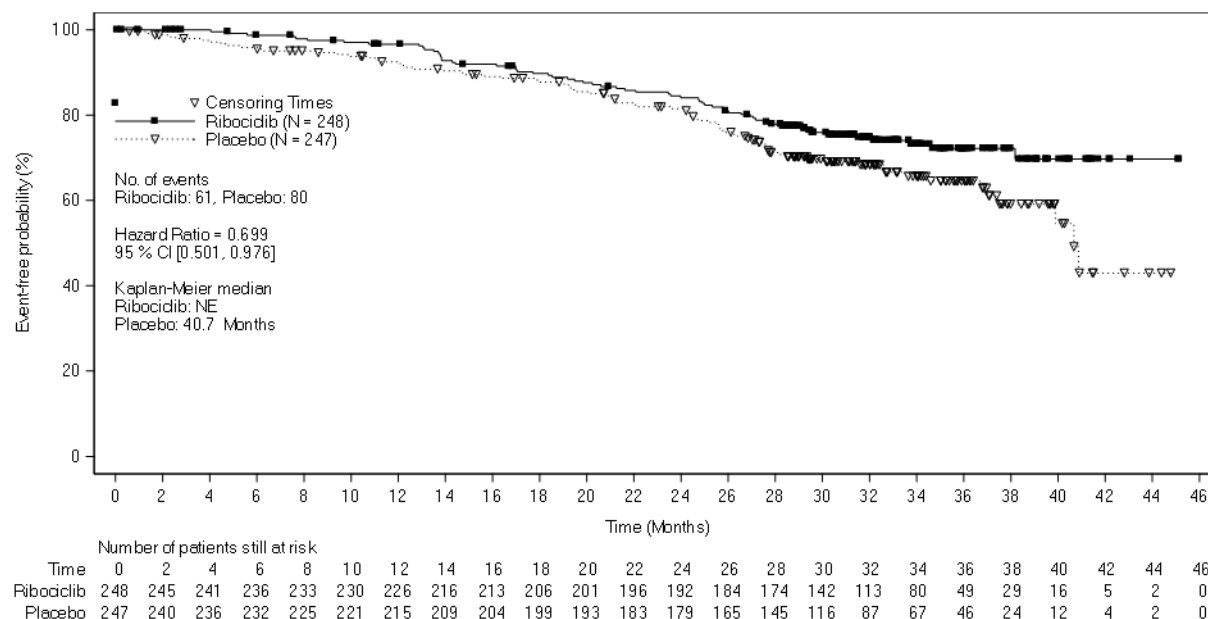
Figure 4 MONALEESA-7 (E2301) Kaplan Meier plot of OS (FAS) (30-Nov-2018 cut-off)



Log-rank test and Cox model are stratified by lung and/or liver metastasis, prior chemotherapy for advanced disease, and endocrine combination partner per IRT

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Figure 5 MONALEESA-7 (E2301) Kaplan Meier plot of OS in patients who received NSAI (30-Nov-18 cut-off)



Hazard ratio is based on unstratified Cox model.

Additionally, time to progression on next-line therapy or death (PFS2) in patients in the Kisqali arm was longer compared to patients in the placebo arm (HR: 0.692 (95% CI: 0.548, 0.875)) in the overall study population. The median PFS2 was 32.3 months (95% CI: 27.6, 38.3) in the placebo arm and was not reached (95% CI: 39.4, NE) in the Kisqali arm. Similar results were observed in the NSAI sub-group (HR: 0.660 (95% CI: 0.503, 0.868); median PFS2: 32.3 months (95% CI: 26.9, 38.3) in the placebo arm vs not reached (95% CI: 39.4, NE) in the ribociclib arm).

MONALEESA-3 Study CLEE011F2301)

MONALEESA-3 was a randomised double-blind, placebo-controlled, multicentre clinical study of KISQALI plus fulvestrant versus placebo plus fulvestrant for the treatment of men and postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who had received no or only one line of prior endocrine treatment for advanced disease.

A total of 726 patients were randomised to receive either KISQALI plus fulvestrant (n=484) or placebo plus fulvestrant (n=242), stratified according to the presence of liver and/or lung metastases and prior endocrine therapy. First-line patients with advanced breast cancer (A) include *de novo* advanced breast cancer with no prior endocrine therapy, and patients who relapsed after 12 months of (neo) adjuvant endocrine therapy completion.

Second-line patients' subgroup (B) includes those patients whose disease relapsed during adjuvant therapy or less than 12 months after endocrine adjuvant therapy completion, and those who progressed to first line endocrine therapy. Fulvestrant 500 mg was administered intramuscularly on days 1, 15, 29, and once monthly thereafter, with either KISQALI 600 mg or placebo given orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity.

Patients enrolled in MONALEESA-3 had a median age of 63 years (range 31 to 89), and 14% were at least 75 years old. The majority of patients were Caucasian (85%), Asian

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(9%) or Black (1%), and nearly all patients (99.7%) had an ECOG performance status of 0 or 1. First and second line patients were enrolled in this study (of which 19% had de novo metastatic disease). Of the 726 patients, 43% had received chemotherapy in the adjuvant setting, 13% had received chemotherapy in the neoadjuvant setting, 59% had received endocrine therapy in the adjuvant setting and 1% had received endocrine therapy in the neoadjuvant setting. At study entry, 21% of patients had bone only disease and 61% had visceral disease. Demographics and baseline disease characteristics were balanced and comparable between study arms.

Primary analysis

The primary efficacy endpoint for the study was investigator-assessed PFS using RECIST v1.1, based on the investigator assessment in the full analysis set (all randomized patients) and confirmed by a random central audit of 40% imaging subset by a blinded independent review committee (BIRC). The median follow-up time at the time of primary PFS analysis was 20.4 months.

PFS analyses based on the BIRC were supportive of the primary efficacy results, the PFS hazard ratio was 0.492 (95% CI, 0.345 to 0.703).

The efficacy results from MONALEESA-3 are summarised in Table 18 and Figure 6. Consistent results were observed in stratification subgroups of disease site and prior endocrine treatment for advanced disease.

At the time of the PFS analysis, 17% of patients had died, and overall survival data were immature.

Table 18 Efficacy results from MONALEESA-3 (investigator-assessed, ITT population)

| | KISQALI + fulvestrant | Placebo + fulvestrant |
|--|-----------------------|-----------------------|
| Progression free survival | N=484 | N=242 |
| Median PFS [months] (95% CI) | 20.5 (18.5 – 23.5) | 12.8 (10.9 – 16.3) |
| Hazard ratio (95% CI) | 0.593 (0.480 - 0.732) | |
| p-value ^a | 0.00000041 | |
| Patients with measurable disease | N=379 | N=181 |
| Overall response rate (ORR)^b | 40.9 (35.9 , 45.8) | 28.7 (22.1, 35.3) |
| Time to response (TTR) | N=484 | N=282 |
| Median TTR [months] (95% CI) | NE (NE , NE) | NE (NE , NE) |
| Probability of response by 6 months | 26.6 (22.7, 31.0) | 16.2 (12.0, 21.6) |

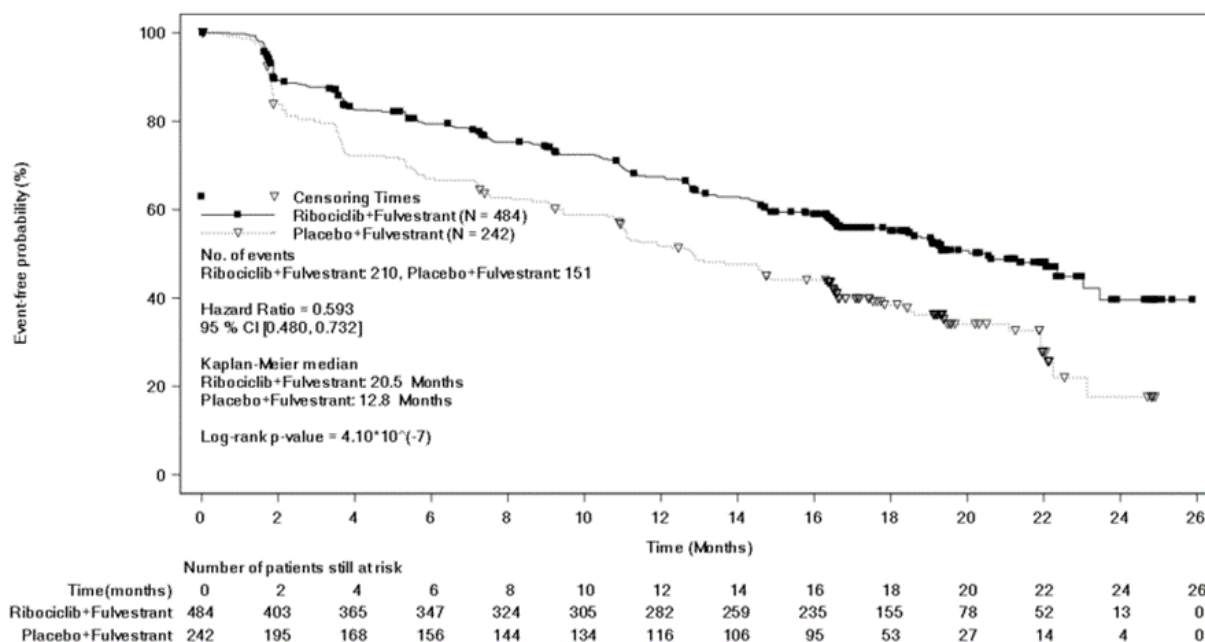
CI = confidence interval; N = number of patients; NE = not estimable.

^a p-value is obtained from the one-sided stratified log-rank test

^b Based on confirmed responses, ORR: Overall Response Rate = proportion of patients with complete response + partial response

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Figure 6 Kaplan-Meier curve for PFS from MONALEESA-3 (investigator-assessed, ITT population)



The clinical benefit rate in the Kisqali plus fulvestrant arm and in the placebo plus fulvestrant arm is summarized in Table 19.

Table 19 MONALEESA-3 (F2301) efficacy results (ORR, CBR) based on investigator assessment (03-Nov-17 cut-off)

| Analysis | Kisqali plus fulvestrant (%, 95% CI) | Placebo plus fulvestrant (%, 95% CI) | p-value |
|---|---|---|----------|
| Full analysis set | N=484 | N=242 | |
| Overall Response Rate ^a | 32.4 (28.3, 36.6) | 21.5 (16.3, 26.7) | 0.000912 |
| Clinical Benefit Rate ^b | 70.2 (66.2, 74.3) | 62.8 (56.7, 68.9) | 0.020 |
| Patients with measurable disease | N=379 | N=181 | |
| Overall Response Rate ^a | 40.9 (35.9, 45.8) | 28.7 (22.1, 35.3) | 0.003 |
| Clinical Benefit Rate ^b | 69.4 (64.8, 74.0) | 59.7 (52.5, 66.8) | 0.015 |

^a ORR: proportion of patients with complete response + partial response

^b CBR: proportion of patients with complete response + partial response + (stable disease or non-complete response/non-progressive disease ≥24 weeks)

The global health status/ QoL were similar between the Kisqali plus fulvestrant arm and the placebo plus fulvestrant arm. The main pre-specified QoL measure was TTD in global health status. A definitive 10% deterioration was defined as a worsening in score (EORTC QLQ-C30 global health scale score) by at least 10% compared to baseline, with no later

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improvement above this threshold observed during the treatment period, or death due to any cause. Addition of Kisqali to fulvestrant resulted in delaying TTD in the EORTC QLQ-CLEE11F2301 (MONALEESA-3) global health scale score compared with placebo plus fulvestrant, (median not estimable versus 19.4 months; HR: 0.795 [95% CI: 0.602,1.050]; p-value 0.051.

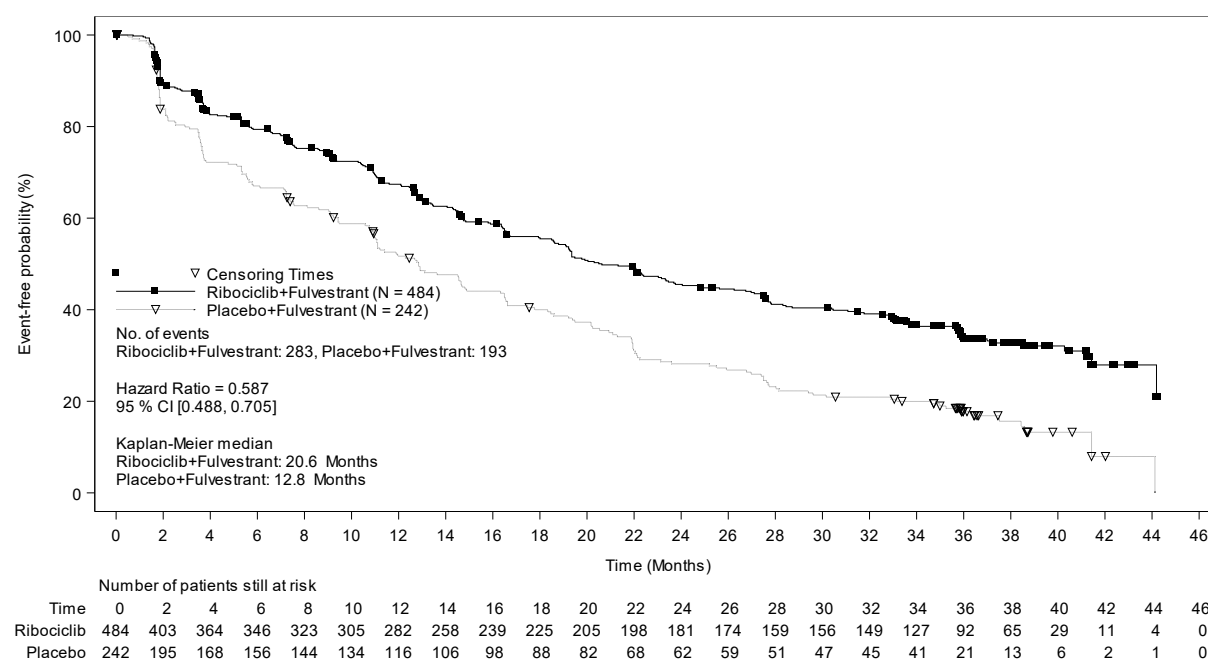
Final OS Analysis

Since the median PFS for first line patients had not been reached at the time of the primary analysis, a descriptive update of primary efficacy results (PFS) was performed at the time of the second OS interim analysis, and the updated PFS results are summarized in Table 20 and the Kaplan-Meier curve is provided in Figure 7.

Table 20 MONALEESA-3 (F2301) primary efficacy results (PFS) based on investigator assessment (03-Jun-19 cut-off)

| | Kisqali plus fulvestrant N=484 | Placebo plus fulvestrant N=242 |
|----------------------------------|-----------------------------------|-----------------------------------|
| Progression-free survival | | |
| Median PFS [months] (95% CI) | 20.6 (18.6, 24.0) | 12.8 (10.9, 16.3) |
| Hazard ratio (95% CI) | 0.587 (0.488, 0.705) | |

Figure 7 MONALEESA-3 (F2301) Kaplan-Meier plot of PFS based on investigator assessment (FAS) (03-Jun-19 cut-off)



Results were consistent across pre-specified sub-groups of age, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone only metastatic disease. The subgroup analysis based on prior endocrine therapy is presented in Table 21.

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Table 21 MONALEESA-3 (F2301) efficacy results (PFS) for prior endocrine therapy subgroup (03-Jun-19 cut-off)

| | Updated analysis PFS subgroup for prior endocrine therapy (3 Jun 19 cut-off) | |
|--|---|-------------------|
| First-line setting | Ribociclib 600 mg N=237 | Placebo N=128 |
| Number of events – n [%] | 112 (47.3) | 95 (74.2) |
| Median PFS [months] (95% CI) | 33.6 (27.1, 41.3) | 19.2 (14.9, 23.6) |
| Hazard ratio (95% CI) | 0.546 (0.415, 0.718) | |
| Second-line setting or with an early relapse | Ribociclib 600 mg N=237 | Placebo N=109 |
| Number of events – n [%] | 167 (70.5) | 95 (87.2) |
| Median PFS [months] (95% CI) | 14.6 (12.5, 18.6) | 9.1 (5.8, 11.0) |
| Hazard ratio (95% CI) | 0.571 (0.443, 0.737) | |

CI=confidence interval

First-line setting = newly diagnosed (de novo) advanced breast cancer or relapse after 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced or metastatic disease

Second-line setting or with an early relapse = relapse on or within 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced or metastatic disease (early relapse), relapse after 12 months from completion of (neo)adjuvant therapy with subsequent progression after one line of endocrine therapy for advanced or metastatic disease, or advanced or metastatic breast cancer at diagnosis that progressed after one line of endocrine therapy for advanced disease with no prior (neo)adjuvant treatment for early disease

In the pre-specified second OS interim analysis, the study crossed pre-specified Lan-DeMets (O'Brien-Fleming) stopping boundary, demonstrating a statistically significant improvement in OS.

The OS results from this interim analysis with a 03-Jun-19 cut-off are provided in Table 22 and Figure 8.

Table 22 MONALEESA-3 (F2301) efficacy results (OS) (03-Jun-19 cut-off)

| | Kisqali 600 mg | Placebo |
|-----------------------------|--------------------|-------------|
| Overall study population | N=484 | N=242 |
| Number of events - n [%] | 167 (34.5) | 108 (44.6) |
| Median OS [months] (95% CI) | NE, (NE, NE) | 40 (37, NE) |
| HR (95% CI) | 0.724 (0568, 0924) | |
| p value | 0.00455 | |

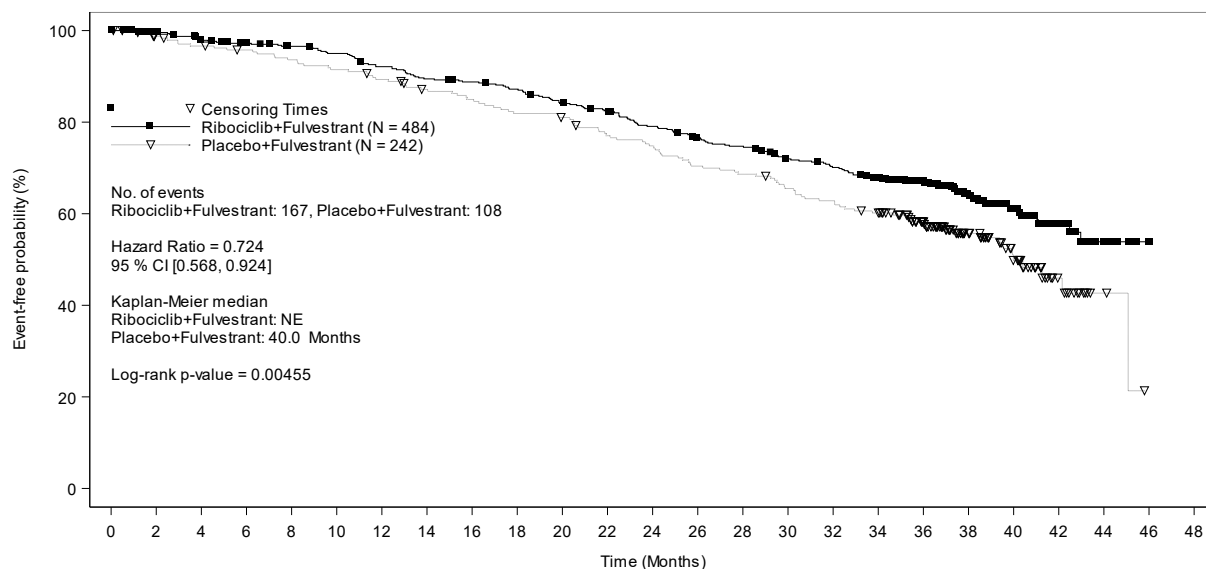
- [1] One-sided P-value is obtained from log-rank test stratified by lung and/or liver metastasis, previous endocrine therapy per IRT. P-value is one-sided and is compared against a threshold of 0.01129 as determined by the Lan-DeMets (O'Brien-Fleming) alpha-spending function for an overall significance level of 0.025.

- [2] Hazard ratio is obtained from the Cox PH model stratified by lung and/or liver metastasis, previous endocrine therapy per IRT.

NE = Not estimable

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Figure 8 MONALEESA-3 (F2301) Kaplan Meier plot of OS (FAS) (03-Jun-19 cut-off)

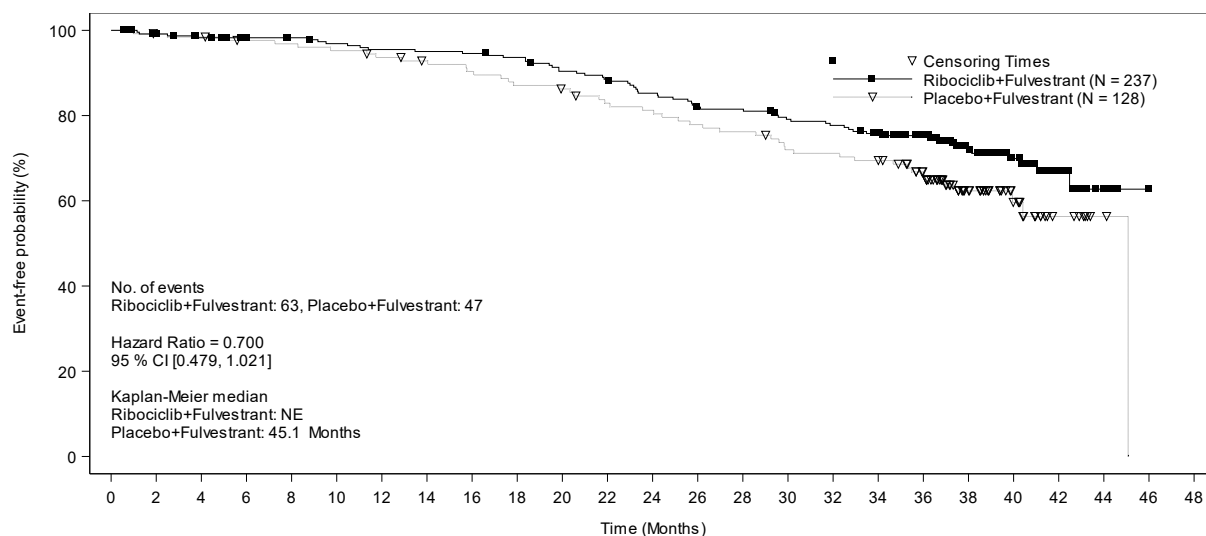


| Number of patients still at risk | |
|----------------------------------|--|
| Time | 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 |
| Ribociclib | 484 470 454 444 436 428 414 402 397 389 374 365 348 334 326 309 300 287 237 159 92 41 14 2 0 |
| Placebo | 242 233 227 223 218 213 207 199 194 187 184 174 169 159 155 147 141 134 107 64 37 14 3 0 0 |

Log-rank test and Cox model are stratified by lung and/or liver metastasis, prior chemotherapy for advanced disease, and endocrine combination partner per IRT.

OS results for subgroups analyses are presented in Figures 9 and 10.

Figure 9 MONALEESA-3 (F2301) Kaplan Meier plot of OS treatment naïve patients in the metastatic/advanced disease setting (FAS) (03-Jun-19 cut-off)

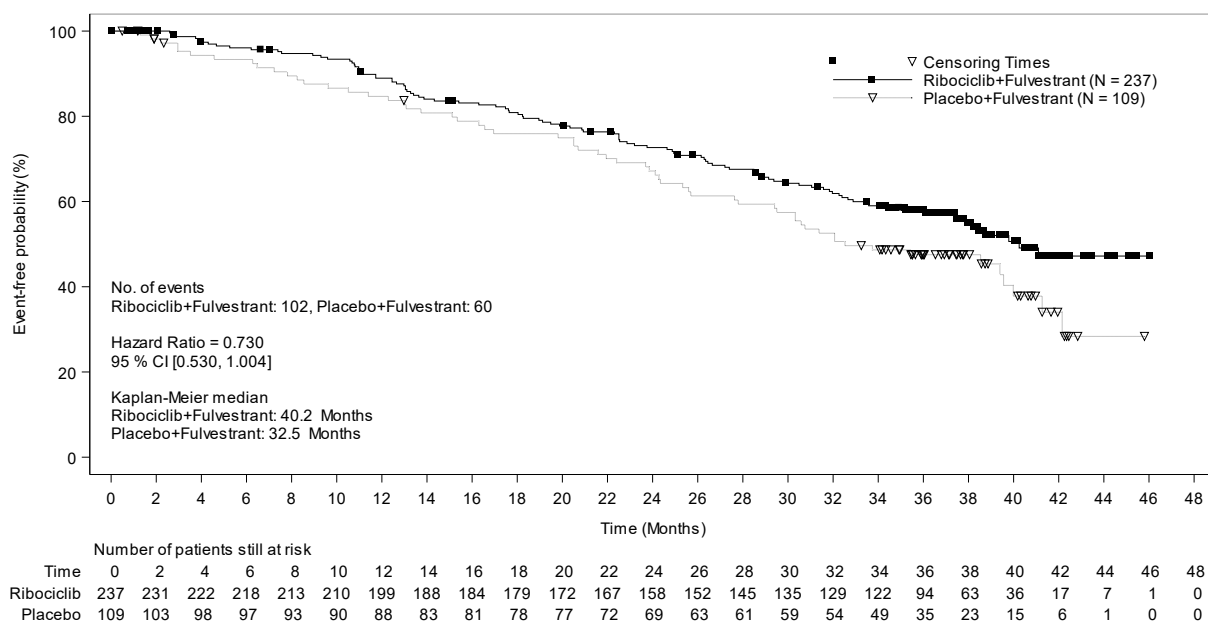


| Number of patients still at risk | |
|----------------------------------|--|
| Time | 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 |
| Ribociclib | 237 229 222 217 214 210 207 206 205 202 194 190 182 174 173 166 163 157 138 92 54 22 6 1 0 |
| Placebo | 128 126 125 122 121 119 116 113 110 106 104 99 97 93 91 85 84 82 70 40 21 8 2 0 0 |

Hazard ratio is based on unstratified Cox model

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Figure 10 MONALEESA-3 (F2301) Kaplan Meier plot of OS in patients who received up to 1 line of treatment for metastatic/advanced disease setting (FAS) (03-Jun-19 cut-off)



Hazard ratio is based on unstratified Cox model

Additionally, time to progression on next-line therapy or death (PFS2) in patients in the Kisqali arm was longer compared to patients in the placebo arm (HR: 0.670 (95% CI: 0.542, 0.830)) in the overall study population. The median PFS2 was 39.8 months (95% CI: 32.5, NE) for the Kisqali arm and 29.4 months (95% CI: 24.1, 33.1) in the placebo arm.

Study CLEE011A2404 (COMPLEMENT-1)

COMPLEMENT-1 was an open-label, single arm, multicentre phase IIIb clinical study comparing ribociclib in combination with letrozole in pre/post-menopausal women and men with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease. Premenopausal women, and men, also received goserelin or leuprolide.

The study enrolled 3246 patients, including 39 male patients who received Kisqali 600 mg orally once daily for 21 consecutive days followed by 7 days off; and letrozole 2.5 mg orally once daily for 28 days; and goserelin 3.6 mg as injectable subcutaneous implant or leuprolide 7.5 mg as intramuscular injection administered on Day 1 of each 28 day cycle. Patients were treated until disease progression or unacceptable toxicity occurred.

Male patients enrolled in this study had a median age of 62 years (range 33 to 80). Of these patients, 39% were 65 years and older, including 10% aged 75 years and older. The male patients enrolled were Caucasian (72%), Asian (8%), and Black (3%), with 17% unknown. Nearly all male patients (97%) had an ECOG performance status of 0 or 1. The majority of male patients (97%) had 4 or less metastatic sites, which were primarily bone and visceral (69% each). Table 23 summarises the efficacy results in male patients.

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Table 23 COMPLEEMENT-1 (A2402) efficacy results in male patients¹ based on investigator assessment (intent-to-treat population)

| | Kisqali + Letrozole + Goserelin or Leuprolide |
|---|---|
| Overall Response Rate*² | N = 32 |
| (95% CI) | 46.9 (29.1, 65.3) |
| Duration of Response³ | N = 15 |
| Median (months, 95% CI) | NR (21.3, NR) |
| Patients with DoR \geq 12 months, n (%) | 12 (80.0%) |
| Clinical Benefit Rate⁴ | |
| (95% CI) | 71.9 (53.3, 86.3) |

Abbreviations: CI, confidence interval, NR, not reached.

**Based on confirmed responses.*

¹Patients with measurable disease; 7 patients did not have measurable disease.

²Investigator Assessment.

³Proportion of patients with complete response or partial response.

⁴Proportion of patients with complete response + partial response + (stable disease or non-complete response/non-progressive disease \geq 24 weeks)

5.2 Pharmacokinetic (PK) Properties

The pharmacokinetics of ribociclib was investigated in patients with advanced cancer following oral daily doses ranging from 50 mg to 1,200 mg. Healthy subjects received single oral doses ranging from 400 mg to 600 mg or repeated daily oral doses (for 8 days) at 400 mg. At the recommended dose of ribociclib 600 mg, the inter-patient variability in pharmacokinetics was approximately 60%.

Absorption

Following oral administration of KISQALI to patients with advanced solid tumours or lymphomas, peak plasma levels (C_{max}) of ribociclib were achieved between 1 and 4 hours (time to reach maximum concentration, T_{max}). The geometric mean absolute bioavailability of ribociclib after a single oral dose of 600 mg was 65.8% in healthy subjects. 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).

Linearity/non-linearity

Ribociclib exhibited slightly over-proportional increases in exposure (C_{max} and AUC) across the dose range of 50 mg to 1,200 mg following both single dose and repeated doses. The observed over-proportional increases in exposure might be attributed to auto-inhibition of CYP3A4. 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.

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Food effect

Compared to the fasted state, oral administration of a single 600 mg dose of KISQALI with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib. The geometric mean ratio (GMR) for C_{max} GMR was 1.00; 90% CI: 0.898, 1.11 and for AUC_{inf} was 1.06; 90% CI: 1.01, 1.12.

Distribution

Binding of ribociclib to human plasma proteins *in vitro* was approximately 70% and independent of concentration (10 ng/mL to 10000 ng/mL). Ribociclib was equally distributed between red blood cells and plasma with a mean *in vivo* blood-to-plasma ratio of 1.04. The mean apparent volume of distribution at steady-state (V_{ss}/F) was 1090 L based on population PK analysis.

Biotransformation

In vitro and *in vivo* studies indicated that ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of [^{14}C] 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 I metabolites involved N-acetylation, sulphation, cysteine conjugation, glycosylation and glucuronidation. Ribociclib was the major circulating drug-derived entity in plasma (44%). The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide), each representing an estimated 9%, 9%, and 8% of total radioactivity, and 22%, 20%, and 18% of ribociclib exposure respectively. Clinical activity (pharmacological and safety) of ribociclib was due primarily to the parent drug, with negligible contribution from the circulating metabolites.

Ribociclib was extensively metabolized with unchanged drug accounting for 17% and 12% of the dose in feces and urine respectively. Metabolite LEQ803 was a significant metabolite in excreta and represented approximately 14% and 4% of the administered dose in faeces and urine, respectively. Numerous other metabolites were detected in both faeces and urine in minor abundance ($\leq 3\%$ of the administered dose).

Elimination

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. The geometric mean apparent plasma terminal half-life ($t_{1/2}$) 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 in healthy subjects.

Ribociclib is eliminated mainly via feces, with some elimination by the renal route. In six healthy male subjects, following a single oral dose of [^{14}C] ribociclib, 92% of the total administered radioactive dose was recovered within 22 days; faeces was the major route of excretion (69%), with 23% of the dose recovered in urine. The estimated oral absorption of ribociclib was 59%.

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Characteristics in Special Populations

Renal Impairment

The effect of renal function on the pharmacokinetics of ribociclib was assessed in a renal impairment study in non-cancer subjects that included 14 subjects with normal renal function (aGFR ≥ 90 mL/min), 8 subjects with mild renal impairment (aGFR 60 to < 90 mL/min), 6 subjects with moderate renal impairment (aGFR 30 to < 60 mL/min), 7 subjects with severe renal impairment (aGFR 15 to < 30 mL/min), and 3 subjects with end stage renal disease (ESRD) (aGFR < 15 mL/min) at a single oral ribociclib dose of 400 mg/day. AUC_{inf} increased to 1.62-fold, 1.94-fold and 2.67-fold, and C_{max} increased to 1.80-fold, 1.79-fold and 2.30-fold in subjects with mild, moderate and severe renal impairment, relative to the exposure in subjects with normal renal function. A fold difference for subjects with ESRD was not calculated due to the small number of subjects (see section 4.2 Dose and method of administration).

No dose adjustment is necessary in patients with mild or moderate renal impairment.

The effect of renal function on the pharmacokinetics of ribociclib was also assessed in cancer patients. Based on a population pharmacokinetic analysis that included 438 patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m²), 488 patients with mild renal impairment (eGFR 60 to < 90 mL/min/1.73 m²) and 113 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.

In addition, in a sub-group analysis of PK data from studies in cancer patients following oral administration of ribociclib 600 mg as a single dose or repeat doses (MONALEESA-7, CLEE011X2101 and CLEE011X2107), AUC and C_{max} of ribociclib following a single dose or at steady state in patients with mild or moderate renal impairment were comparable to patients with normal renal function, suggesting no clinically meaningful effect of mild or moderate renal impairment on ribociclib exposure (see section 4.2 Dose and method of administration).

Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A); a dose adjustment is required in patients with moderate (Child-Pugh B), or severe hepatic impairment (Child-Pugh C) and starting dose of 400 mg is recommended (see section 4.2 Dose and method of administration). Based on a PK trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib (see section 4.2 Dose and method of administration). The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.44 for C_{max} ; 1.28 for AUC_{inf}) and severe (GMR: 1.32 for C_{max} ; 1.29 for AUC_{inf}). Based on a population PK analysis that included 160 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 Dose and method of administration).

Use in the elderly

Of the 334 patients who received KISQALI in MONALEESA-2 (ribociclib plus letrozole arm), 150 patients (45%) were ≥ 65 years of age and 35 patients (10%) were ≥ 75 years of age. Of 483 patients who received KISQALI in MONALEESA-3, (ribociclib plus fulvestrant arm), 226 patients (47%) were ≥ 65 years of age and 65 patients (14%) were ≥ 75 years of

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age. No overall differences in the safety or effectiveness of KISQALI were observed between these patients and younger patients (see section 4.2 Dose and method of administration).

Paediatric use

No studies have been conducted to investigate the pharmacokinetics of ribociclib in paediatric patients.

Effect of age, weight, gender and race

Population PK analysis showed that there are no clinically relevant effects of age, body weight, gender, or race on the systemic exposure of ribociclib that would require a dose adjustment.

5.3 Preclinical Safety Data

Safety pharmacology

QT prolongation

In vivo cardiac safety studies 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. As well, there is potential to induce incidences of premature ventricular contractions (PVCs) at elevated exposures (approximately 5-fold the anticipated clinical C_{max}).

Phototoxicity

Ribociclib was shown to absorb light in the UV-B and UV-A range. An *in vitro* phototoxicity test did not identify a relevant phototoxicity potential for ribociclib. The risk that KISQALI causes photosensitization in patients is considered very low.

Repeat dose toxicity

Repeated-dose toxicity studies (treatment schedule of 3 weeks on/1 week off) of up to 27 weeks' duration in rats and up to 39 weeks' duration in dogs, revealed the hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) 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. Exposure to ribociclib in animals in the toxicity studies was generally less than or equal to that observed in patients receiving multiple doses of 600 mg/day (based on AUC).

Reproductive toxicity/fertility

Ribociclib showed foetotoxicity and teratogenicity at doses which did not show maternal toxicity in the rats or rabbits. Following prenatal exposure, increased incidences of post-implantation loss and reduced foetal weights were observed in rats and ribociclib was teratogenic in rabbits at exposures lower than or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC.

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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.

In a fertility study in female rats, ribociclib did not affect reproductive function, fertility or early embryonic development at doses up to 300 mg/kg/day (approximately 0.6 times the clinical exposure in patients at the highest recommended dose of 600 mg/day based on AUC).

Ribociclib has not been evaluated in male fertility studies. However, atrophic changes in the testes were reported in rat and dog toxicity studies at exposures that were less than or equal to human exposure at the highest recommended daily dose of 600 mg/day based on AUC. These effects can be linked to direct anti-proliferative effects on the testicular germ cells resulting in atrophy of the seminiferous tubules.

Ribociclib and its metabolites passed readily into rat milk. In lactating rats administered a single dose of 50 mg/kg, exposure to ribociclib was 4-fold higher in milk compared to maternal plasma.

Carcinogenicity

Ribociclib was assessed for carcinogenicity in a 2-year rat study.

Oral administration of ribociclib for 2 years resulted in an increased incidence of endometrial epithelial tumours and glandular and squamous hyperplasia in the uterus/cervix of female rats at doses ≥ 300 mg/kg/day as well as an increased incidence in follicular tumours in the thyroid glands of male rats at a dose of 50 mg/kg/day. Mean exposure at steady state (AUC_{0-24h}) in female and male rats in whom neoplastic changes were seen was 1.2 and 1.4-fold that achieved in patients at the recommended dose of 600 mg/day, respectively. Mean exposure at steady state (AUC_{0-24h}) in female and male rats in whom neoplastic changes were seen was 2.2- and 2.5-fold that achieved in patients at a dose of 400 mg/day, respectively.

Additional non-neoplastic proliferative changes consisted of increased liver altered foci (basophilic and clear cell) and testicular interstitial (Leydig) cell hyperplasia in male rats at doses of ≥ 5 mg/kg/day and 50 mg/kg/day, respectively.

The effects on the uterus/cervix and on the testicular interstitial (Leydig) cell may be related to prolonged hypoprolactinemia secondary to CDK4 inhibition of lactotrophic cell function in the pituitary gland, altering the hypothalamus-pituitary-gonadal axis.

Potential mechanisms for the thyroid findings in males include a rodent-specific microsomal enzyme induction in the liver and/or a dysregulation of the hypothalamus-pituitary-testis-thyroid axis secondary to a persistent on-target hypoprolactinemia.

Any potential increase of oestrogen/progesterone ratio in humans by this mechanism would be compensated by an inhibitory action of concomitant anti-oestrogen therapy on oestrogen synthesis as in humans KISQALI is indicated in combination with oestrogen-lowering agents.

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Considering important differences between rodents and humans with regard to synthesis and role of prolactin, this mode of action is not expected to have consequences in humans.

Genotoxicity

Genotoxicity studies in bacteria, and in mammalian cells (human lymphocytes and mouse lymphoma cells) *in vitro* with and without metabolic activation, and in a micronucleus test in rats did not reveal any evidence for a mutagenic potential of ribociclib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each film coated tablet contains ribociclib succinate equivalent to 200 mg ribociclib. Each tablet contains microcrystalline cellulose, hypromellose, croscopolidone, colloidal silicon dioxide, magnesium stearate (vegetable source), polyvinyl alcohol, titanium dioxide (E171), iron oxide black CI77499, iron oxide red CI77491, purified talc, lecithin (soya), and xanthan gum. KISQALI does not contain sucrose, lactose, gluten, or synthetic colours.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30°C.

Store in original container.

6.5 Nature and Contents of Container

KISQALI 200 mg film-coated tablets

Supplied in Aclar/aluminium blisters platforms in packs containing either 63, 42, or 21 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements. Return KISQALI tablets to a pharmacy for safe disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Novartis New Zealand Limited

PO Box 99102 Newmarket

Auckland 1149 New Zealand

Telephone number (free call within New Zealand): 0800 354 335

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Fax number: (09) 361 8181

E-mail: medinfo.phauno@novartis.com.

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to first distribute the medicine:
06 June 2019.

10. DATE OF REVISION OF THE TEXT

07 July 2022.

Summary table of changes

| Section | Summary of changes |
|-----------|--|
| 4.4 & 4.8 | Subheadings Interstitial Lung Disease (ILD)/Pneumonitis and Post Marketing Experience: Additional cases of ILD/pneumonitis have been observed with Kisqali in the post-marketing setting frequency unknown |

Internal document code: kis150722iNZ based on Novartis CDS 2.5 dated 09 May 2022.