NEW ZEALAND DATA SHEET

KISQALI® 200 mg film coated tablet

1. NAME OF THE MEDICINAL PRODUCT

KISQALI® 200 mg film coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect

Each film-coated tablet contains 0.344 mg soya lecithin.

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

3. PHARMACEUTICAL FORM

Film-coated tablets.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Early breast cancer

KISQALI 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, in combination with an aromatase inhibitor.

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

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 an initial endocrine-based therapy or following prior endocrine therapy.

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

4.2 Dose and method of administration

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

KISQALI may be taken with or without food (see section 4.5 Interaction with other medicines and other forms of interaction).

Luteinising hormone-releasing hormone (LHRH) agonist

In pre- or peri-menopausal women or men, treatment with KISQALI should include co-administration with a luteinising hormone-releasing hormone (LHRH) agonist, according to current local clinical practice standards.

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

Dose

Early breast cancer

The recommended dose of KISQALI is 400 mg (2 x 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days.

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

Aromatase inhibitor

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

Advanced or metastatic breast cancer

The recommended dose of KISQALI is 600 mg (three 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days, followed by 7 days off treatment, resulting in a complete cycle of 28 days.

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

Aromatase inhibitor

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

Fulvestrant

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

Patients with early breast cancer and advanced or metastatic breast cancer should be encouraged to take their dose of KISQALI and aromatase inhibitor at approximately the same time each day, preferably in the morning.

Dose Modifications

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

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

Table 1 Recommended dose modification guidelines for ADRs

		Kisqali
Early breast cancer	**Dose**	**Number of Tablets**
Starting dose	400 mg/day	2 x 200 mg tablets
Dose reduction	200 mg*/day	1 x 200 mg tablets
Advanced or 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 tablets

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

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

Table 2 Dose modification and management for QT prolongation

On treatment ECGs with QTcF* value of:	Early breast cancer	Advanced or metastatic breast cancer
> 480 ms and ≤500 ms	1. Interrupted 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 on at least 2 separate ECGs (on the same visit)	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:** • Torsade 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.

ECG should be performed prior to initiation of treatment in all patients.

Repeat ECGs at approximately day 14 of the first cycle and as clinically indicated.

In patients with higher risk of QTcF prolongation or ventricular arrhythmias, more frequent ECG monitoring is recommended in patients with early breast cancer and advanced or metastatic breast cancer.

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
- More frequent ECG monitoring is recommended, e.g. 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 to grade ≤ 2, then resume KISQALI at the next lower dose level.	Dose interruption until recovery of neutropenia to grade ≤ 2. Resume KISQALI at the next lower dose level.	Dose interruption until recovery to grade ≤ 2. Resume KISQALI at the next lower dose level.

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

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

*****Grade 3 neutropenia with a single episode of fever >38.3°C (or) 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 Interstitial Lung Disease (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.	Interrupt KISQALI until recovery to Grade ≤1, then resume KISQALI at the next lower dose level*.	Discontinue KISQALI

Grading according to CTCAE Version 4.03.

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

Table 6 Dose modification and management for other toxicities*

	Grade 1 or 2	Grade 3	Grade 4
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, and QT interval prolongation.

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

Dose modification for use of KISQALI with strong CYP3A inhibitors

Avoid concomitant use of KISQALI with strong CYP3A inhibitors and consider an alternative concomitant medication with less potential for CYP3A inhibition.

In patients with early breast cancer, if a strong CYP3A inhibitor must be co-administered, patients should be monitored for adverse reactions and, if necessary, a reduction of Kisqali dose to 200 mg should be considered.

In patients with advanced or metastatic breast cancer, if a strong CYP3A inhibitor must be co-administered, reduce the KISQALI dose to 400 mg once daily.

Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients, therefore close monitoring of signs of toxicity is recommended. If the strong inhibitor is discontinued, the KISQALI dose should be changed (after 5 elimination half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor (see section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicines and other forms of interaction and section 5.2 Pharmacokinetic (PK) Properties).

Special Populations

Renal Impairment

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

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

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

Hepatic Impairment

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

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

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

Paediatric population

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

Elderly

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

Method of administration

KISQALI should be administered orally once daily at the same time every day, preferably in the morning, with or without food. If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

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

4.3 Contraindications

KISQALI is contraindicated in patients with corrected QT interval (QTcF) > 450 milliseconds (ms) prior to treatment or who have long QT syndrome or who are at significant risk of developing QTc prolongation (see section 4.4 Special warnings and precautions for use).

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

4.4 Special warnings and precautions for use

QT interval prolongation

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

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

- QTcF >450 ms prior to treatment (see section 4.3 Contraindications)
- a history of ventricular arrhythmias
- long QT syndrome
- significant risk of developing QTc prolongation including:
    - uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
    - electrolyte abnormalities.

KISQALI should be avoided in patients taking medicinal products that are known to prolong the QTc interval (see section 4.5 Interaction with other medicines and other forms of interaction) and/or strong CYP3A inhibitors as this may lead to clinically meaningful prolongation of the QTcF (see section 4.2 Dose and method of administration, section 4.5 Interaction with other medicines and other forms of interaction and section 5.1 Pharmacodynamic properties). If treatment with a strong CYP3A4 inhibitor cannot be avoided, the dose should be reduced to 400 mg once daily (see sections 4.2 Dose and method of administration, 4.5 Interaction with other medicines and other forms of interaction and 5.2 Pharmacokinetic (PK) Properties). Based on the findings in MONALEESA-7 (E2301), increased QT prolongation occurs with co-administration of KISQALI and tamoxifen and the use of KISQALI with tamoxifen is not recommended (see sections 4.8 Undesirable effects and 5.1 Pharmacodynamic properties, clinical trials).

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

In phase III clinical studies (MONALEESA-2, MONALEESA-7 and MONALEESA-3), excluded patients with certain conditions known to increase QT prolongation risk, such as heart failure, cardiomyopathy, or recent coronary disease. Across these studies in patients with advanced or metastatic breast cancer who received the combination of 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 *Torsade de Pointes*.

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

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

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

Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation in patients with early breast cancer and advanced or metastatic breast cancer as described in Table 2 (see sections 4.2 Dose and method of administration, section 4.8 Undesirable effects), and section 5.2 Pharmacokinetic (PK) Properties).

Hepatobiliary toxicity

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

In the phase III clinical studies 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 ULN and of total bilirubin >2 x ULN, with normal alkaline phosphatase levels, 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 elevations of bilirubin. In MONALEESA-2 and MONALEESA-3, concurrent elevations of ALT or AST

greater than three times the upper limit of normal (ULN) and of total bilirubin greater than two times the ULN, with normal alkaline phosphatase levels, in the absence of cholestasis occurred in 6 patients (1%), and all patients recovered after discontinuation of KISQALI. There were no such cases in MONALEESA-7.

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

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

Neutropenia

Severity of neutropenia is concentration dependent. Physicians should inform patients to promptly report any fever (see 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 the patients who had Grades 2, 3, or 4 neutropenia, the median time to onset 17 days. The median time to resolution of Grade ≥3 neutropenia (to normalisation or < Grade 3) was 12 days in patients treated with KISQALI plus an aromatase inhibitor or fulvestrant. Febrile neutropenia was reported in 2% of patients exposed to KISQALI plus an aromatase inhibitor or fulvestrant.

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

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

Severe cutaneous reactions

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

Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis has been reported with CDK4/6 inhibitors including reports of fatal cases.

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

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

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

Reproductive toxicity and fertility

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

4.5 Interaction with other medicines and other forms of interaction

Drugs that may increase the QT interval

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

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

Interactions with co-administered anticancer medicines

Ribociclib and letrozole

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

Ribociclib and exemestane

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

Ribociclib and anastrozole

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

Ribociclib and fulvestrant

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

Ribociclib and tamoxifen

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

In vitro interaction data

Effect of ribociclib on cytochrome P450 enzymes

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

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

Effect of transporters on ribociclib

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

Effect of ribociclib on transporters

In vitro evaluations indicated that ribociclib has a potential to inhibit the activities of drug transporters Pgp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1, MATE2K and BSEP. Caution and monitoring for toxicity are advised during concomitant treatment with sensitive substrates of these transporters which exhibit a narrow therapeutic index, including but not limited to digoxin, pitavastatin, pravastatin, rosuvastatin, and metformin. Ribociclib did not inhibit OAT1, OAT3 or MRP2 at clinically relevant concentrations *in vitro*.

Drugs that may increase ribociclib plasma concentrations

CYP3A4 inhibitors

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

treatment with a moderate CYP3A4 inhibitor is initiated, close monitoring for ribociclib-related AEs is recommended.

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

In patients with early breast cancer who are receiving 400 mg KISQALI, if co-administration of KISQALI with strong CYP3A inhibitor cannot be avoided, patients should be monitored for adverse reactions and, if necessary, a reduction of KISQALI dose to 200 mg should be considered.

In patients with advanced or metastatic breast cancer who are receiving 600 mg KISQALI, if co-administration of ribociclib with a strong CYP3A inhibitor cannot be avoided, reduce KISQALI dose to 400 mg. However, there are no clinical data with this dose adjustment (see section 4.2 Dose and method of administration).

In patients with early breast cancer and advanced or metastatic breast cancer, if the strong inhibitor is discontinued, resume the KISQALI dose (after at least 5 elimination half-lives of the CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Due to inter-patient variability, the recommended dose adjustments may not be optimal in all individual patients, therefore close monitoring for ribociclib related AEs is recommended. In case of ribociclib related toxicity, dose should be modified or treatment should be interrupted until toxicity is resolved (see section 4.2 Dose and method of administration and 5.2 Pharmacokinetic (PK) Properties.

Ritonavir

A drug interaction trial in healthy subjects was conducted with ritonavir (strong CYP3A inhibitor). Compared to ribociclib alone, ritonavir (100 mg bid for 14 days) increased ribociclib C_{max} and AUC_{inf} by 1.7-fold and 3.2-fold, respectively, following a single 400 mg ribociclib dose. C_{max} and AUC_{last} for LEQ803 (a prominent metabolite of LEE011, accounting for < 10 % of parent exposure) decreased by 96 % and 98 %, respectively. Physiologically-based pharmacokinetic (PBPK) simulation estimated that co-administration of ritonavir (100 mg twice daily) with multiple daily doses of 400mg ribociclib may increase ribociclib steady-state Cmax and AUC_{0-24h} by 1.29 and 1.47-fold, respectively, in patients with advanced or metastatic breast cancer.

Erythromycin

Simulations using physiologically-based pharmacokinetic modelling (PBPK) suggested that erythromycin, a moderate CYP3A4 inhibitor, may increase ribociclib 400 mg C_{max} and AUC steady state by 1.1 and 1.2 fold, respectively, in patients with early breast cancer, and 1.1-fold and 1.1-fold, respectively, in patients with advanced breast cancer.

Drugs that may decrease ribociclib plasma concentrations

CYP3A4 inducers

Avoid concomitant use of strong CYP3A inducers, including, but not limited to, phenytoin, rifampin, carbamazepine, and St John's Wort (*Hypericum perforatum*). Consider an

alternate concomitant medication with no or minimal potential to induce CYP3A (see section 4.4 Special warnings and precautions for use).

Rifampicin

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

Efavirenz

Simulations using PBPK suggested that efavirenz, a moderate CYP3A inducer, may decrease ribociclib single dose C_{max} and AUC by 45% and 69%, respectively, in patients with early breast cancer, and by 37% and 60%, respectively, in patients with advanced breast cancer.

Effect of ribociclib on other drugs

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

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

The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, 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% (1.2-fold) in healthy subjects, compared with administration of caffeine alone. At the clinically relevant dose of 600 mg, simulations using PBPK models predicted only weak inhibitory effects of ribociclib on CYP1A2 substrates (less than 2-fold increase in AUC).

Drug-food interactions

Patients should be instructed to avoid fruits (including fruit juices) that are known to be strong inducers or inhibitors of cytochrome CYP3A enzymes and may therefore increase

exposure to ribociclib. These include grapefruit, grapefruit hybrids, pummelos, star fruit, and Seville oranges.

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

Gastric pH elevating medicines

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

Use in pregnancy (Category D)

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

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

Pregnancy testing

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

Contraception in females

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

Breastfeeding

It is not known if KISQALI is present in human milk. There are no data on the effects of KISQALI on the breastfed child or the effects of KISQALI on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats (see section 5.3 Preclinical Safety Data).

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable Effects

Early breast cancer

The overall safety profile reported below is based on the data set of 2,525 patients who received KISQALI in combination with aromatase inhibitor (AI) in the open-label phase III clinical study (NATALEE) in HR-positive, HER2-negative early breast cancer. The median duration of exposure to ribociclib across the study was 32.9 months with 69.4% patients exposed for ≥24 months and 42.8% patients have completed the 36 months ribociclib regimen.

Dose reductions due to adverse events (AEs), regardless of causality, occurred in 22.8% of patients receiving KISQALI plus AI.

Permanent discontinuations of ribociclib due to adverse events were reported in 19.7% of patients receiving KISQALI plus AI.

The most common AEs leading to permanent discontinuation of KISQALI were ALT increase (7.1%), AST increase (2.8%), and arthralgia (1.5%).

On-treatment deaths were reported in 20 patients (0.8%) treated with KISQALI plus AI. Fatal AEs were seen in 11 patients (0.4%) in KISQALI plus AI arm, none of which were ribociclib related.

The most common ADRs across the NATALEE study (reported at a frequency of ≥20% and exceeding the frequency for AI alone) were neutropenia, infections, nausea, headache, fatigue, leukopenia, and abnormal liver function tests.

The most common Grade ≥3 ADRs (reported at a frequency of ≥2% and for which the frequency for KISQALI exceeds the frequency for AI alone) were neutropenia, abnormal liver function tests, and leukopenia.

ARs and laboratory abnormalities occurring in patients in NATALEE are listed in Table 7 and Table 8, respectively.

Table 7 Adverse reactions based on data from phase III NATALEE study in patients with early breast cancer

Adverse drug reactions	KISQALI N=2525 n (%) All Grades	AI N=2442 n (%) All Grades	KISQALI N=2525 n (%) Grade ≥3	AI N=2442 n (%) Grade ≥3	Frequency category All Grades
Infections and infestations					
Infections[1]	917 (36.3)	642 (26.3)	49 (1.9)	23 (0.9)	Very common
Blood and lymphatic system disorder					
Neutropenia	1,577 (62.5)	113 (4.6)	1113 (44.1)	22 (0.9)	Very common
Leukopenia	564 (22.3)	88 (3.6)	184 (7.3)	8 (0.3)	Very common
Anaemia	215 (8.5)	75 (3.1)	8 (0.3)	7 (0.3)	Common
Thrombocytopenia	162 (6.4)	56 (2.3)	6 (0.2)	3 (0.1)	Common
Lymphopenia	124 (4.9)	39 (1.6)	30 (1.2)	2 (0.1)	Common
Febrile neutropenia	7 (0.3)	0	7 (0.3)	0	Uncommon

Adverse drug reactions	KISQALI N=2525 n (%) All Grades	AI N=2442 n (%) All Grades	KISQALI N=2525 n (%) Grade ≥3	AI N=2442 n (%) Grade ≥3	Frequency category All Grades
Metabolism and nutrition disorders					
Hypocalcaemia	134 (5.3)	26 (1.1)	1 (<0.1)	0	Common
Hypokalaemia	121 (4.8)	41 (1.7)	8 (0.3)	7 (0.3)	Common
Decreased appetite	120 (4.8)	47 (1.9)	1 (<0.1)	0	Common
Nervous system disorders					
Headache	580 (23.0)	417 (17.1)	11 (0.4)	4 (0.2)	Very common
Dizziness	225 (8.9)	112 (4.6)	5 (0.2)	2 (0.1)	Common
Respiratory, thoracic and mediastinal disorders					
Cough	332 (13.1)	201 (8.2)	3 (0.1)	2 (0.1)	Very common
Dyspnoea	166 (6.6)	102 (4.2)	13 (0.5)	10 (0.4)	Common
Gastrointestinal disorders					
Nausea	588 (23.3)	190 (7.8)	6 (0.2)	1 (<0.1)	Very common
Diarrhoea	366 (14.5)	135 (5.5)	16 (0.6)	3 (0.1)	Very common
Constipation	335 (13.3)	123 (5.0)	5 (0.2)	0	Very common
Abdominal pain[2]	277 (11.0)	179 (7.3)	12 (0.5)	9 (0.4)	Very common
Vomiting	198 (7.8)	96 (3.9)	10 (0.4)	1 (<0.1)	Common
Stomatitis[3]	154 (6.1)	24 (1.0)	2 (0.1)	0	Common
Hepatobiliary disorders					
Hepatotoxicity[4]	36 (1.4)	13 (0.5)	16 (0.6)	1 (<0.1)	Common
Skin and subcutaneous tissue disorders					
Alopecia	380 (15.0)	109 (4.5)	0	0	Very common
Rash[5]	233 (9.2)	85 (3.5)	4 (0.2)	3 (0.1)	Common
Pruritus	188 (7.4)	77 (3.2)	2 (0.1)	1 (<0.1)	Common
General disorders and administration site conditions					
Fatigue	564 (22.3)	322 (13.2)	19 (0.8)	4 (0.2)	Very common
Asthenia	428 (17.0)	291 (11.9)	14 (0.6)	3 (0.1)	Very common
Pyrexia	280 (11.1)	147 (6.0)	5 (0.2)	2 (0.1)	Very common
Peripheral oedema	183 (7.2)	121 (5.0)	1 (<0.1)	0	Common
Oropharyngeal pain	154 (6.1)	81 (3.3)	0	0	Common
Investigations					
Abnormal liver function tests[6]	563 (22.3)	186 (7.6)	197 (7.8)	25 (1.0)	Very common
Electrocardiogram QT prolonged	109 (4.3)	18 (0.7)	7 (0.3)	1 (<0.1)	Common

Adverse drug reactions	KISQALI N=2525 n (%) All Grades	AI N=2442 n (%) All Grades	KISQALI N=2525 n (%) Grade ≥3	AI N=2442 n (%) Grade ≥3	Frequency category All Grades
Blood creatinine increased	98 (3.9)	22 (0.9)	3 (0.1)	0	Common

[1] Infections: urinary tract infections; respiratory tract infections.
[2] Abdominal pain: abdominal pain, abdominal pain upper.
[3] Stomatitis: stomatitis, mucositis
[4] Hepatotoxicity: hepatic cytolysis, drug induced liver injury, hepatotoxicity, autoimmune hepatitis (single case).
[5] Rash: rash, rash maculopapular, rash pruritic.
[6] Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

Table 8 Laboratory abnormalities based on data from NATALEE study in patients with early breast cancer

Laboratory abnormalities	KISQALI N=2525 n (%) All Grades	AI N= 2442 n (%) All Grades	KISQALI N= 2525 n (%) Grades 3/4	AI N= 2442 n (%) Grades 3/4	Frequency category All Grades
Haematological parameters					
Lymphocyte count decreased	2,460 (97.4)	2,151 (88.1)	480 (19.0)	153 (6.3)	Very common
Leukocyte count decreased	2,407 (95.3)	1,103 (45.2)	693 (27.4)	14 (0.6)	Very common
Neutrophil count decreased	2,363 (93.6)	859 (35.2)	1,138 (45.1)	41 (1.7)	Very common
Haemoglobin decreased	1,192 (47.2)	627 (25.7)	14 (0.6)	8 (0.3)	Very common
Platelet count decreased	715 (28.3)	320 (13.1)	10 (0.4)	8 (0.3)	Very common
Biochemical parameters					
ALT increased	1,131 (44.8)	862 (35.3)	205 (8.1)	25 (1.0)	Very common
AST increased	1,111 (44.0)	806 (33.0)	133 (5.3)	26 (1.1)	Very common
Creatinine increased	822 (32.6)	278 (11.4)	7 (0.3)	0	Very common

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% patients exposed for ≥ 12

months. Dose reductions due to adverse reactions (ARs) occurred in 49% of patients receiving KISQALI plus letrozole and in 3% of patients receiving placebo plus letrozole. Among patients receiving KISQALI plus letrozole, 11% were reported to have permanently discontinued both KISQALI and letrozole, and 9% were reported to have permanently discontinued KISQALI alone due to ARs. Among patients receiving placebo plus letrozole, 3% were reported to have permanently discontinued both and 2% were reported to have permanently discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation of KISQALI in patients receiving KISQALI plus letrozole were ALT increased (5%), AST increased (3%) and vomiting (2%). Antiemetics and antidiarrhoea medications were used to manage symptoms as clinically indicated.

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

The most common ARs (reported at an incidence ≥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 (all grades)

	KISQALI + letrozole N = 334			Placebo + letrozole N = 330		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Adverse drug reactions	**%**	**%**	**%**	**%**	**%**	**%**
Infections and Infestations						
Infections[1]	49	4	<1	36	<1	<1
Blood and lymphatic system disorders						
Neutropenia	77	54	10	6	1	0
Leukopenia	35	21	1	5	< 1	0
Anaemia	24	3	< 1	8	2	0
Lymphopenia	13	7	1	3	1	0
Thrombocytopenia	11	<1	0	<1	<1	0

	KISQALI + letrozole N = 334			Placebo + letrozole N = 330		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Adverse drug reactions	%	%	%	%	%	%
Metabolism and nutrition disorders						
Decreased appetite	22	1	0	18	< 1	0
Nervous system disorders						
Headache	29	< 1	0	23	< 1	0
Insomnia	16	0	0	14	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	16	2	0	13	< 1	0
Musculoskeletal and connective tissue disorders						
Back pain	27	3	0	23	1	0
Eye disorders						
Lacrimation increased	12	0	0	2	0	0
Gastrointestinal disorders						
Nausea	55	3	0	32	< 1	0
Diarrhoea	41	2	0	26	< 1	0
Vomiting	35	4	0	19	< 1	0
Constipation	30	1	0	22	0	0
Abdominal pain	21	1	0	14	< 1	0
Stomatitis	12	< 1	0	7	0	0
Dry mouth	14	<1	0	11	<1	0
Dyspepsia	11	<1	0	8	0	0
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

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

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) (all grades)

	KISQALI + NSAI + goserelin N = 248			Placebo + NSAI + goserelin N = 247		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Adverse drug reactions	**%**	**%**	**%**	**%**	**%**	**%**
Infections and Infestations						
Infections[1]	43	2	0	32	< 1	0
Blood and lymphatic system disorders						
Neutropenia	80	57	12	10	4	< 1
Leukopenia	33	15	< 1	4	< 1	0
Anaemia	20	4	0	9	2	0
Lymphopenia	13	5	<1	3	1	<1
Thrombocytopenia	10	0	<1	2	0	<1
Nervous system disorders						
Headache	29	0	0	26	<1	0
Respiratory, thoracic and mediastinal disorders						
Cough	20	0	0	11	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	43	< 1	0	38	1	0

Back pain	24	<1	0	21	2	0
Gastrointestinal disorders						
Nausea	33	0	0	25	0	0
Diarrhoea	23	2	0	21	2	0
Vomiting	21	<1	0	19	0	0
Abdominal pain[2]	19	1	0	16	<1	0
Constipation	18	0	0	14	0	0
Stomatitis	14	0	0	9	< 1	0
Skin and subcutaneous tissue disorders						
Alopecia	21	0	0	14	0	0
Rash[3]	20	< 1	0	10	0	0
Pruritus	12	0	0	6	0	0
General disorders and administration site conditions						
Abnormal liver function tests[4]	21	7	0	15	3	0
Pyrexia	17	< 1	0	8	< 1	0
Pain in extremity	17	0	0	11	1	0
Asthenia	15	< 1	0	11	0	0
Oedema peripheral	11	0	0	8	0	0
Oropharyngeal pain	10	0	0	4	0	0
Investigations						
Electrocardiogram 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		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory parameters	**%**	**%**	**%**	**%**	**%**	**%**
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

	KISQALI + NSAI + goserelin N = 248			Placebo + NSAI + goserelin N = 247		
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Lymphocyte count decreased	60	17	3	21	3	< 1
Platelet count decreased	31	< 1	1	11	< 1	< 1
Chemistry						
Aspartate aminotransferase increased	48	7	0	41	1	< 1
Gamma-glutamyl transferase increased	46	7	2	44	9	1
Alanine aminotransferase increased	45	6	< 1	34	2	< 1
Phosphorous decreased	17	2	0	15	< 1	< 1
Potassium decreased	17	< 1	< 1	15	< 1	< 1
Glucose serum decreased	15	< 1	< 1	11	< 1	< 1
Creatinine increased	21	2	< 1	20	< 1	< 1

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, 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 (all grades)

	KISQALI + fulvestrant N = 483			Placebo + fulvestrant 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 N = 483			Placebo + fulvestrant 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
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

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

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

The safety of KISQALI in combination with letrozole was evaluated in men (n=39) in an open-label, multicentre clinical study for the treatment of adult patients with HR-positive,

HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease (COMPLEEMENT-1) (see section 5.1 Clinical Studies).

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

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

Description of selected adverse drug reactions

QT prolongation

In the phase III study in patients with early breast cancer 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. In the KISQALI plus AI arm QT interval prolongation events were presented primarily by ECG QT prolonged (4.3%) that was the only confirmed adverse drug reaction with KISQALI. 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 at least one post-baseline QTcF of > 480 ms occurred in 5% ribociclib-treated patients and 2% of placebo-treated patients. Among the ribociclib-treated patients who had QTcF prolongation of >480 ms, the median time to onset is 15 days regardless of what treatment ribociclib was combined with, and these changes were reversible with dose interruption and/or dose reduction (see sections 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic (PK) Properties).

In MONALEESA-7, the observed mean QTcF increase from baseline was >10 ms higher in the tamoxifen plus placebo subgroup compared with NSAI plus placebo subgroup, suggesting that tamoxifen contributed to the QTcF prolongation observed in the ribociclib plus tamoxifen group (see section 5.1 Pharmacodynamic properties). A QTcF increase of >60 ms from baseline occurred in zero patients who received placebo plus 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 (26.4% vs 11.2%, 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 12.4% of patients with early breast cancer treated with KISQALI plus AI, primarily due to ALT increased (10.1%) and/or AST increased (6.8%). 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 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 the placebo-treated patients (27% and 20%), and more Grade 3/4 adverse events were reported in the ribociclib-treated patients than placebo-treated patients (13% versus 6%). Dose interruptions and/or adjustments due to hepatobiliary toxicity events were reported in 12% of ribociclib-treated patients, primarily due to ALT increased (8%) and/or AST increased (7%). Discontinuation of treatment with KISQALI due to abnormal liver function tests, and hepatotoxicity occurred at rates of 2% and 0.3 % respectively (see sections 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties).

Neutropenia

Severity of neutropenia is concentration dependent.

In the phase III study in patients with early breast cancer, neutropenia was a frequently reported laboratory finding. Treatment discontinuation due to neutropenia was low (1.1%) in patients receiving KISQALI plus AI (see sections 4.1 Dose and method of administration and 4.4 Special warnings and precautions for use.

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

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.

Post marketing experience

The following adverse reactions 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 which is therefore categorized as not known.

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

Adverse reaction
Respiratory, thoracic and mediastinal disorders
Interstitial lung disease (ILD)/pneumonitis
Skin and subcutaneous tissue disorders
Toxic epidermal necrolysis (TEN)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after the authorisation of the medicine is important. It allows for continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to Medsafe via the following web site: https://pophealth.my.site.com/carmreportnz/s/.

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 advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - protein- kinase inhibitors.

Anatomical Therapeutic Chemical (ATC) code: L01EF02.

Mechanism of action

Ribociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signalling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb).

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

In vivo studies using a 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. When administered to patients, ribociclib can also be immunomodulatory, decreasing regulatory T-cells and relative levels of CD3+ T-cells. Additionally, the combination of ribociclib and fulvestrant

resulted in tumour growth inhibition in an oestrogen receptor positive breast cancer xenograft model.

Pharmacodynamic effects

Ribociclib inhibits the CDK4/cyclin-D1 and CDK6/cyclin-D3 enzyme complexes with concentration resulting in 50% inhibition (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 0.08µM (34.8ng/mL). When tested in a panel of breast cancer cell lines with known ER status, ER-positive cell lines were more sensitive than ER-negative cell lines to the anti-proliferation effects of ribociclib. Ribociclib had no inhibitory activity against pRb-negative breast cancer cell lines. In the preclinical models tested so far, intact pRb was required for ribociclib activity.

Cardiac electrophysiology

Serial, triplicate electrocardiograms (ECGs) were collected following a single dose and at steady-state to evaluate the effect of ribociclib on the QTc interval in patients with advanced cancer. *In vitro* studies have shown that both ribociclib and its major metabolite, LEQ803, interact with hERG channels. A pharmacokinetic-pharmacodynamic analysis included a total of 997 patients treated with ribociclib at doses ranging from 50 mg to 1,200 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval.

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, 23.0) and 23.7 ms (90% CI: 22.3, 25.1), respectively, and was 34.7 ms (90% CI: 31.6, 37.8) in combination with tamoxifen at the geometric mean C_{max} at steady-state (see section 4.4 Special warnings and precautions for use).

Clinical Trials

NATALEE (Study CLEE011O12301C)

KISQALI was evaluated in a randomised, open-label, multicentre phase III clinical study in the treatment of pre/post-menopausal women, and men, with HR-positive, HER2-negative, early breast cancer with Anatomic Stage II or III irrespective of nodal status in combination with an aromatase inhibitor (AI, letrozole or anastrozole) versus AI alone. Stage IIA patients with no nodal involvement had tumour grade 2 with high risk genomic profile or Ki67 ≥20% or grade 3. Premenopausal women, and men, also received goserelin. Applying TN 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.

A total of 5,101 patients, including 20 male patients, were randomised in a 1:1 ratio to receive either KISQALI 400 mg and AI (n=2549) or AI alone (n=2,552). Randomisation to

the treatment was stratified by Anatomic Stage (group II [n=2,154 (42.2%)] vs group III [n=2,947 (57.8%)]), prior treatment (adjuvant/ neoadjuvant chemotherapy Yes [n=4,432 (86.9%)] vs No [n=669 (13.1%)]), menopausal status (premenopausal women and men [n=2,253 (44.2%)] vs postmenopausal women [n=2,848 (55.8%)]) and region (North America/Western Europe/Oceania [n=3,128 (61.3%)] vs rest of the world [n=1,973 (38.7%)]). Demographics and baseline disease characteristics were balanced and comparable between the two study arms. 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 was given at a dose of 3.6 mg as injectable subcutaneous implant administered on Day 1 of each 28-day cycle. Therapy with KISQALI continued until completion of 3-year treatment from the randomization date (approximately 39 cycles).

Patients enrolled in this study had a median age of 52 years (range 24 to 90). 15.2% patients were aged 65 years and older, including 123 patients (2.4%) aged 75 years and older. The patients included were White (73.4%), Asian (13.2%) and Black or African American (1.7%). All patients had an ECOG performance status of 0 or 1. A total of 88.2% of patients had received chemotherapy in the neoadjuvant or adjuvant setting and 71.1% 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 randomization 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).

The primary endpoint of the study was met at the primary analysis (11-Jan-2023 cut-off). A statistically significant improvement 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 patients receiving KISQALI plus AI over AI alone.

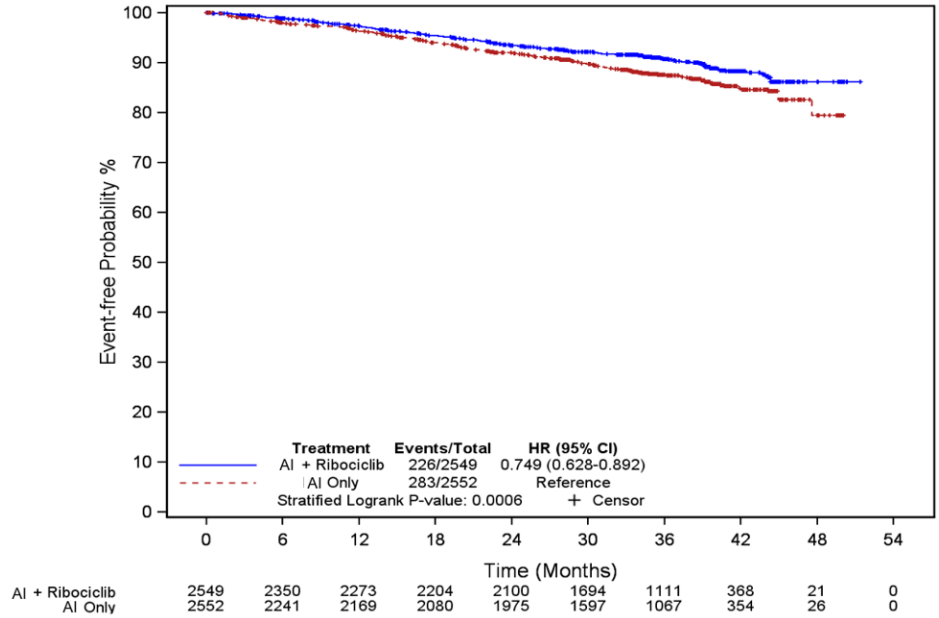
Data from a further analysis (21-Jul-23 cut-off) is summarised in Table 16 and the Kaplan-Meier curve for iDFS is provided in Figure 1. The median treatment duration at the time of the final iDFS analysis was approximately 30 months with the median follow-up time for iDFS 33.3 months across the two study arms. The overall survival (OS) remains immature. A total of 172 patients (3.5%) had died (83/2,525 in the ribociclib arm versus 89/2,442 in the AI arm alone arm, HR 0.892).

Table 16 NATALEE (O12301C) final efficacy results (iDFS) based on investigator assessment (FAS) (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 randomization 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 (FAS) (21-Jul-2023 cut-off) (FAS)



AI - aromatase inhibitor

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

The results for recurrence-free survival (RFS) events and distant disease-free survival (DDFS) events after the final iDFS are provided in Table 17.

Table 17 NATALEE (O12301C) efficacy results (RFS, DDFS) based on investigator assessment (21-Jul-23 cut-off)

	KISQALI plus AI (N=2549)	AI (N=2552)
Recurrence-free survival (n, %)	192 (7.5%)	248 (9.7%)
Hazard ratio (95% CI)	0.727 (0.602 to 0.877)	
Distant disease-free survival (n, %)	204 (8.0%)	256 (10%)
Hazard ratio (95% CI)	0.749 (0.623 to 0.900)	

MONALEESA 2 (Study CLEE011A2301)

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

A total of 668 patients were randomized to receive either KISQALI plus letrozole (n= 334) or placebo and letrozole (n=334), stratified according to the presence of liver and/or lung metastases. Demographics and baseline disease characteristics were balanced and comparable between study arms. Letrozole 2.5 mg was given orally once daily for 28 days, with either KISQALI 600 mg or placebo once daily for 21 consecutive days followed by 7 days off treatment until progression or unacceptable toxicity. Patients who had prior (neo-)

adjuvant or adjuvant therapy with anastrozole or letrozole must have completed at least 12 months before randomisation, and patients were not allowed to cross over from placebo to KISQALI during the study or after disease progression. The primary efficacy endpoint for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

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

Primary analysis

The efficacy findings are summarised in Table 18 and Figure 2. The results shown are from the pre-planned primary interim efficacy analysis of PFS and from an updated analysis performed at the time of the second interim analysis of overall survival (OS). Results were consistent across patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastatic disease. The PFS assessment based on a blinded independent central radiological review was consistent with investigator assessment.

Table 18 Efficacy results from MONALEESA 2 (investigator-assessed, intent-to-treat (ITT) population)

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

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

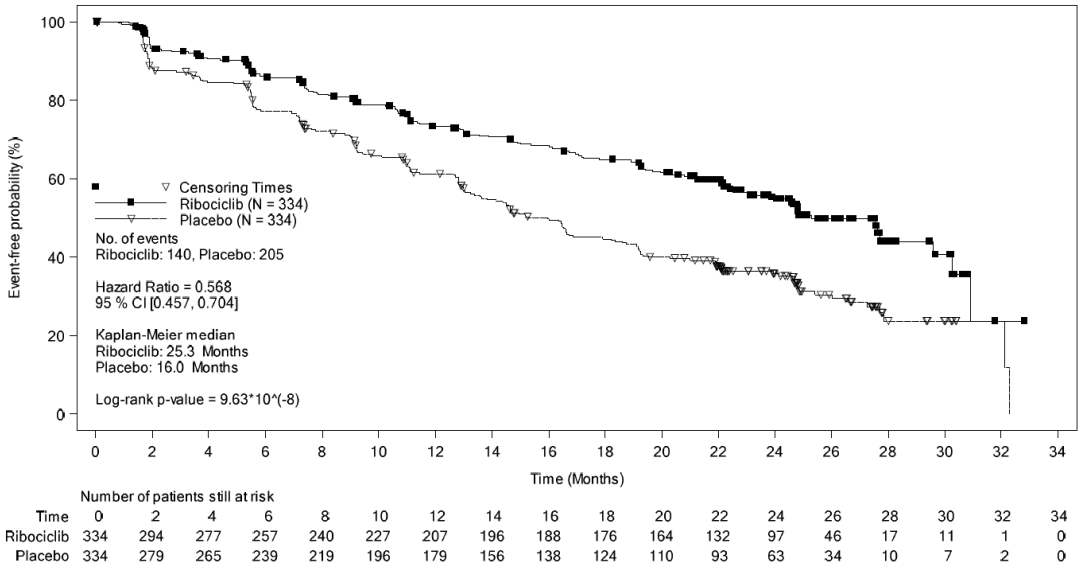
[a] Median duration of study follow up = 15.3 months

[b] Median duration of study follow up = 26.4 months

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

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

Figure 2 Kaplan-Meier plot 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 and clinically meaningful improvement in OS with a 24% relative reduction in risk of death (HR: 0.765, 95% CI: 0.628, 0.932; p-value=0.004).

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

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

The OS results from this final analysis are summarized in Table 19 and Figure 3.

Table 19 Efficacy results from MONALEESA 2 (OS 10 Jun 2021 cut-off)

Overall survival, overall study population	KISQALI plus letrozole n=334	Placebo plus letrozole n=334
Number of events, n (%)	181 (54.2%)	219 (65.6%)
Median OS [months] (95% CI)	63.9 (52.4, 71.0)	51.4 (47.2, 59.7)
Hazard ratio[a] (95% CI)	0.765 (0.628, 0.932)	
p-value[b]	0.004	
OS event-free rate, (%) (95% CI)		
24 months	86.6 (82.3, 89.9)	85.0 (80.5, 88.4)

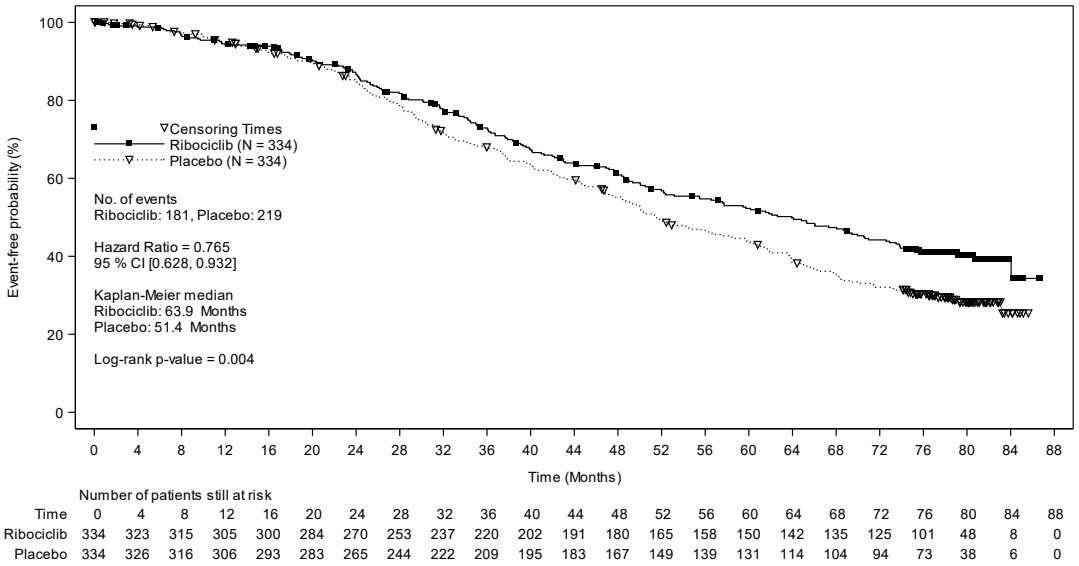
Overall survival, overall study population	KISQALI plus letrozole n=334	Placebo plus letrozole n=334
60 months	52.3 (46.5, 57.7)	43.9 (38.3, 49.4)
72 months	44.2 (38.5, 49.8)	32.0 (26.8, 37.3)

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)



Number of patients still at risk

Time	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88
Ribociclib	334	323	315	305	300	284	270	253	237	220	202	191	180	165	158	150	142	135	125	101	48	8	0
Placebo	334	326	316	306	293	283	265	244	222	209	195	183	167	149	139	131	114	104	94	73	38	6	0

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

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

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

MONALEESA-7 (Study CLEE011E2301)

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

A total of 672 patients were randomised to receive either KISQALI plus goserelin plus NSAI/tamoxifen (n=335) or placebo plus goserelin plus NSAI/tamoxifen (n=337), stratified 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 20 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.

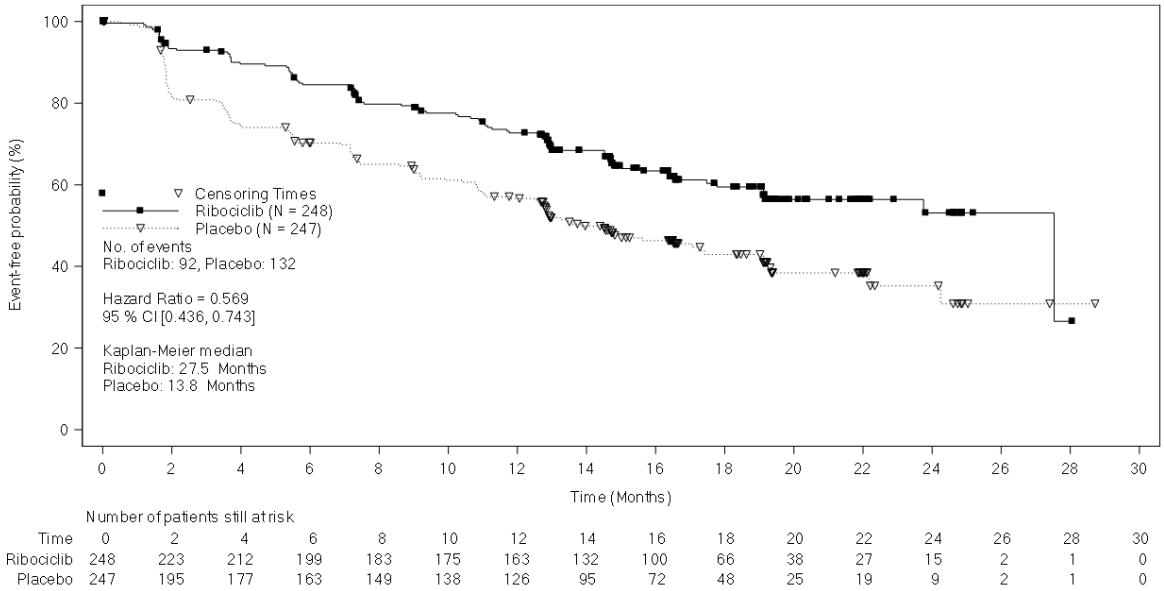
Table 20 Efficacy results from MONALEESA-7 (investigator-assessed, NSAI subgroup)

	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.

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

A more mature update of overall survival data (30-Nov-2018 cut-off) is provided in Table 21 as well as in Figures 5 and 6.

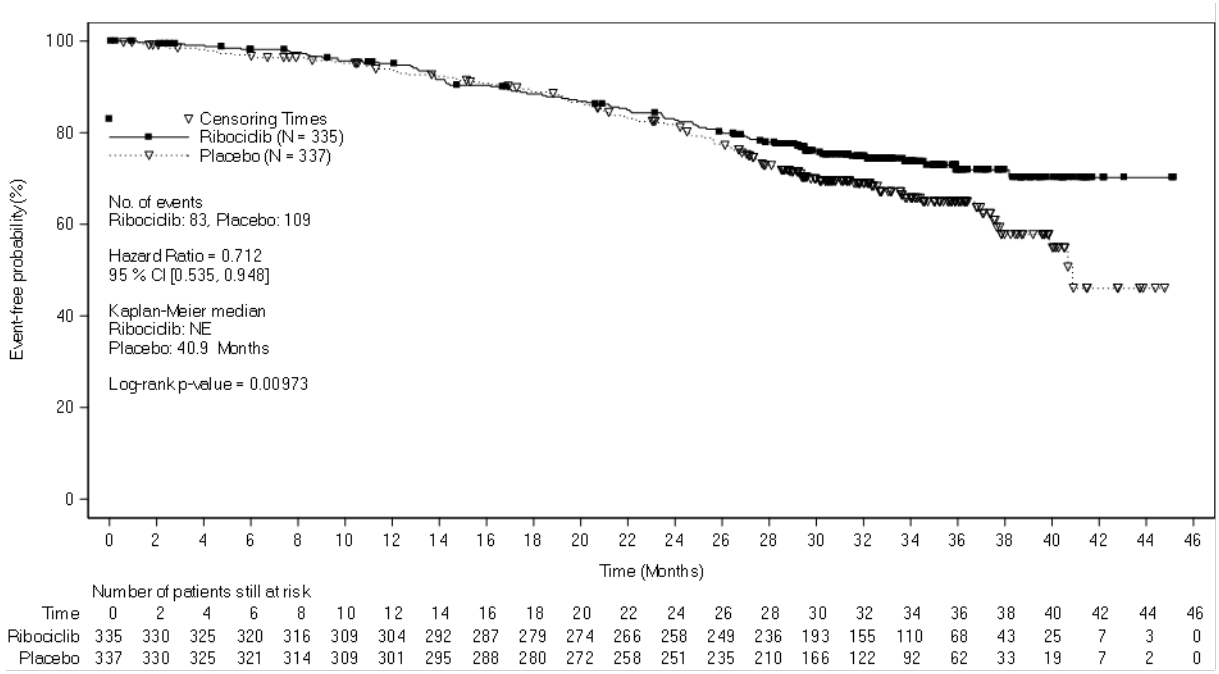
Table 21 MONALEESA-7 (E2301) efficacy results (OS) (30-Nov-18 cut-off)

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

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

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

Figure 5 MONALEESA-7 (E2301) Kaplan Meier plot of OS (FAS) (30-Nov-2018 cut-off)

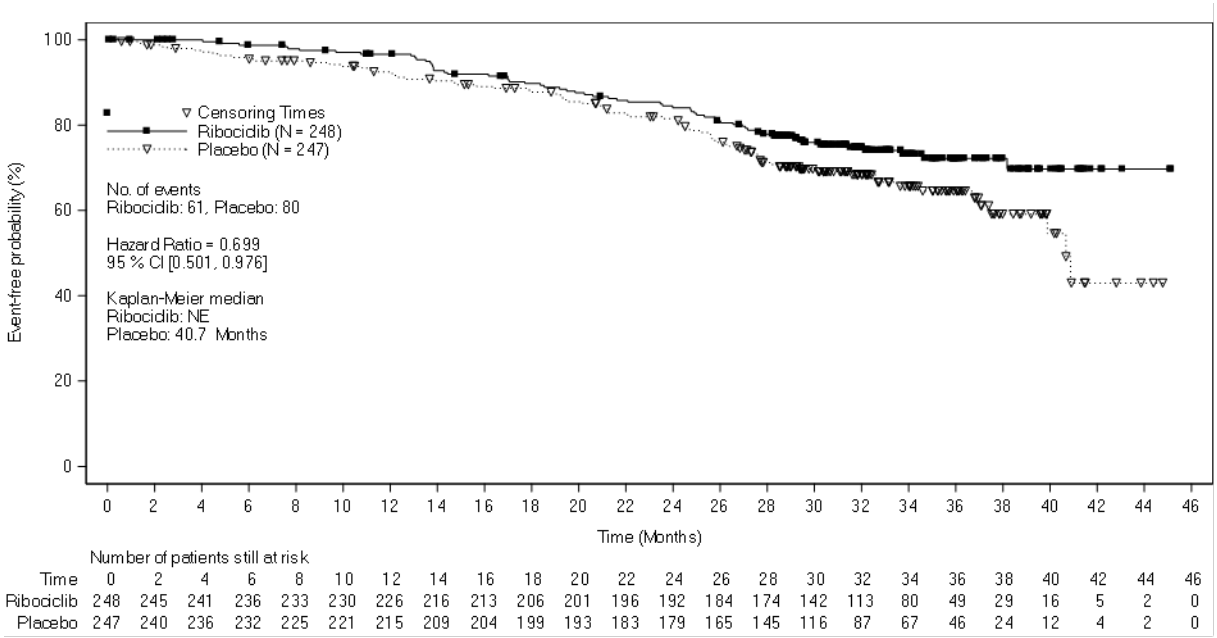


Number of patients still at risk

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
Ribociclib	335	330	325	320	316	309	304	292	287	279	274	266	258	249	236	193	155	110	68	43	25	7	3	0
Placebo	337	330	325	321	314	309	301	295	288	280	272	258	251	235	210	166	122	92	62	33	19	7	2	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

Figure 6 MONALEESA-7 (E2301) Kaplan Meier plot of OS in patients who received NSAI (30-Nov-18 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
Ribociclib	248	245	241	236	233	230	226	216	213	206	201	196	192	184	174	142	113	80	49	29	16	5	2	0
Placebo	247	240	236	232	225	221	215	209	204	199	193	183	179	165	145	116	87	67	46	24	12	4	2	0

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 analysis 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 22 and Figure 7. 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 22 Efficacy results from MONALEESA-3 (investigator-assessed, ITT population)

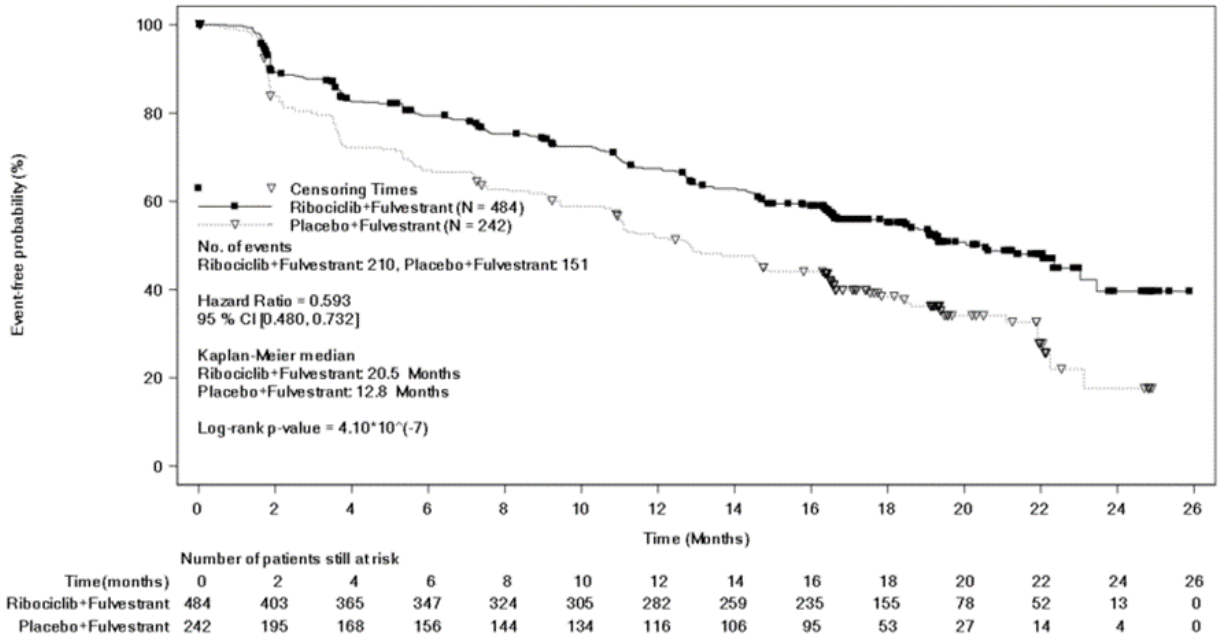
	KISQALI + fulvestrant	Placebo + fulvestrant
Progression free survival	**N=484**	**N=242**
Median PFS [months] (95% CI)	20.5 (18.5 – 23.5)	12.8 (10.9 – 16.3)
Hazard ratio (95% CI)	0.593 (0.480 - 0.732)	
p-value[a]	0.00000041	
Patients with measurable disease	**N=379**	**N=181**
Overall response rate (ORR)[b]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

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

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

[B] Based on confirmed responses, ORR: Overall Response Rate = proportion of patients with complete response + partial response

Figure 7 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 23.

Table 23 MONALEESA-3 (F2301) efficacy results (ORR, CBR) based on investigator assessment (03-Nov-17 cut-off)

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

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

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

The global health status/ QoL were similar between the KISQALI plus fulvestrant arm and the placebo plus fulvestrant arm. The main pre-specified QoL measure was TTD in global health status. A definitive 10% deterioration was defined as a worsening in score (EORTC QLQ-C30 global health scale score) by at least 10% compared to baseline, with no later improvement above this threshold observed during the treatment period, or death due to any cause. Addition of KISQALI to fulvestrant resulted in delaying TTD in the EORTC QLQ-CLEE11F2301 (MONALEESA-3) global health scale score compared with placebo plus fulvestrant, (median not estimable versus 19.4 months; HR: 0.795 [95% CI: 0.602,1.050]; p-value 0.051.

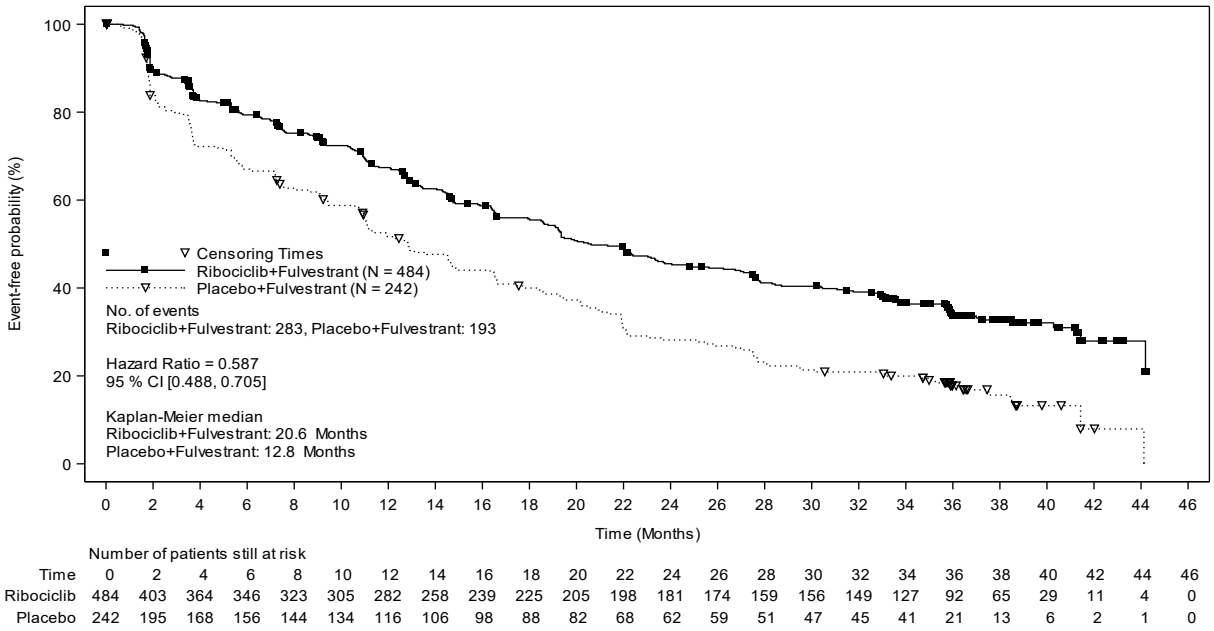
Final OS Analysis

Since the median PFS for first line patients had not been reached at the time of the primary analysis, a descriptive update of primary efficacy results (PFS) was performed at the time of the second OS interim analysis, and the updated PFS results are summarized in Table 24 and the Kaplan-Meier curve is provided in Figure 8.

Table 24 MONALEESA-3 (F2301) primary efficacy results (PFS) based on investigator assessment (03-Jun-19 cut-off)

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

Figure 8 MONALEESA-3 (F2301) Kaplan-Meier plot of PFS based on investigator assessment (FAS) (03-Jun-19 cut-off)



Results were consistent across pre-specified sub-groups of age, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone only metastatic disease. The subgroup analysis based on prior endocrine therapy is presented in Table 25.

Table 25 MONALEESA-3 (F2301) efficacy results (PFS) for prior endocrine therapy subgroup (03-Jun-19 cut-off)

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

CI=confidence interval

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

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

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

The OS results from this interim analysis with a 03-Jun-19 cut-off are provided in Table 26 and Figure 9.

Table 26 MONALEESA-3 (F2301) efficacy results (OS) (03-Jun-19 cut-off)

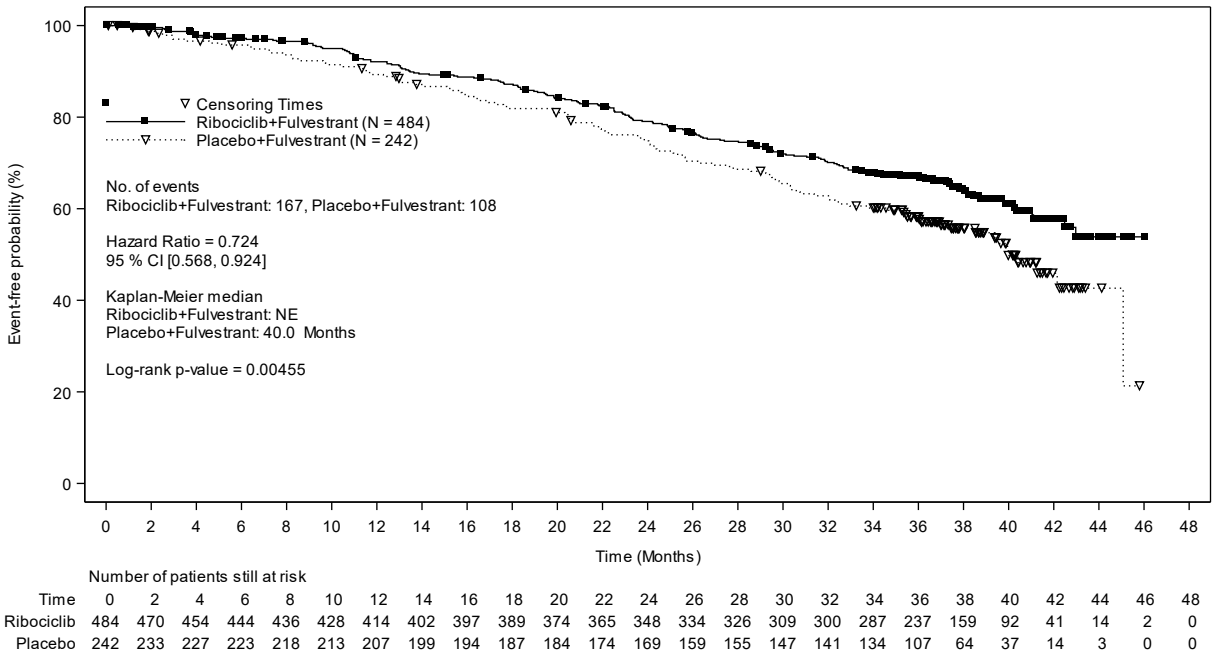
	KISQALI 600 mg	Placebo
Overall study population	N=484	N=242
Number of events - n [%]	167 (34.5)	108 (44.6)
Median OS [months] (95% CI)	NE, (NE, NE)	40 (37, NE)
HR (95% CI)	0.724 (0568, 0924)	
p value	0.00455	

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



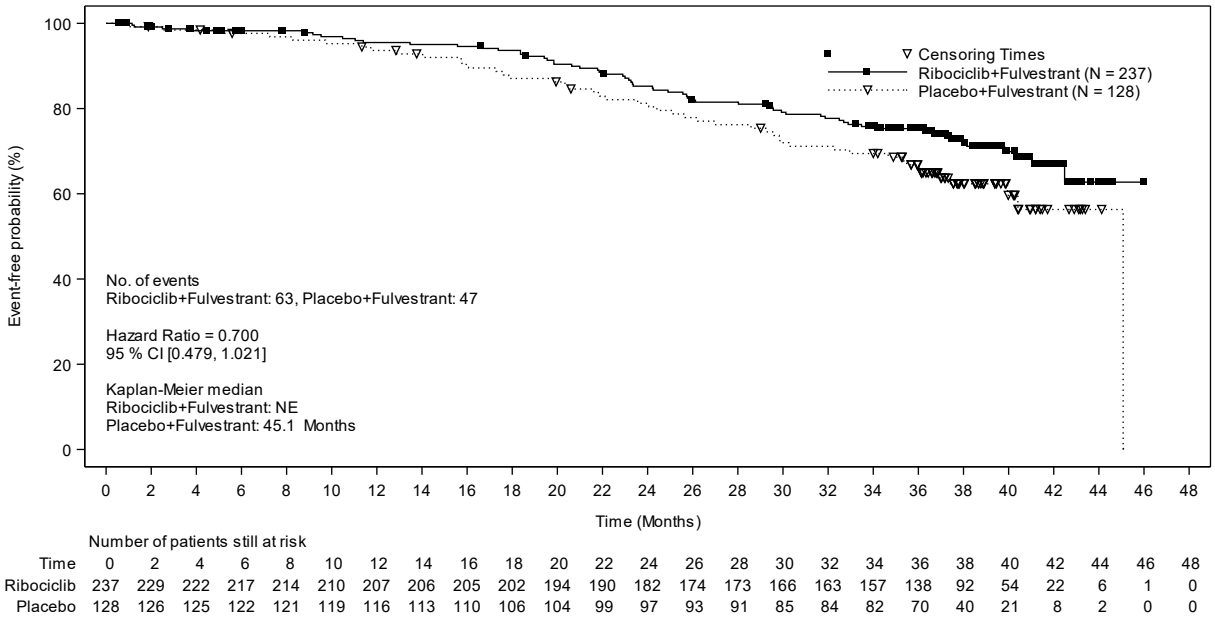
Number of patients still at risk

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

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

OS results for subgroups analyses are presented in Figures 10 and 11.

Figure 10 MONALEESA-3 (F2301) Kaplan Meier plot of OS treatment naïve patients in the metastatic/advanced disease setting (FAS) (03-Jun-19 cut-off)

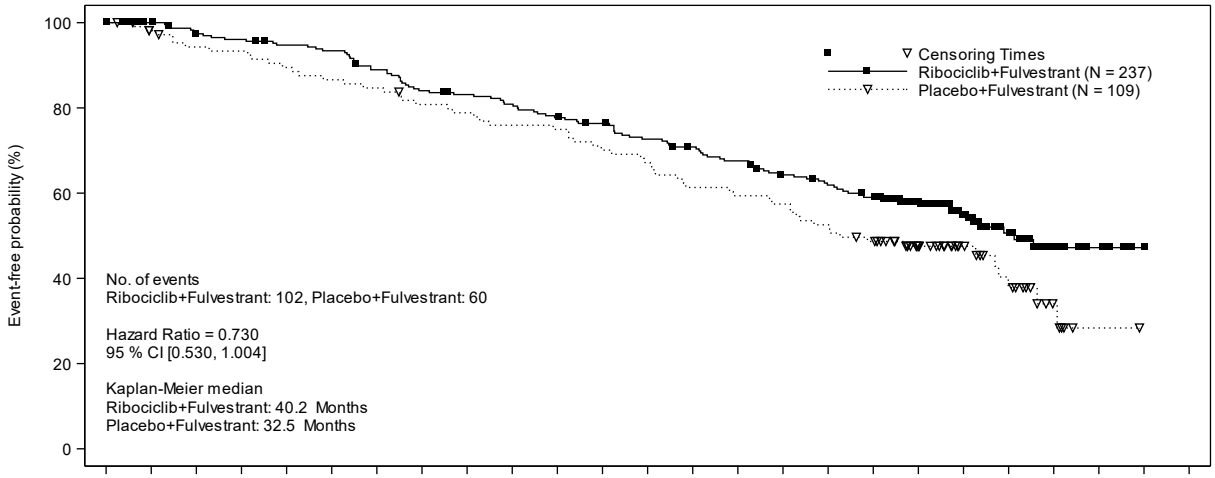


Number of patients still at risk

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

Hazard ratio is based on unstratified Cox model

Figure 11 MONALEESA-3 (F2301) Kaplan Meier plot of OS in patients who received up to 1 line of treatment for metastatic/advanced disease setting (FAS) (03-Jun-19 cut-off)



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Ribociclib	237	231	222	218	213	210	199	188	184	179	172	167	158	152	145	135	129	122	94	63	36	17	7	1	0
Placebo	109	103	98	97	93	90	88	83	81	78	77	72	69	63	61	59	54	49	35	23	15	6	1	0	0

Hazard ratio is based on unstratified Cox model

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

Study CLEE011A2404 (COMPLEEMENT-1)

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

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

Male patients enrolled in this study had a median age of 62 years (range 33 to 80). Of these patients, 39% were 65 years and older, including 10% aged 75 years and older. The male patients enrolled were Caucasian (72%), Asian (8%), and Black (3%), with 17% unknown. Nearly all male patients (97%) had an ECOG performance status of 0 or 1. The majority of male patients (97%) had 4 or less metastatic sites, which were primarily bone and visceral (69% each). Table 27 summarises the efficacy results in male patients.

Table 27 COMPLEEMENT-1 (A2402) efficacy results in male patients[1] based on investigator assessment (intent-to-treat population)

	KISQALI + Letrozole + Goserelin or Leuprolide
Overall Response Rate*,[2]	N = 32
(95% CI)	46.9 (29.1, 65.3)
Duration of 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)

5.2 Pharmacokinetic (PK) Properties

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

Absorption

Following oral administration of KISQALI to patients with advanced solid tumours or lymphomas, peak plasma levels (C_{max}) of ribociclib were achieved between 1 and 4 hours (time to reach maximum concentration, T_{max}). The geometric mean absolute bioavailability of ribociclib after a single oral dose of 600 mg was 65.8% in healthy subjects. Following repeated once daily dosing, steady-state was generally achieved after 8 days and ribociclib accumulated with a geometric mean accumulation ratio of 2.51 (range: 0.97 to 6.40).

Linearity/non-linearity

Ribociclib exhibited slightly over-proportional increases in exposure (C_{max} and AUC) across the dose range of 50 mg to 1,200 mg following both single dose and repeated doses. The observed over-proportional increases in exposure might be attributed to auto-inhibition of CYP3A4. This analysis is limited by the small sample sizes for most of the dose cohorts with a majority of the data coming from the 600 mg dose cohort.

Food effect

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

Distribution

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

Biotransformation

In vitro and *in vivo* studies indicated that ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of [^{14}C] ribociclib to humans, the primary metabolic pathways for ribociclib involved oxidation {dealkylation, C and/or N-oxygenation, oxidation (-2H)} and combinations thereof. Phase II conjugates of ribociclib Phase I metabolites involved N-acetylation, sulphation, cysteine conjugation, glycosylation and glucuronidation. Ribociclib was the major circulating drug-derived entity in plasma (44%). The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide), each representing an estimated 9%, 9%, and 8% of total radioactivity, and 22%, 20%, and 18% of ribociclib exposure respectively. Clinical activity (pharmacological and safety) of ribociclib was due primarily to the parent drug, with negligible contribution from the circulating metabolites.

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

Elimination

The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63% CV) and the geometric mean apparent oral clearance (CL/F) was 25.5 L/hr

(66% CV) at steady-state at 600 mg in patients with advanced cancer. The 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 feces, with some elimination by the renal route. In six healthy male subjects, following a single oral dose of [^{14}C] ribociclib, 92% of the total administered radioactive dose was recovered within 22 days; faeces was the major route of excretion (69%), with 23% of the dose recovered in urine. The estimated oral absorption of ribociclib was 59%.

Characteristics in Special Populations

Renal Impairment

The effect of renal function on the pharmacokinetics of ribociclib was assessed in a renal impairment study in non-cancer subjects that included 14 subjects with normal renal function (aGFR ≥90 mL/min), 8 subjects with mild renal impairment (aGFR 60 to <90 mL/min), 6 subjects with moderate renal impairment (aGFR 30 to <60 mL/min), 7 subjects with severe renal impairment (aGFR 15 to <30 mL/min),), and 3 subjects with end stage renal disease (ESRD) (aGFR <15 mL/min) at a single oral ribociclib dose of 400 mg/day

AUC_{inf} increased to 1.62-fold, 1.94-fold and 2.67-fold, and C_{max} increased to 1.80-fold, 1.79-fold and 2.30-fold in subjects with mild, moderate and severe renal impairment, relative to the exposure in subjects with normal renal function. A fold difference for subjects with ESRD was not calculated due to the small number of subjects (see section 4.2 Dose and method of administration).

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

The effect of renal function on the pharmacokinetics of ribociclib was also assessed in cancer patients. Based on a population pharmacokinetic analysis that included 438 advanced patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2), 488 patients with mild renal impairment (eGFR 60 to < 90 mL/min/1.73 m^2) and 113 patients with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m^2), mild and moderate renal impairment had no effect on the exposure of ribociclib.

In addition, in a sub-group analysis of PK data from studies in advanced cancer patients following oral administration of ribociclib 600 mg as a single dose or repeat doses (MONALEESA-7, CLEE011X2101 and CLEE011X2107), AUC and C_{max} of ribociclib following a single dose or at steady state in patients with mild or moderate renal impairment were comparable to patients with normal renal function, suggesting no clinically meaningful effect of mild or moderate renal impairment on ribociclib exposure (see section 4.2 Dose and method of administration). A sub-group analysis of PK data from early breast cancer study O12301C also showed no clinically meaningful effect of mild or moderate renal impairment on steady state ribociclib exposure following oral administration of ribociclib 400 mg as repeat doses.

Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A); in patients with advanced or metastatic breast cancer, a dose adjustment is required in patients with moderate (Child-Pugh B), or severe hepatic impairment (Child-Pugh C) and starting dose of 400 mg is recommended (see section 4.2 Dose and method of administration). Based on a PK trial in patients with hepatic impairment, mild hepatic

impairment had no effect on the exposure of ribociclib (see section 4.2 Dose and method of administration). The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.44 for C_{max}; 1.28 for AUC_{inf}) and severe (GMR: 1.32 for C_{max}; 1.29 for AUC_{inf}). Based on a population PK analysis that included 160 advanced cancer patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib, further supporting the findings from the dedicated hepatic impairment study (see section 4.2 Dose and method of administration). In early breast cancer study O12301C, no apparent increase in ribociclib exposure was observed in patients with mild hepatic impairment.

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 the 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 the safety or effectiveness of KISQALI were observed between these patients and younger patients (see section 4.2 Dose and method of administration).

Paediatric use

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

Effect of age, weight, gender and race

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

5.3 Preclinical Safety Data

Safety pharmacology

QT prolongation

In vivo cardiac safety studies in dogs demonstrated dose and concentration related QTc interval prolongation at an exposure that would be expected to be achieved in patients following the highest recommended dose of 600 mg. As well, there is potential to induce incidences of premature ventricular contractions (PVCs) at elevated exposures (approximately 5-fold the anticipated clinical C_{max}).

Phototoxicity

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

Repeat dose toxicity

Repeated-dose toxicity studies (treatment schedule of 3 weeks on/1 week off) of up to 27 weeks' duration in rats and up to 39 weeks' duration in dogs, revealed the hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated

bile) as the primary target organ of toxicity of ribociclib. Target organs associated with the pharmacological action of ribociclib in repeat-dose studies include bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation), kidney (concurrent degeneration and regeneration of tubular epithelial cells) and testes (atrophy). Besides the atrophic changes seen in the testes, which showed a trend towards reversibility, all other changes were fully reversible after a 4-week treatment-free period. Exposure to ribociclib in animals in the toxicity studies was generally less than or equal to that observed in patients receiving multiple doses of 600 mg/day (based on AUC).

Reproductive toxicity/fertility

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

In rats, reduced foetal weights accompanied by skeletal changes considered to be transitory and/or related to the lower foetal weights were noted. In rabbits, there were adverse effects on embryo-foetal development as evidenced by increased incidences of foetal abnormalities (malformations and external, visceral and skeletal variants) and foetal growth (lower foetal weights). These findings included reduced/small lung lobes and additional vessel on the aortic arch and diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes and reduced/small accessory lung lobe (30 and 60 mg/kg), extra/rudimentary thirteenth ribs and misshapen hyoid bone and reduced number of phalanges in the pollex. There was no evidence of embryo-foetal mortality.

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

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

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

Carcinogenicity

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

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

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

The mechanisms 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 in humans.

Genotoxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

18 months.

6.4 Special precautions for storage

Store at 2°C to 8°C. (Refrigerate, do not freeze.)

Store in original container.

6.5 Nature and Contents of Container

KISQALI 200 mg film-coated tablets

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

6.6 Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Novartis New Zealand Limited

PO Box 99102 Newmarket

Auckland 1149 New Zealand

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

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

9. DATE OF FIRST APPROVAL

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

10. DATE OF REVISION OF THE TEXT

6 March 2025.

Summary table of changes

Section	Summary of changes
4.1, 4.2	Early breast cancer – addition of new indication, dose and method of administration. Revision to ECG monitoring requirements.
4.4, 4.5, 4.8	Update to special warnings and precautions for use, interactions, adverse effects
5.1, 5.2	Addition of NATALEE Study
6.3	Change to storage conditions.

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