AUSTRALIAN Product Information - KISQALI® (ribociclib) tablets

1. NAME OF THE MEDICINE

Ribociclib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

Each film coated tablet contains ribociclib succinate equivalent to 200 mg ribociclib.

Excipients

Excipients with known effect: each film-coated tablet contains 0.344 mg soya lecithin.

For full list of excipients see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Light greyish violet, 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

Early breast cancer

KISQALI in combination with an aromatase inhibitor is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.

Advanced or metastatic breast cancer

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 initial endocrine-based therapy or following prior endocrine therapy.

4.2 Dose and method of administration

Early breast cancer

The recommended dose of KISQALI when given in combination with an aromatase inhibitor for the treatment of early breast cancer is 400 mg (two 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.

In patients with early breast cancer, continue KISQALI until completion of 3 years of treatment or until disease recurrence or unacceptable toxicity occurs.

Advanced or metastatic breast cancer

The recommended dose of KISQALI when given in combination with an aromatase inhibitor or fulvestrant for advanced or metastatic breast cancer 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.

In patients with advanced or metastatic breast cancer, treatment should be continued as long as the patient is deriving clinical benefit from therapy, unless unacceptable toxicity occurs.

General dosing advice (across indications)

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

KISQALI may be taken with or without food (see section 4.5 Interactions with other medicines and other forms of interaction), but should be taken at approximately the same time each day, preferably in the morning.

If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

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

Co-administered medicines

LHRH agonist

In pre/perimenopausal women, and in men, endocrine therapy for breast cancer should be co-administered with a luteinising hormone-releasing hormone (LHRH) agonist according to current clinical practice standards. Please refer to the full Product information of the LHRH agonist.

Aromatase inhibitor

When co-administered with KISQALI, an aromatase inhibitor is taken daily throughout the 28-day cycle. Please refer to the full Product Information of the aromatase inhibitor.

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 Product Information of fulvestrant.

Special populations

Renal impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment, but the recommended starting dose is 200 mg KISQALI once daily for patients with severe renal impairment (see section 5.2 Pharmacokinetic properties). There is no experience in cancer patients with severe renal failure or who require haemodialysis with the use of KISQALI. Caution and close monitoring for toxicity should be used in patients with severe renal impairment.

Hepatic impairment

No dose adjustment is necessary in patients with early breast cancer and hepatic impairment.

In patients with advanced/metastatic breast cancer, no dose adjustment is necessary for mild hepatic impairment (Child-Pugh class A), but for moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) the starting dose of KISQALI should be reduced to 400 mg once daily. KISQALI has not been studied in patients with advanced or metastatic breast cancer with moderate and severe hepatic impairment. KISQALI has not been studied in patients with early breast cancer with severe hepatic impairment (see section 5.2 Pharmacokinetic properties).

Review the full Product Information for co-administered medicines (aromatase inhibitor, fulvestrant, or LHRH agonist) for dose modifications related to hepatic impairment.

Paediatric use

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

Use in the elderly

No dose adjustment is necessary (see section 5.2 Pharmacokinetic properties).

Dose modifications

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 by 200 mg.

Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients. Monitor closely for signs of toxicity and manage with further dose reduction or interruption as needed.

If the strong inhibitor is discontinued, the KISQALI dose should be changed back (after 5 elimination half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor (see sections 4.4 Special warnings and precautions for use, 4.5 Interactions with other medicines and other forms of interactions, and 5.2 Pharmacokinetic properties).

Dose modification for adverse reactions

Management of severe or intolerable adverse reactions may require temporary dose interruption, dose reduction, or permanent discontinuation of KISQALI.

Table 1 contains KISQALI dose reduction guidelines in case of adverse reactions. Refer to the full Product Information of co-administered medicines (aromatase inhibitor, fulvestrant or LHRH agonist) for dose modification guidelines and other relevant safety information.

Table 1 Recommended dose modification guidelines for adverse reactions

	KISQALI	
Early breast cancer	**Dose**	**Number of Tablets**
Starting dose	400 mg/day	2 × 200 mg tablets
Dose reduction	200 mg*/day	1 × 200 mg tablet

Advanced/metastatic breast cancer	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 tablet

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

Tables 2 to 6 contain KISQALI dose modification guidelines for specific adverse reactions (see also section 4.4 Special warnings and precautions for use and section 4.8 Adverse effects (undesirable effects)).

Table 2 Dose modification and management for QT prolongation

On treatment ECGs with QTcF* value of:	Early breast cancer	Advanced/metastatic breast cancer
>480 ms and ≤500 ms	1. Interrupt KISQALI treatment	
	2. If QTcF prolongation resolves to <481 ms resume treatment at the same dose.	2. If QTcF prolongation resolves to <481 ms resume treatment at the next lower dose level.
	3. If QTcF ≥481 ms recurs, dose interrupt until QTcF <481 ms, and then resume KISQALI at next lower dose level.	
>500 ms	Interrupt KISQALI until QTcF <481 ms then resume KISQALI at next lower dose level. If QTcF > 500ms recurs, discontinue KISQALI.	
>500 ms or >60 ms change from baseline With either: • Torsades de Pointes;or • polymorphic ventricular tachycardia; or • unexplained syncope; or • signs/symptoms of serious arrhythmia	Permanently discontinue KISQALI	

Note: If further dose reductions are required at the 200 mg dose, KISQALI should be discontinued.

Perform ECG prior to initiation of treatment in all patients, then repeat at approximately day 14, and then as clinically indicated. Monitor ECG more frequently in patients with higher risk of QTcF prolongation or ventricular arrhythmias.

Serum electrolytes (including potassium, calcium, phosphorous and magnesium) should be performed prior to initiation of treatment and at the beginning of the next 6 cycles, with abnormalities corrected prior to commencement/ resumption of treatment. Cycle commencement must be accompanied by active review of all concomitantly administered medicines.

**QTcF = QT interval corrected by Fridericia's formula.*

In case of QTcF prolongation at any given time during treatment:

- 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
- Monitor ECGs more frequently (e.g. at 7 and 14 days) after resumption of KISQALI

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, 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.
Full (FBC) should be performed before initiating treatment with KISQALI. After initiating treatment with KISQALI, FBC should be monitored every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.				
*****Grade 3 neutropenia with a single episode of fever >38.3°C (or) 38°C or above 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.

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.

If Grade 2, 3 or 4 abnormalities are noted, more frequent monitoring is recommended.

ULN = upper limit of normal

*Baseline = prior to treatment initiation. Grading according to CTCAE Version 4.0. CTCAE=Common Terminology Criteria for Adverse Events

Table 5 Dose modification and management for ILD/Pneumonitis

ILD/pneumonitis	**Grade 1** (asymptomatic)	**Grade 2** (symptomatic)	**Grade 3 or 4** (severe)
	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to Grade ≤ 1 then consider resuming KISQALI at the next lower dose level*. If Grade 2 recurs, discontinue KISQALI.	Discontinue KISQALI.

Grading according to CTCAE Version 4.03.

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

ILD = Interstitial Lung Disease

Table 6 Dose modification and management for other toxicities*

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

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

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

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 significant risk of developing Torsades de Points (see section 4.4 Special warnings and precautions for use).

KISQALI is contraindicated in patients with hypersensitivity to ribociclib succinate or 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 - Cardiac electrophysiology).

Avoid KISQALI in patients who are at significant risk of developing Torsades de Pointes (TdP). Risk assessment should consider carefully the following factors:

- QTcF >450 ms prior to treatment (see section 4.3 Contraindications)
- Long QT syndrome or a history of ventricular arrhythmias
- Uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, bradyarrhythmias, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism
- Electrolyte abnormalities
- Co-administration of medicines or other substances known to prolong the QT interval, (see section 4.5 Interactions with other medicines and other forms of interactions)
- Co-administration of strong CYP3A inhibitors as this may increase ribociclib exposure and thus the prolongation of the QTcF interval (see section 4.2 Dose and method of administration if co-administration is unavoidable).

Perform a baseline ECG prior to commencing treatment. Do not commence treatment with KISQALI if the baseline QTcF is 450 ms or longer. Perform repeat ECG on approximately day 14, then as clinically indicated. Consider more frequent ECG monitoring 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).

Check serum electrolytes (including potassium, calcium, phosphorous and magnesium) before initiating treatment, at the beginning of each of the first 6 cycles, and then as clinically indicated. Do not commence or continue KISQALI therapy until abnormalities are corrected.

Interrupt, reduce dose or discontinue treatment to manage QTc prolongation as described in Table 2 (see section 4.2 Dose and method of administration).

Based on MONALEESA-7 (E2301), co-administration of KISQALI with tamoxifen is associated with increased risk of QT prolongation (see section 5.1 Clinical studies). KISQALI is not indicated for use with tamoxifen.

Clinical trial data regarding QT prolongation

In the NATALEE study, in patients with early breast cancer who received 400 mg KISQALI plus AI, 3 patients (0.1%) had a post-baseline QTcF interval of >500 ms value and 19 patients (0.8%) had a QTcF interval increase of >60 ms from baseline. There were no reported cases of sudden death or TdP.

The 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 600 mg 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 TdP.

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 also section 4.8 Adverse effects (undesirable effects).

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

Severe, life threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI and other CDK4/6 inhibitors.

In the phase III clinical study in patients with early breast cancer, ILD was reported in 1 patient (Grade 1) in the KISQALI plus AI arm with no cases in the AI alone arm. Pneumonitis (any Grade 0.6%, vs 0.4%) was reported in the KISQALI plus AI arm and in the AI alone arm, respectively, with 2 cases of a Grade 3 event in the AI arm. No cases of Grade 3 pneumonitis were reported in the KISQALI plus AI arm.

In the phase III clinical studies in patients with advanced or metastatic breast cancer (MONALEESA-2, MONALEESA-3, MONALEESA-7), 1.6% of KISQALI treated patients had ILD/pneumonitis of any grade, 0.4% had Grade 3 or 4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting (see section 4.8 Adverse effects (undesirable effects)), with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough and dyspnoea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt KISQALI immediately and evaluate the patient. Permanently discontinue KISQALI in patients with recurrent symptomatic or severe ILD/pneumonitis. (See section 4.2 Dose and method of administration for dosing adjustment table).

Hepatobiliary toxicity

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

In the phase III clinical studies in patients with early breast cancer and advanced or metastatic breast cancer, increases in transaminases were observed.

In patients with early breast cancer, Grade 3 or 4 increases in ALT (7.6% vs. 0.7%) and AST (4.7% vs. 0.5%) were reported in the KISQALI plus AI arm and AI alone arm, respectively. Grade 4 increases in ALT (1.5%) and AST (0.8%) were reported in the KISQALI plus AI arm. No Grade 4 increase in AST was reported in the AI alone arm, 1 case (<0.1%) of Grade 4 increase in ALT was reported in the AI alone arm.

In the phase III clinical study, 80.9% (165/204) of Grade 3 or 4 ALT or AST elevation events occurred within the first 6 months of treatment (see section 4.8 Adverse effects (undesirable effects)). The majority of increases in ALT and AST were reported without concurrent elevations of bilirubin. Among the patients who had Grade 3 or 4 ALT/AST elevation, the median time-to-onset was 2.8 months for the KISQALI plus AI arm. The median time to resolution (to normalisation or Grade ≤2) was 0.7 months in the KISQALI plus AI arm.

Concurrent elevations of ALT or AST >3 x upper limit of normal (ULN) and of total bilirubin >2 x ULN, with normal alkaline phosphatase levels (Hy's Law), occurred in 8 patients treated with KISQALI plus AI (in 6 patients ALT or AST levels recovered to normal within 65 to 303 days after discontinuation of KISQALI).

In patients with advanced or metastatic breast cancer, 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 ≤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 elevation of bilirubin. In MONALEESA-2 and MONALEESA-3, concurrent elevations of ALT or AST >3 x ULN and of total bilirubin >2 x ULN, with normal alkaline phosphatase levels, in the absence of cholestasis (Hy's law) 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 in patients with early breast cancer and advanced or metastatic breast cancer. LFTs should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and then 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

Severity of neutropenia is concentration dependent. Inform patients to promptly report any fever (see section 4.8 Adverse effects (undesirable effects)). In patients with early breast cancer (phase

III clinical study NATALEE (O12301C)), neutropenia was the most frequently reported adverse drug reaction (62.5%) and a Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 45.1% of patients receiving KISQALI plus aromatase inhibitor (AI).

Among the patients with early breast cancer who had Grade 2, 3 or 4 neutropenia in the phase III clinical study, the median time to Grade 2, 3 or 4 neutropenia was 0.6 months. The median time to resolution of Grade ≥3 (to normalization or Grade <3) was 0.3 months in the KISQALI plus AI arm. Febrile neutropenia was reported in 0.3% of patients receiving KISQALI plus AI.

In patients with advanced or metastatic breast cancer, (three phase III clinical studies MONALEESA-2 (A2301), MONALEESA-7 (E2301-NSAI) and MONALEESA-3 (F2301), neutropenia was the most frequently reported adverse reaction (75%) and a Grade 3 or 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 these patients who had Grades 2, 3 or 4 neutropenia, the median time to onset was 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.

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, at the beginning of each of the subsequent 4 cycles, and 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).

Blood creatinine increase

Ribociclib may cause blood creatinine increase as an inhibitor of the renal transporters organic cation transporter 2 (OCT2) and multidrug and toxin extrusion protein 1 (MATE1), which are involved in the active secretion of creatinine from the proximal tubules (see section 4.5 Interactions with other medicines and other forms of interactions). In case of blood creatinine increase while on treatment, it is recommended that further assessment of the renal function be performed to exclude renal impairment.

Thromboembolic events

Thromboembolic events, including pulmonary embolism, were reported in patients treated with CDK4/6 inhibitors in combination with endocrine therapy. Patients at risk of thromboembolic events should be closely monitored while receiving KISQALI.

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 Interactions with other medicines and other forms of interactions

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.

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 (see section 4.5 Interactions with other medicines and other forms of interactions - Drugs that may increase ribociclib plasma concentrations). 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 clinical trials 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 anastrozole

Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug-drug interaction between ribociclib and anastrazole 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.

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 metabolised by CYP3A4 and is a time-dependent inhibitor of CYP3A4 *in vitro* (see section 5.2 Pharmacokinetic properties: metabolism). 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 section 4.2 Dose and method of administration, section 4.4 Special warnings and precautions for use, and section 5.2 Pharmacokinetic properties: Metabolism).

If co-administration of KISQALI with a strong CYP3A inhibitor cannot be avoided, reduce the KISQALI dose (see section 4.2 Dose and method of administration).

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.

Erythromycin

Simulations using physiologically-based pharmacokinetic modelling (PBPK) predict that co-administration of ribociclib with erythromycin (a moderate CYP3A4 inhibitor), may increase steady-state ribociclib C_{max} and AUC by 1.1-fold and 1.1-fold, respectively, at the 600 mg dose; by 1.1-fold and 1.2-fold, respectively, at the 400 mg dose; and by 1.3-fold and 1.5-fold, respectively, at the 200 mg dose of ribociclib.

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

The effect of a moderate CYP3A4 inducer on ribociclib exposure has not been studied. PBPK simulations suggested that a moderate CYP3A4 inducer (efavirenz) may decrease steady-state ribociclib Cmax and AUC by 55% and 74%, respectively, at a ribociclib dose of 400 mg, and by 52% and 71%, respectively, at a ribociclib dose of 600 mg. The concomitant use of moderate CYP3A4 inducers may therefore lead to decreased exposure and consequently a potential risk for impaired efficacy.

Effect of ribociclib on other drugs

CYP3A substrates

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, pimozide, 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.

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% in healthy subjects, compared with administration of caffeine alone. At the clinically relevant ribociclib 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, pommelos, 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 properties).

Gastric pH elevating medications

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.

Use in Pregnancy (Category D)

There are no adequate and well-controlled clinical studies regarding the use of ribociclib in pregnancy. Based on findings in animals, ribociclib can cause fetal harm (including fetal developmental abnormalities and fetal loss) when administered during pregnancy (see section 5.3 Preclinical safety data). Use of KISQALI is not recommended during pregnancy, or in patients who could become pregnant and are not using highly effective contraception.

Pregnancy testing

The pregnancy status of a patient should be verified prior to initiating treatment with KISQALI.

Contraception

Patients who could become pregnant should use effective contraception (methods that result in less than 1% pregnancy rates) whilst receiving KISQALI and for at least 21 days after stopping treatment.

Use in Lactation

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

4.8 Adverse effects (undesirable effects)

Early breast cancer

The safety of KISQALI was evaluated in NATALEE, an open-label, randomised clinical trial of 5101 patients who received KISQALI plus AI or AI alone, with or without goserelin (see section 5.1 Pharmacodynamic properties - Clinical trials) for the treatment of HR-positive, HER2-negative early breast cancer. The median duration of exposure to ribociclib across the study was 33 months with 69% of patients exposed for at least 2 years and 43% of patients having completed the 3-year ribociclib regimen.

Serious adverse reactions occurred in 14% of patients who received KISQALI. Serious adverse reactions in >0.5% of patients who received KISQALI included COVID-19 (1.1%), pneumonia (0.8%), and pulmonary embolism (0.6%).

Fatal adverse reactions occurred in 0.6% of patients who received KISQALI. Fatal adverse reactions in ≥0.1% of patients receiving KISQALI included COVID-19 or COVID-19 pneumonia (0.2%) and pulmonary embolism (0.1%).

Permanent discontinuation of KISQALI due to an adverse reaction occurred in 20% of patients. Adverse reactions which resulted in permanent discontinuation of KISQALI in ≥2% of patients were alanine aminotransferase or aspartate aminotransferase increased (8%).

Dosage interruptions of both KISQALI plus AI due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in ≥5% of patients included neutropenia or neutrophil count decreased (43%), alanine aminotransferase or aspartate aminotransferase increased (11%), COVID-19 (10%), and hypomagnaesemia (5%).

Dose reductions of KISQALI due to an adverse reaction occurred in 23% of patients. Adverse reactions which required dose reductions in ≥2% of patients included neutropenia or neutrophil count decreased (14%) and liver function abnormal (2.3%).

Table 7 summarises the most common adverse reactions in NATALEE.

Table 7 Adverse reactions occurring in ≥10% and ≥2% higher than AI only arm in NATALEE

Adverse drug reactions	KISQALI plus AI N=2525		AI only N=2442	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Infections and infestations				
Infections[1]	36	2	267	0.9
Blood and lymphatic system disorders				
Neutropenia	62	44	5	0.9
Leukopenia	22	7	4	0.3
Nervous system disorders				
Headache	23	0.4	17	0.2

Adverse drug reactions	KISQALI plus AI N=2525		AI only N=2442	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Respiratory, thoracic and mediastinal disorders				
Cough	13	0.1	(8	0.1
Gastrointestinal disorders				
Nausea	23	0.2	8	0.1
Diarrhoea	15	0.6	6	0.1
Constipation	13	0.2	5	0
Abdominal pain[2]	11	0.5	7	0.4
Skin and subcutaneous tissue disorders				
Alopecia	15	0	5	0
General disorders and administration site conditions				
Fatigue	22	0.8	13	0.2
Asthenia	17	0.6	12	0.1
Pyrexia	11	0.2	6	0.1
Investigations				
Abnormal liver function tests[3]	22	8	8	1

[1] *Infections: urinary tract infections; respiratory tract infections.*
[2] *Abdominal pain: abdominal pain, abdominal pain upper.*
[3] *Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.*

Clinically relevant adverse reactions reported in less than 10% of patients who received KISQALI plus AI included rash (9%), dizziness (9%), vomiting (8%), peripheral oedema (7%), pruritis (7%), dyspnoea (7%), stomatitis (6%), oropharyngeal pain (6%), hypocalcaemia (5%), hypokalaemia (4.8%), and decreased appetite (4.8%).

Table 8 summarises the laboratory abnormalities in NATALEE.

Table 8 Laboratory abnormalities occurring in ≥10% of patients in NATALEE

Laboratory abnormalities	KISQALI plus AI (N=2525)		AI (N= 2442)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Haematological parameters				
Lymphocyte count decreased	97	19	88	6

Laboratory abnormalities	KISQALI plus AI (N=2525)		AI (N= 2442)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Leukocyte count decreased	95	27	45	0.6
Neutrophil count decreased	94	45	35	1.7
Haemoglobin decreased	47	0.6	26	0.3
Platelet count decreased	28	0.4	13	0.3
Biochemical parameters				
ALT increased	45	8	35	1
AST increased	44	5	33	1
Creatinine increased	33	0.3	11	0

Advanced or metastatic breast cancer

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% of 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%), 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 a frequency ≥20% in the KISQALI arm and ≥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 ≥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.

ARs and laboratory abnormalities occurring in patients in MONALEESA-2 are listed in Table 9 and Table 10, respectively.

Table 9 Adverse reactions occurring in ≥10% and ≥2% higher than placebo arm in MONALEESA-2

	KISQALI + letrozole			Placebo + letrozole		
		N = 334			N = 330	
Adverse drug reactions	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
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

	KISQALI + letrozole			Placebo + letrozole		
		N = 334			N = 330	
Adverse drug reactions	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Diarrhoea	41	2	0	26	<1	0
Vomiting	35	4	0	19	<1	0
Constipation	30	1	0	22	0	0
Abdominal pain[2]	21	1	0	14	<1	0
Stomatitis	16	< 1	0	7	0	0
Dry mouth	14	<1	0	11	<1	0
Dyspepsia	11	<1	0	8	0	0
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)
[1]Infections: urinary tract infections; respiratory tract infections, gastroenteritis, sepsis (<1%).
[2]Abdominal pain: abdominal pain; abdominal pain upper.
[3]Rash: rash, rash maculo-papular and rash pruritic.
[4]abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased

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

	KISQALI + letrozole N = 334			Placebo + letrozole N = 330		
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
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
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 ≥20% in the KISQALI arm and ≥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 ≥5%) were neutropenia, leukopenia, abnormal liver function tests and lymphopenia.

Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-7 are listed in Table 11 and Table 12, respectively.

Table 11 Adverse reactions occurring in ≥10% and ≥2% higher than placebo arm in MONALEESA-7 (NSAI-treated patients only)

	KISQALI + NSAI + goserelin N = 248			Placebo + NSAI + goserelin N = 247		
Adverse drug reactions	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
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	0	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
Pyrexia	19	< 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 QT prolonged	10	1	0	2	0	0

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

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

[2]Abdominal pain: abdominal pain; abdominal pain upper.

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

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

Table 12 Laboratory abnormalities occurring in ≥10% of patients in MONALEESA-7

	KISQALI + NSAI + goserelin N = 248			Placebo + NSAI + goserelin N = 247		
Laboratory parameters	**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	8	<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	12	0	< 1	4	0	0

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 ≥20% in the KISQALI arm and ≥2% higher than placebo) were neutropenia, infections, nausea, diarrhoea, leukopenia, vomiting, constipation, rash, cough, headache, pruritis, alopecia and anaemia. The most common Grade 3/4 ARs (reported at a frequency ≥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 13 and Table 14 respectively.

Table 13 Adverse reactions occurring in ≥10% and ≥2% higher than placebo arm in MONALEESA-3

	KISQALI + fulvestrant			Placebo + fulvestrant		
		N = 483			N = 241	
Adverse drug reactions	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**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
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)

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

[2]Abdominal pain: abdominal pain; abdominal pain upper.

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

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

Table 14 Laboratory abnormalities occurring in ≥10% of patients in MONALEESA-3

	KISQALI + fulvestrant			**Placebo + fulvestrant**		
		N = 483			**N = 241**	
Laboratory parameters	**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

	KISQALI + fulvestrant			Placebo + fulvestrant		
		N = 483			N = 241	
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
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 for male patients was 19.2 months (range: 0.5 to 30.6 months).

Adverse reactions occurring in men treated with KISQALI plus letrozole and were similar to those occurring in women treated with KISQALI plus endocrine therapy. No men received leuprolide in the study.

Post marketing data

The following ADRs are derived from post-marketing experience with KISQALI via spontaneous case reports and literature cases. As these reactions are reported voluntarily from a

population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure, therefore the frequency is categorised as not known.

Table 15 Adverse drug reactions derived from spontaneous reports and literature (frequency not known)

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis (TEN), erythema multiforme.
Respiratory disorders: Interstitial lung disease (ILD)/pneumonitis.
Vascular disorders: thrombosis.

Description of selected adverse drug reactions

QT prolongation

In the phase III study in patients with early breast cancer (NATALEE), 5.3% of patients in the KISQALI plus AI arm and 1.4% of patients in the AI alone arm reported events of QT interval prolongation. Dose interruptions were reported in 1.1% of KISQALI treated patients due to ECG QT prolonged and syncope. Dose adjustments were reported in 0.1% of KISQALI treated patients due to ECG QT prolonged.

A central analysis of ECG data showed 10 patients (0.4%) and 4 patients (0.2%) with at least one post-baseline QTcF interval >480 ms for the KISQALI plus AI arm and the AI alone arm, respectively. Among the patients who had QTcF interval prolongation of >480 ms in the KISQALI plus AI arm, the median time to onset was 15 days and these changes were reversible with dose interruption and/or dose adjustment (see sections 4.1 Dose and method of administration, 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties). QTcF interval >60 ms change from baseline was observed in 19 patients (0.8%) in the KISQALI plus AI arm and post-baseline QTcF interval >500 ms was observed in 3 patients (0.1%) in the KISQALI plus AI arm.

In the phase III clinical studies in patients with advanced or metastatic breast cancer, 9% of ribociclib-treated patients and 4% of placebo-treated patients had at least one event of QT interval prolongation or syncope. Dose interruptions/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 that 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 was 15 days regardless of what treatment ribociclib was combined with, and these changes were reversible with dose interruption and/or dose reduction (see section 4.2 Dose and method of administration, section 4.4 Special warnings and precautions for use, and section 5.2 Pharmacokinetic properties).

In MONALEESA-7, the observed mean QTcF increase from baseline was >10 ms higher in the tamoxifen plus placebo subgroup compared with NSAI plus placebo subgroup, suggesting that tamoxifen contributed to the QTcF prolongation observed in the ribociclib plus tamoxifen group (see section 5.1 Pharmacological properties - Cardiac electrophysiology). A QTcF increase of >60 ms from baseline occurred in zero patients who received placebo plus NSAI, 7% of patients who received placebo plus tamoxifen, 7% of patients who received ribociclib plus NSAI, 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

In the phase III study in patients with early breast cancer, hepatobiliary toxicity events occurred in a higher proportion of patients in the KISQALI plus AI arm vs AI alone arm (26% vs 11%, respectively), with more Grade 3/4 AEs reported in patients treated with KISQALI plus AI (8.6% vs 1.7%, respectively). Dose interruptions due to hepatobiliary toxicity events were reported in 12% of patients with early breast cancer treated with KISQALI plus AI, primarily due to ALT increased (10%) and/or AST increased (7%). Dose adjustment due to hepatobiliary toxicity events was reported in 2.6% of patients treated with KISQALI plus AI, primarily due to ALT increased (1.9%) and/or AST increased (0.6%). Discontinuation of treatment with KISQALI due to abnormal liver function tests and hepatotoxicity occurred in 8.9% and 0.1% of patients, respectively (see section 4.4 Special warnings and precautions for use).

In the the phase III clinical studies in patients with advanced or metastatic breast cancer, hepatobiliary toxicity events occurred in a higher proportion of ribociclib–treated patients compared with placebo-treated patients (27% vs 20%), and more Grade 3/4 adverse events were reported in ribociclib-treated than placebo-treated patients (13% vs 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 section 4.2 Dose and method of administration, section 4.4 Special warnings and precautions for use, and section 5.2 Pharmacokinetic properties).

Neutropenia

Severity of neutropenia is concentration-dependent.

Neutropenia was a frequent laboratory finding in clinical studies. Permanent treatment discontinuation due to neutropenia was reported in 0.8% of patients receiving KISQALI for advanced breast cancer and 1.1% of patients receiving KISQALI for early breast cancer, however, dose interruptions and/or modifications were required in 43.5% of ribociclib-treated patients (see section 4.2 Dose and method of administration, and section 4.4 Special warnings and precautions for use).

Based on its severity, neutropenia was managed by laboratory monitoring, dose interruption and/or dose modification. All patients should be instructed to report any fever promptly.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdosage

Symptoms and Signs

Limited experience in humans suggests that in the event of KISQALI overdosage, 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 information on the management of overdose, contact the Poison Information Centre on telephone number 13 11 26 (local call in all areas).

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 resulting in arrest in the G1 phase of the cell cycle, reduced proliferation in breast cancer-derived models. In vivo, treatment with single agent ribociclib in a rat xenograft model with human tumour cells led to decreased tumour volumes, which correlated with inhibition of pRb phosphorylation.

In vivo studies using patient-derived oestrogen receptor-positive breast cancer xenograft models, combinations of ribociclib and antioestrogen therapies (e.g. letrozole) resulted in increased tumour growth inhibition compared to each drug alone. Additionally, the combination of ribociclib and fulvestrant resulted in tumour growth inhibition in an estrogen 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 (IC_{50}) 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 IC_{50} of 0.06 μM (26 ng/mL). Ribociclib halts G1 to S-phase cell cycle progression measured by flow cytometry with IC_{50} of 0.11 μM (47.8 ng/mL). Ribociclib also inhibits cellular proliferation measured by bromodeoxyuridine uptake with IC_{50} of 0.08-μM (34.8 ng/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 in the tested pRb-negative cancer cell lines.

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 1200 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval.

In patients with early breast cancer, the estimated geometric mean QT interval change from baseline for KISQALI 400 mg starting dose in combination with non-steroidal aromatase inhibitor (NSAI) was 10.00 ms (90% CI: 8.0, 11.9), at the geometric mean Cmax at steady state (see section 4.4 Special warnings and precautions for use).

In patients with advanced or metastatic breast cancer, 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) 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

NATALEE (Study CLEE011O12301C)

NATALEE was a randomised (1:1), open-label, multicenter study in adults (N=5101) with HR-positive, HER2-negative early breast cancer that was:

- Anatomic Stage Group IIB-III, or
- Anatomic Stage Group IIA that is either:
    - Node positive or
    - Node negative, with:
        - Histologic grade 3, or
        - Histologic grade 2, with any of the following criteria:
            - Ki67 ≥ 20%
            - High risk by gene signature testing.

Applying TNM criteria, NATALEE included patients with any lymph node involvement, or if no nodal involvement either tumour size > 5 cm, or tumour size 2-5 cm with either grade 2 (and high genomic risk or Ki67 ≥ 20%) or grade 3.

Participants were randomised to receive KISQALI 400 mg plus a non-steroidal aromatase inhibitor (AI) or AI only, and goserelin as indicated. Randomisation was stratified by Anatomic Stage, prior receipt of neo/adjuvant chemotherapy (yes versus no), menopausal status (premenopausal and males versus postmenopausal) and region (North America/Western Europe/Oceania versus rest of the world).

KISQALI was given orally at a dose of 400 mg once daily for 21 consecutive days followed by 7 days off treatment in combination with letrozole 2.5 mg or anastrozole 1 mg orally once daily for 28 days; goserelin 3.6 mg was administered on Day 1 of each 28-day cycle. KISQALI was administered for up to 36 months in the absence of recurrence or unacceptable toxicity. AI was administered for at least 5 years.

Patients enrolled in this study had a median age of 52 years (range 24 to 90); 15% were at least 65 years old, and 2.4% were at least 75 years old. The majority were female (0.4% were male) and Caucasian (73%), while 13% were Asian and 1.7% were Black or African American. ECOG performance status was 0 for 83% and was 1 for 17%. Most patients (88%) had node-positive disease, 88% had received prior neo/adjuvant chemotherapy, and 71% had received antihormonal therapy in the neo/adjuvant setting prior to study entry.

The primary endpoint for the study was invasive disease-free survival (iDFS) defined as the time from randomisation to the first occurrence of: local invasive breast recurrence, regional invasive

recurrence, distant recurrence, death (any cause), contralateral invasive breast cancer, or second primary non-breast invasive cancer (excluding basal and squamous cell carcinomas of the skin). Overall survival (OS) was an additional outcome measure.

A statistically significant increase in iDFS (HR: 0.748, 95% CI: 0.618 to 0.906; one-sided stratified log-rank test p-value=0.0014) was demonstrated in the intent-to-treat (ITT) population at an interim iDFS analysis (11-Jan-2023 cut-off).

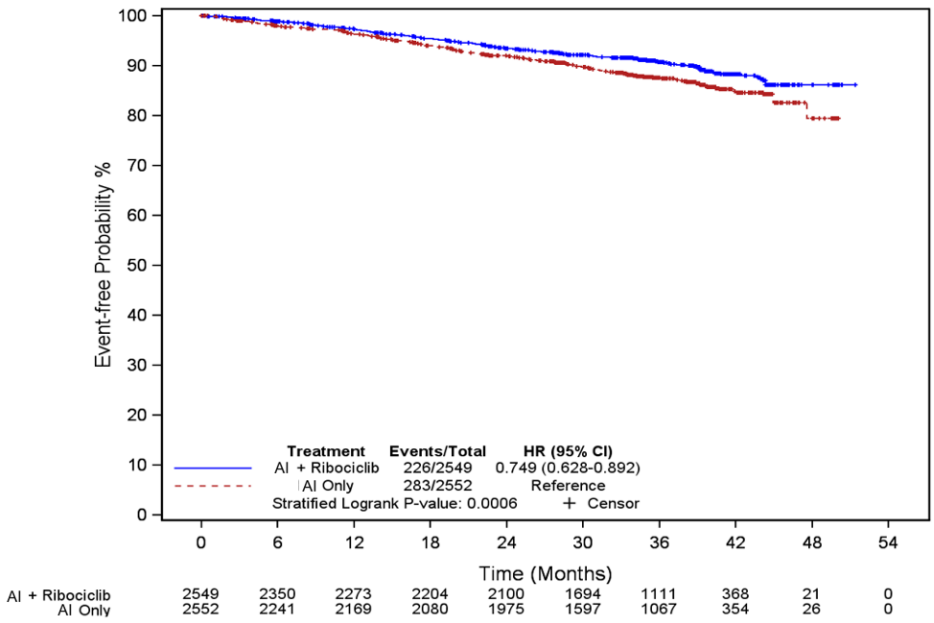
The efficacy results from the final iDFS analysis (21-Jul-23 cut-off) are summarised in Table 16 and Figure 1. The median duration of study follow-up at that time was 40 months, and overall survival (OS) was immature: a total of 172 patients (3.5%) had died across both study arms.

Table 16 NATALEE (O12301C) final efficacy results (iDFS) based on investigator assessment (ITT) (21-Jul-23 cut-off)

	KISQALI plus AI* N=2549	AI N=2552
Invasive disease-free survival (iDFS[a])		
Number of patients with an event (n, %)	226 (8.9%)	283 (11.1%)
Hazard ratio (95% CI)	0.749 (0.628 to 0.892)	
p-value[b]	0.0006	
iDFS at 36 months (%, 95% CI)	90.7 (89.3, 91.8)	87.6 (86.1, 88.9)

CI=confidence interval; N=number of patients.
[a] iDFS defined as the time from randomisation to the first occurrence of: locoregional relapse, distant relapse, ipsilateral and contralateral invasive breast cancer, second primary non-breast invasive cancer or death from any cause.
b nominal p-value is obtained from the one-sided stratified log-rank test.
* Letrozole or anastrozole

Figure 1 NATALEE (O12301C) Kaplan-Meier plot of iDFS based on investigator assessment (ITT) (21-Jul-2023 cut-off) (FAS)



AI - aromatase inhibitor

P-value from stratified log-rank test is one-sided.

MONALEESA-2 (Study CLEE011A2301)

MONALEESA-2 was a randomised, double-blind, placebo-controlled, multicentre 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 randomised to receive either KISQALI plus letrozole (n= 334) or placebo plus 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 orally once daily for 21 consecutive days followed by 7 days off treatment, until disease progression or unacceptable toxicity. Patients who had prior neoadjuvant or adjuvant therapy with anastrozole or letrozole must have completed it at least 12 months before study 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 Tumours (RECIST) v1.1.

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. 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 17 and Figure 2. The results shown are from 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.

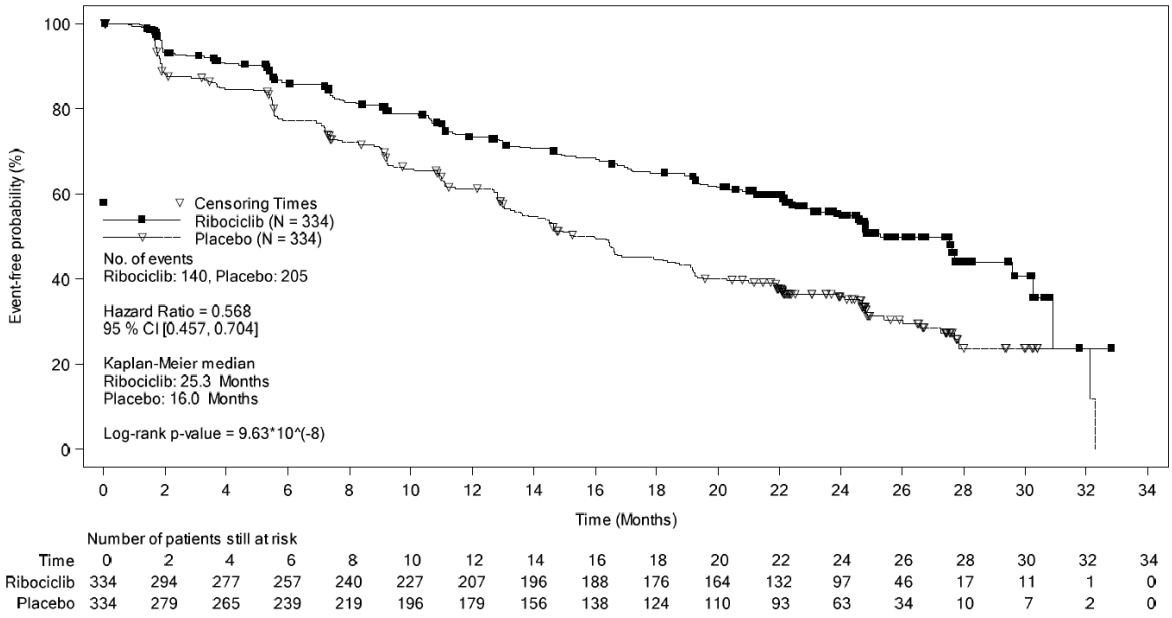
Table 17 Efficacy results from MONALEESA 2 (investigator-assessed, intent-to-treat (ITT) population)

	First interim analysis (29 Jan 2016 data cut-off)[a]		**Updated analysis** (2 Jan 2017 data cut-off)[b]	
	KISQALI plus letrozole n=334	**Placebo plus letrozole n=334**	**KISQALI plus letrozole n=334**	**Placebo plus letrozole n=334**
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 (95% CI)	0.556 (0.429, 0.720)		0.568 (0.457, 0.704)	
p-value[c]	0.00000329		0.0000000963	

	First interim analysis (29 Jan 2016 data cut-off)[a]		Updated analysis (2 Jan 2017 data cut-off)[b]	
	KISQALI plus letrozole n=334	**Placebo plus letrozole n=334**	**KISQALI plus letrozole n=334**	**Placebo plus letrozole n=334**
Patients with measurable disease	**n=256**	**n=245**	**n=257**	**n=245**
Overall Response Rate[b] (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 [b] ORR: Overall Response Rate = proportion of patients with complete response + partial response;

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



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 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).

The OS results from this final analysis are summarised in Table 18 and Figure 3.

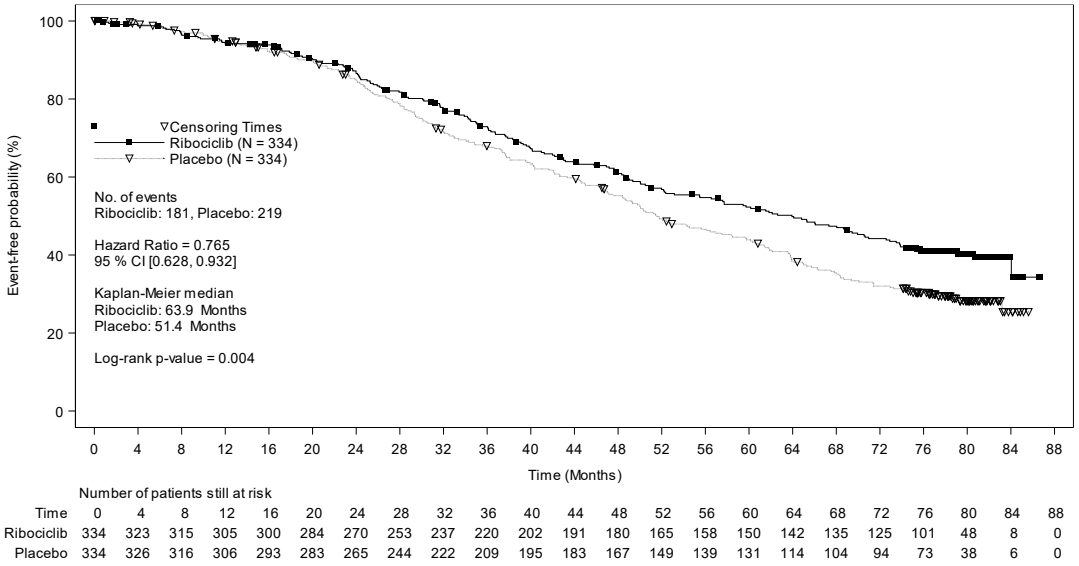
Table 18 Efficacy results from MONALEESA 2 (OS 10 Jun 2021 cut-off)

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	

Overall survival, overall study population	KISQALI plus letrozole n=334	Placebo plus letrozole n=334
OS event-free rate, (%) (95% CI)		
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;
[a]Hazard ratio is obtained from stratified Cox PH model;
[b]p-value is obtained from the one-sided log-rank test. Stratification performed by lung and/or liver metastases status as per IRT.

Figure 3 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.

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 perimenopausal 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 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 19 and Figure 4. 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.

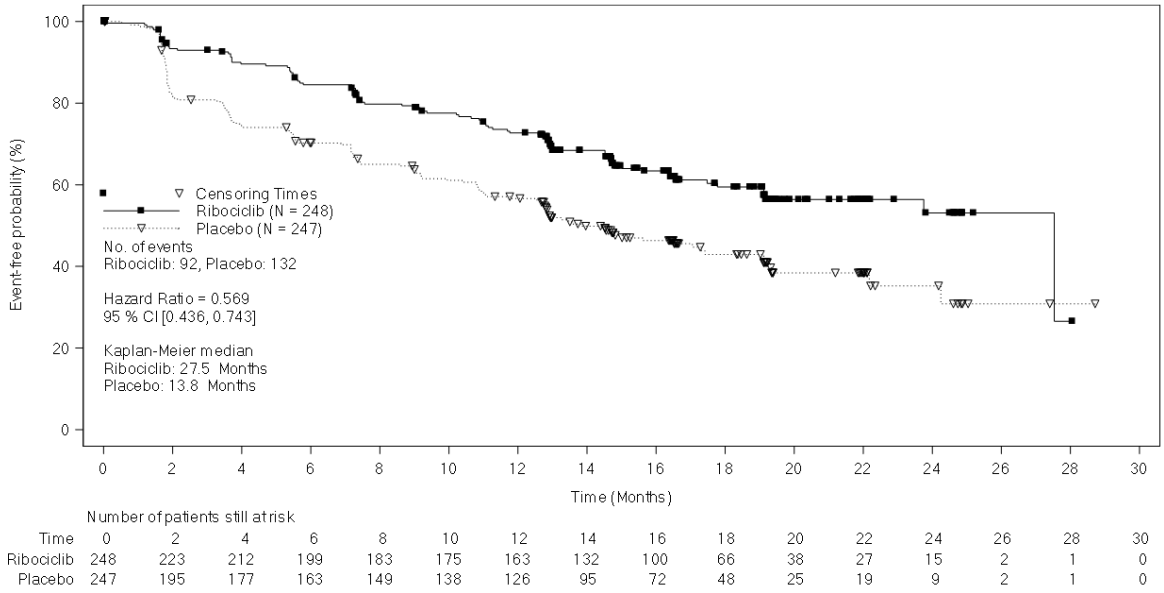
Table 19 Efficacy results from MONALEESA-7 (investigator-assessed, NSAI subgroup)

	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.*

Figure 4 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 (HR: 0.712; 95% CI: 0.535, 0.948; one-sided stratified log-rank test p-value: 0.00973), and is consistent across exploratory subgroups. Median OS was not reached in the KISQALI arm and was 40.9 months (95% CI: 37.8, NE) in the placebo arm.

The safety profile of both treatment arms remained consistent with the results from the primary analysis.

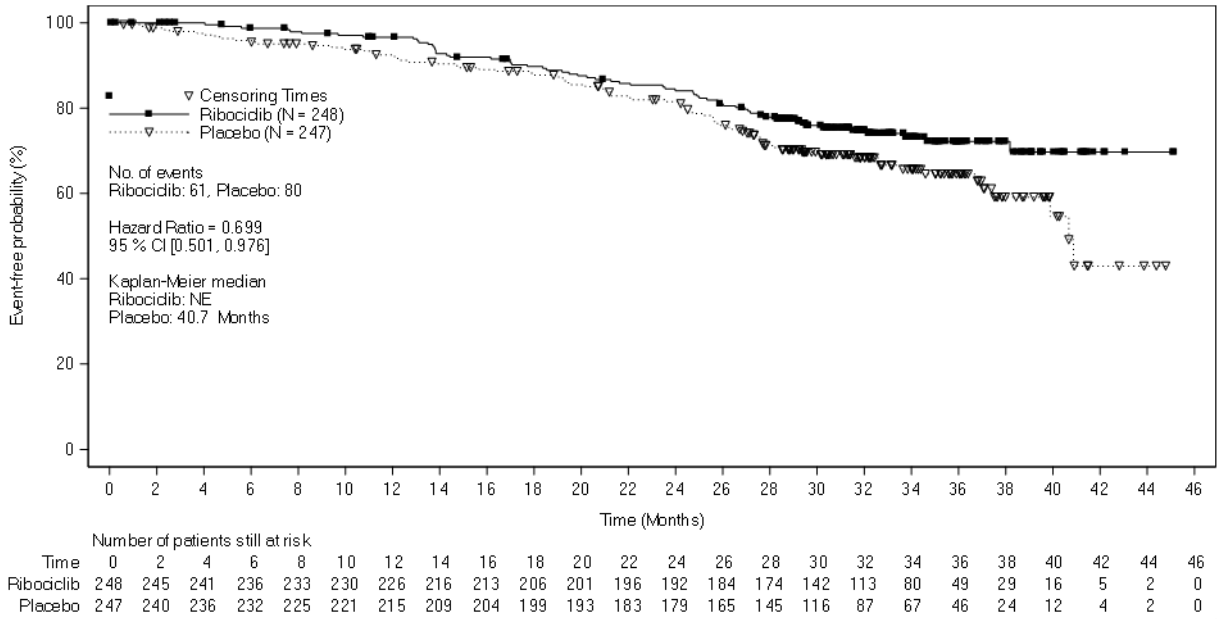
A more mature update of overall survival data (30-Nov-2018 cutoff) is provided in Table 20 as well as in Figure 5 .

Table 20 MONALEESA-7 (E2301) efficacy results (OS) (30-Nov-18 cut-off)

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;

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 (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 analyisis set (all randomised 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 21 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 21 Efficacy results from MONALEESA-3 (investigator-assessed, ITT population)

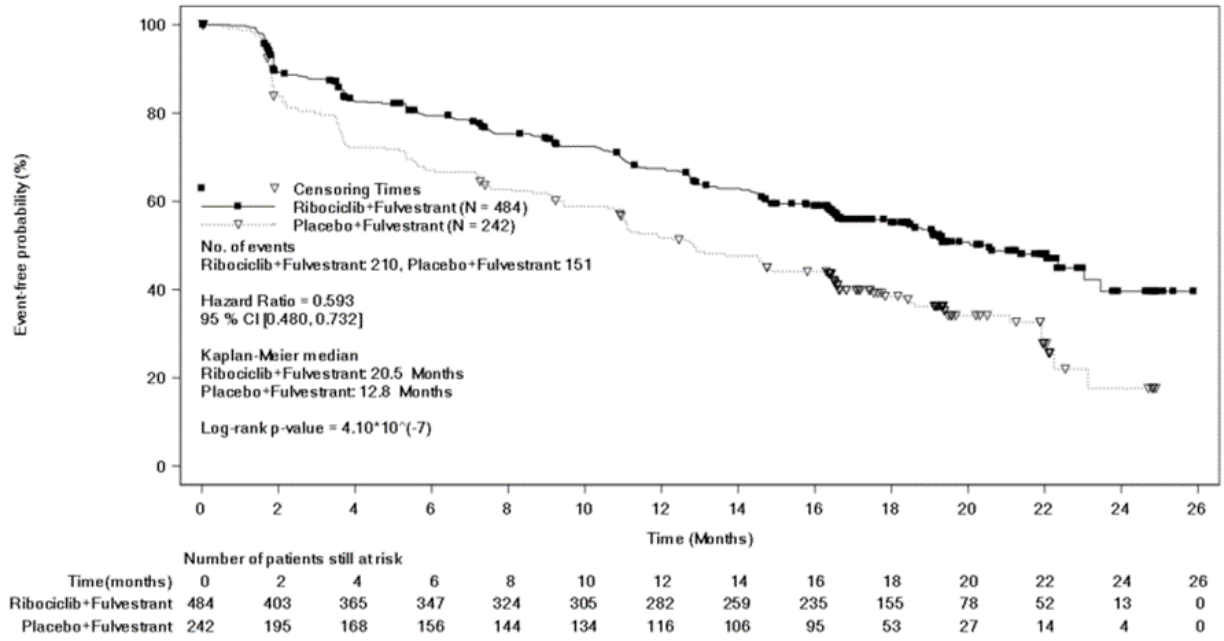
	KISQALI + fulvestrant	**Placebo + fulvestrant**
Progression free survival	**N=484**	**N=242**
Median PFS [months] (95% CI)	20.5 (18.5 – 23.5)	12.8 (10.9 – 16.3)
Hazard ratio (95% CI)	0.593 (0.480 - 0.732)	
p-value[a]	0.00000041	
Patients with measurable disease	**N=379**	**N=181**
Overall response rate (ORR)[b]	40.9 (35.9 , 45.8)	28.7 (22.1, 35.3)

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

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 22.

Table 22 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

[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)*

Final OS Analysis

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.

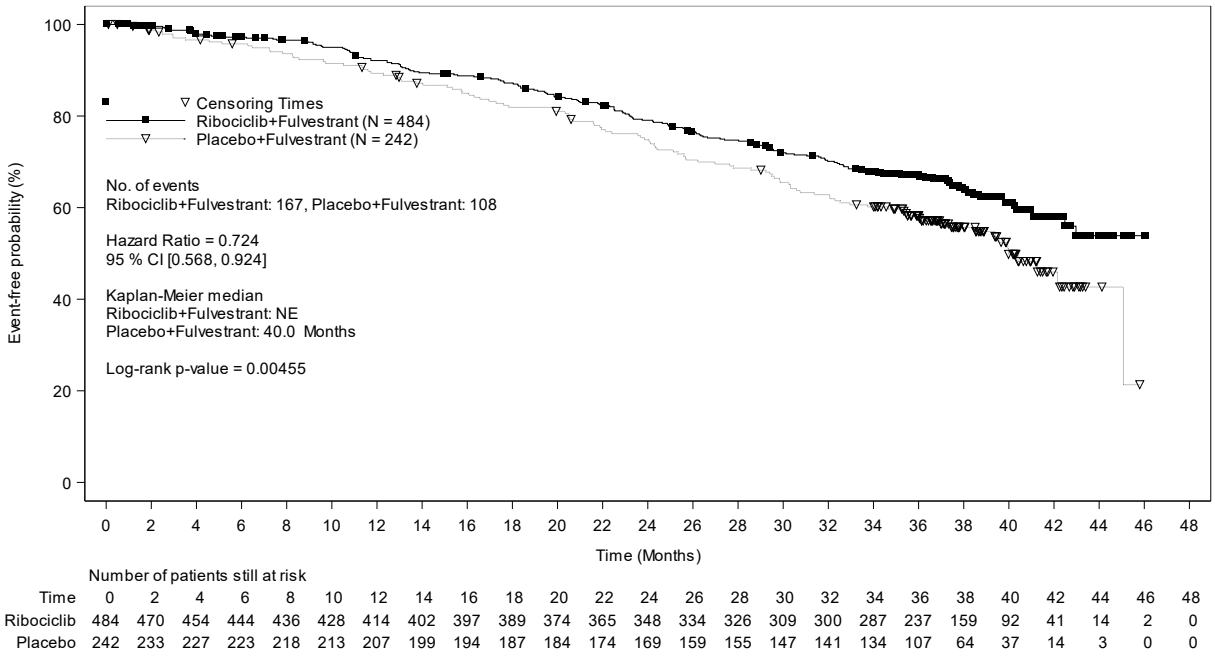
The OS results from this interim analysis with a 03-Jun-19 cut-off are provided in Table 23 and Figure 7.

Table 23 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

Figure 7 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

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 (COMPLEEMENT-1)

COMPLEEMENT-1 was an open-label, single arm, multicentre phase IIIb clinical study of 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.

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. Premenopausal women also received goserelin or leuprolide, and men received goserelin (no men received leuprolide). 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 24 summarises the efficacy results in male patients.

Table 24 COMPLEEMENT-1 (A2402) efficacy results in male patients[1] based on investigator assessment (intent-to-treat population)

	KISQALI + Letrozole + Goserelin or Leuprolide[5]
Overall Response Rate*, [2]	N = 32
(95% CI)	46.9 (29.1, 65.3)
Duration of Response[3]	N = 15
Median (months, 95% CI)	NR (21.3, NR)
Patients with DoR ≥ 12 months, n (%)	12 (80.0%)
Clinical Benefit Rate[4]	
(95% CI)	71.9 (53.3, 86.3)

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

**Based on confirmed responses.*

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

[2]Investigator Assessment.

[3]Proportion of patients with complete response or partial response.

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

[5]No men received leuprolide.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of ribociclib was investigated in patients with advanced cancer following oral daily doses ranging from 50 mg to 1200 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 (Cmax and AUC) across the dose range of 50 mg to 1200 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 the majority of data coming from the 600 mg dose cohort.

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} was 1.00 (90% CI: 0.898, 1.11) and for AUC_{inf} was 1.06 (90% CI: 1.01, 1.12).

See also fruits and juices to avoid in section 4.5 Interactions with other medicines and other forms of interactions.

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 (Vss/F) was 1090 L based on population PK analysis.

Metabolism

In vitro and *in vivo* studies indicated 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, sulfation, 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 metabolised with unchanged drug accounting for 17% and 12% in faeces 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 feces and urine in minor abundance (≤3% of the administered dose).

Excretion

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 mean CL/F estimated by population PK analysis was 38.4 L/hr (95% CI: 35.5 to 41.9) at steady state at 400 mg in patients with early breast 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 faeces, 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%.

Special patient 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 (absolute Glomerular Filtration Rate (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.

In subjects with mild, moderate and severe renal impairment, AUC_{inf} was 1.6-fold, 1.9-fold and 2.7-fold higher, respectively, and Cmax was to 1.8-fold, 1.8-fold and 2.3-fold higher, respectively, compared to 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).

A sub-group analysis of data from studies following oral administration of KISQALI in patients with advanced cancer or early breast cancer who have mild to moderate renal impairment, AUC and Cmax were comparable to those in patients with normal renal function, suggesting no clinically meaningful effect of mild or moderate renal impairment on ribociclib exposure.

Hepatic impairment

Compared to adults with normal hepatic function, mild (Child-Pugh class A) hepatic impairment had no effect on the exposure of ribociclib; while in adults with moderate (Child-Pugh class B) hepatic impairment, the mean ratio was 1.44 for C_{max} and 1.28 for AUC_{inf}); and in adults with severe (Child-Pugh class C) hepatic impairment, the mean ratio was 1.32 for C_{max} and 1.29 for AUC_{inf}).

Use in the elderly

Of the 2549 patients with early breast cancer who received KISQALI in the phase III study (NATALEE, ribociclib plus AI arm), 407 patients (16.0%) were ≥65 years of age .

Of 334 patients with advanced or metastatic breast cancer 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 age. No overall differences in 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 highest recommended dose of 600 mg. As well, there is potential to induce incidences of premature ventricular contractions (PVCs) at elevated exposures (approximately 4-fold the anticipated clinical C_{max}).

Phototoxicity

Ribociclib was shown to absorb light in the UV-B and UV-A range, however, phototoxicity was not suggested by *in vitro* testing. The risk that KISQALI causes photosensitisation in patients is considered very low.

Repeated-dose toxicity

Repeated dose toxicity studies (treatment schedule of 3 weeks on/1 week off) in rats up to 26 weeks duration and dogs up to 39 weeks duration, revealed the hepatobiliary system (proliferative changes, cholestasis, sand-like gall bladder calculi, inspissated bile, periportal hepatocyte necrosis and arteriopathy in the hilar region) as the primary target organ of toxicity of ribociclib.

Additionally, effects on bone marrow (hypocellularity), pancytopenia, lymphoid system (lymphoid depletion), testes (atrophy), intestinal mucosa (atrophy), skin (atrophy), bone/ribs (decreased bone formation), lung (increased incidence of alveolar macrophages), and kidney (concurrent degeneration and regeneration of tubular epithelial cells) were described. In general, these changes in rats and dogs demonstrated either reversibility or a clear tendency towards reversibility. Exposure to ribociclib in animals in these 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 and fertility

Ribociclib showed foetotoxicity and teratogenicity at doses which did not show maternal toxicity in 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.

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 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 a 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.

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.

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 (0.9 times the exposure in patients at the maximum recommended human dose of 600 mg/day [based on plasma AUC]) as well as an increased incidence in follicular tumours in the thyroid glands of male rats at a dose of 15 mg/kg/day (0.3 times the exposure in pateints at 600 mg/day based on plasma AUC).

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 (0.03 times the exposure in patients at 600 mg/day based on plasma AUC) and 50 mg/kg/day (equivalen to the exposure in patients based on plasma AUC), respectively.

The mechanism for the thyroid findings in males is considered to be a rodent-specific microsomal enzyme induction in the liver with unclear clinical relevance to humans.

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.

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.

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 for uterine tumours and Leydig cell hyperplasia in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains microcrystalline cellulose, hyprolose, crospovidone, 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

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store KISQALI tablets below 30°C.

6.5 Special precautions for disposal

Any unused product should not be disposed of in household waste or wastewater. Return it to a pharmacist for safe disposal.

6.6 Nature and contents of the container

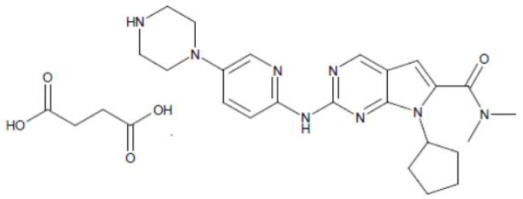
KISQALI tablets are supplied in Aclar/aluminium or polyamide/aluminium/polyvinylchloride (PA/Al/PVC) blisters platforms, packs containing either 63, 42, or 21 tablets.

6.7 Physicochemical properties

KISQALI tablets contain ribociclib succinate which is a light yellow to yellowish brown, crystalline powder. It is soluble in a 1:1 mixture of water and acetonitrile, and the pH of a 1% w/v aqueous solution is about 5.2 at 25°C.

Chemical name:	butanedioic acid - 7-cyclopentyl-*N,N*-dimethyl-2-{[5-(piperazin-1-yl) pyridin-2-yl]amino}-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (1/1)
Molecular formula:	$C_{23}H_{30}N_8O.C_4H_6O_4$
Molecular weight:	As succinate: 552.64, and free base: 434.55

Chemical structure



Chemical Abstracts Service (CAS) numbers:	1374639-75-4 (as succinate) and 1211441-98-3 (as free base)

7. MEDICINE SCHEDULE (POISON SCHEDULE)

Schedule 4 – Prescription medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

23 October 2017

10. DATE OF REVISION

22 June 2026

Summary table of changes

Section changed	Summary of new information
4.4, 4.8	Addition of thromboembolic events per TGA request.
8	Update to Sponsor address

Internal document code (kis220626i) based on CDS dated 22 January 2024