1. NAME OF THE MEDICINAL PRODUCT

Kisqali 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect

Each film-coated tablet contains 0.344 mg soya lecithin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Light greyish violet, unscored, round, curved with bevelled edges (approximate diameter: 11.1 mm), debossed with “RIC” on one side and “NVR” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Posology

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

Kisqali should be used together with 2.5 mg letrozole or another aromatase inhibitor or with 500 mg fulvestrant.

When Kisqali is used in combination with an aromatase inhibitor, the aromatase inhibitor should be taken orally once daily continuously throughout the 28-day cycle. Please refer to the Summary of Product Characteristics (SmPC) of the aromatase inhibitor for additional details.

When Kisqali is used in combination with fulvestrant, fulvestrant is administered intramuscularly on days 1, 15 and 29, and once monthly thereafter. Please refer to the SmPC of fulvestrant for additional details.

Treatment of pre- and perimenopausal women, or men, with the approved Kisqali combinations should also include an LHRH agonist in accordance with local clinical practice.

Kisqali can be taken with or without food (see section 4.5). Patients should be encouraged to take their dose at approximately the same time each day, preferably in the morning. If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

Dose modifications
Management of severe or intolerable adverse events (AEs) may require temporary dose interruption, reduction or discontinuation of Kisqali. If dose reduction is required, the recommended dose reduction guidelines are listed in Table 1.

Table 1 Recommended dose modification guidelines

	Kisqali	
	Dose	Number of 200 mg tablets
Starting dose	600 mg/day	3
First dose reduction	400 mg/day	2
Second dose reduction	200 mg*/day	1

* If further dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.

Tables 2, 3, 4, 5 and 6 summarise recommendations for dose interruption, reduction or discontinuation of Kisqali in the management of specific AEs. The clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment (see section 4.4).

Complete blood counts (CBC) should be performed before initiating treatment with Kisqali. After initiating treatment CBC should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated.

Table 2 Dose modification and management – 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)
Neutropenia	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 and reduce by 1 dose level.	Dose interruption until recovery to grade ≤2. Resume Kisqali and reduce by 1 dose level	Dose interruption until recovery to grade ≤2. Resume Kisqali and reduce by 1 dose level.

* Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)
** Grade 3 neutropenia with a single fever >38.3°C (or above 38°C for more than one hour and/or concurrent infection)
ANC = absolute neutrophil count; LLN = lower limit of normal

Liver function tests (LFTs) should be performed before initiating treatment with Kisqali. After initiating treatment LFTs should be performed every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated. If grade ≥2 abnormalities are noted, more frequent monitoring is recommended.

Table 3 Dose modification and management – 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 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 of Kisqali 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.			

* Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)
** Baseline = prior to treatment initiation
ULN = upper limit of normal

ECG should be assessed before initiating treatment with Kisqali. After initiating treatment, ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated. In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended.

Table 4 Dose modification and management – QT prolongation

ECGs with QTcF >480 msec	1. The dose should be interrupted. 2. If QTcF prolongation resolves to <481 msec, resume treatment at the next lower dose level. 3. If QTcF ≥481 msec recurs, interrupt dose until QTcF resolves to <481 msec and then resume Kisqali at the next lower dose level.
ECGs with QTcF >500 msec	If QTcF is greater than 500 msec, interrupt Kisqali until QTcF is <481 msec then resume Kisqali at next lower dose level. If QTcF interval prolongation to greater than 500 msec or greater than 60 msec change from baseline occurs in combination with torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue Kisqali.

Table 5 Dose modification and management_ILD/pneumonitis

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

*Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)
** An individualised benefit-risk assessment should be performed when considering resuming Kisqali
ILD = interstitial lung disease

Table 6 Dose modification and management – Other toxicities*

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

* Excluding neutropenia, hepatotoxicity, QT interval prolongation and ILD/pneumonitis.
** Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)

Refer to the SmPC for the co-administered aromatase inhibitor, fulvestrant or LHRH agonist for dose modification guidelines and other relevant safety information in the event of toxicity.

Dose modification for use of Kisqali with strong CYP3A4 inhibitors
Concomitant use of strong CYP3A4 inhibitors should be avoided and an alternative concomitant medicinal product with less potential to inhibit CYP3A4 inhibition should be considered. If patients must be given a strong CYP3A4 inhibitor concomitantly with ribociclib, the Kisqali dose should be reduced to 400 mg once daily (see section 4.5).

In patients who have had their dose reduced to 400 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, the dose should be further reduced to 200 mg.

In patients who have had their dose reduced to 200 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, Kisqali treatment should be interrupted.

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 to the dose used prior to the initiation of the strong CYP3A4 inhibitor after at least 5 half-lives of the strong CYP3A4 inhibitor (see sections 4.4, 4.5 and 5.2).

Special populations
Renal impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment. A starting dose of 200 mg is recommended in patients with severe renal impairment. Kisqali has not been studied in breast cancer patients with severe renal impairment (see sections 4.4, 5.1 and 5.2).

Hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). Patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) can have increased (less than 2-fold) exposure to ribociclib and the starting dose of 400 mg Kisqali once daily is recommended (see section 5.2).

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

Elderly
No dose adjustment is required in patients over 65 years of age (see section 5.2).

Method of administration

Kisqali should be taken orally once daily with or without food. The tablets should be swallowed whole and should not be chewed, crushed or split prior to swallowing. No tablet should be ingested if it is broken, cracked or otherwise not intact.

4.3 Contraindications

Hypersensitivity to the active substance or to peanut, soya or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Critical visceral disease

The efficacy and safety of ribociclib have not been studied in patients with critical visceral disease.

Neutropenia

Based on the severity of the neutropenia, treatment with Kisqali may have to be interrupted, reduced or discontinued as described in Table 2 (see sections 4.2 and 4.8).

Hepatobiliary toxicity

Liver function tests should be performed before initiating treatment with Kisqali. After initiating treatment, liver function should be monitored (see sections 4.2 and 4.8).

Based on the severity of the transaminase elevations, treatment with Kisqali may have to be interrupted, reduced or discontinued as described in Table 3 (see sections 4.2 and 4.8). Recommendations for patients who have elevated AST/ALT grade ≥ 3 at baseline have not been established.

QT interval prolongation

In study E2301 (MONALEESA-7), a QTcF interval increase >60 msec from baseline was observed in 14/87 (16.1%) patients receiving Kisqali plus tamoxifen and in 18/245 (7.3%) patients receiving Kisqali plus a non-steroidal aromatase inhibitor (NSAI). Kisqali is not recommended to be used in combination with tamoxifen (see sections 4.8 and 5.1).

ECG should be assessed before initiating treatment. Treatment with Kisqali should be initiated only in patients with QTcF values less than 450 msec. ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated (see sections 4.2 and 4.8).
Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed before initiating treatment, at the beginning of the first 6 cycles and

then as clinically indicated. Any abnormality should be corrected before initiating treatment with Kisqali and during treatment with Kisqali.

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

- with long QT syndrome;
- with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias;
- with electrolyte abnormalities.

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

Based on the observed QT prolongation during treatment, treatment with Kisqali may have to be interrupted, reduced or discontinued as described in Table 4 (see sections 4.2, 4.8 and 5.2).

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 discontinued immediately.

Interstitial lung disease/pneumonitis

ILD/pneumonitis has been reported with CDK4/6 inhibitors including reports of fatal cases. In the 3 phase III clinical studies (MONALEESA-2 [A2301], MONALEESA-7 [E2301-NSAI] and MONALEESA-3 [F2301]), ILD (any grade 0.3%, including 0.1% grade 3) was reported in the Kisqali-treated group, with no cases in the placebo-treated group. Pneumonitis (any grade 0.6%, versus 0.4%) was reported in the Kisqali- and placebo-treated groups, respectively, with no grade 3 or 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).

Based on the severity of the ILD/pneumonitis,Kisqali may require dose interruption, reduction or discontinuation as described in Table 5 (see section 4.2).

Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough and dyspnoea and dose modifications should be managed in accordance with Table 5 (see section 4.2)

Blood creatinine increase

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

CYP3A4 substrates

Ribociclib is a strong CYP3A4 inhibitor at the 600 mg dose and a moderate CYP3A4 inhibitor at the 400 mg dose. Thus, ribociclib may interact with medicinal products which are metabolised via CYP3A4, which may lead to increased serum concentrations of CYP3A4 substrates (see section 4.5). Caution is recommended in case of concomitant use with sensitive CYP3A4 substrates with a narrow therapeutic index and the SmPC of the other product should be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors.

Renal impairment

The recommended starting dose of 200 mg for patients with severe renal impairment is estimated to result in approximately 45% lower exposure compared with the standard starting dose in patients with normal renal function. The efficacy at this starting dose has not been studied. Caution should be used in patients with severe renal impairment with close monitoring for signs of toxicity (see sections 4.2 and 5.2).

Women of childbearing potential

Women of childbearing 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).

Soya lecithin

Kisqali contains soya lecithin. Patients who are hypersensitive to peanut or soya should not take Kisqali (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

Substances that may increase ribociclib plasma concentrations

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

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

If co-administration of Kisqali with a strong CYP3A4 inhibitor cannot be avoided, the dose of Kisqali should be reduced as described in section 4.2. However, there are no clinical data with these dose adjustments. Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients, therefore close monitoring for ribociclib-related AEs is recommended. In the event of ribociclib-related toxicity, the dose should be modified or treatment should be interrupted until toxicity is resolved (see sections 4.2 and 5.2). If the strong CYP3A4 inhibitor is discontinued, and after at least 5 half-lives of the CYP3A4 inhibitor (refer to the SmPC of the CYP3A4 inhibitor in question), Kisqali should be resumed at the same dose used prior to the initiation of the strong CYP3A4 inhibitor.

Physiologically-based pharmacokinetic simulations suggested that at a 600 mg dose of ribociclib, a moderate CYP3A4 inhibitor (erythromycin) may increase ribociclib steady-state C_{max} and AUC 1.2-fold and 1.3-fold, respectively. For patients who had their ribociclib dose reduced to 400 mg once daily, the increase of the steady-state C_{max} and AUC was estimated to be 1.4- and 2.1-fold, respectively. The effect at the 200 mg once-daily dose was predicted to be a 1.7- and 2.8-fold increase, respectively. No dose adjustments of ribociclib are required at initiation of treatment with mild or moderate CYP3A4 inhibitors. However, monitoring of ribociclib-related AEs is recommended.

Patients should be instructed to avoid grapefruit or grapefruit juice. These are known to inhibit cytochrome CYP3A4 enzymes and may increase the exposure to ribociclib.

Substances that may decrease ribociclib plasma concentrations

Co-administration of the strong CYP3A4 inducer rifampicin (600 mg daily for 14 days) with a single 600 mg dose of ribociclib decreased the ribociclib AUC_{inf} and C_{max} by 89% and 81%, respectively, relative to a single 600 mg ribociclib dose given alone in healthy subjects. LEQ803 C_{max} increased 1.7-fold and AUC_{inf} decreased by 27%, respectively. The concomitant use of strong CYP3A4 inducers may therefore lead to decreased exposure and consequently a risk for lack of efficacy. The concomitant use of strong CYP3A4 inducers should be avoided, including, but not limited to, phenytoin, rifampicin, carbamazepine and St John's Wort *(Hypericum perforatum)*. An alternative concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered.

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

Substances that may have plasma concentrations altered by Kisqali

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.

Co-administration of midazolam (CYP3A4 substrate) with multiple doses of Kisqali (400 mg) increased the midazolam exposure by 280% (3.80-fold) in healthy subjects, compared with administration of midazolam alone. Simulations using physiologically-based pharmacokinetic models suggested that Kisqali given at the clinically relevant dose of 600 mg is expected to increase the midazolam AUC by 5.2-fold. Therefore, in general, when ribociclib is co-administered with other medicinal products, the SmPC of the other medicinal product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors. Caution is recommended in case of concomitant use with sensitive CYP3A4 substrates with a narrow therapeutic index (see section 4.4). The dose of a sensitive CYP3A4 substrate with a narrow therapeutic index, including but not limited to alfentanil, ciclosporin, everolimus, fentanyl, sirolimus and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

Concomitant administration of ribociclib at the 600 mg dose with the following CYP3A4 substrates should be avoided: alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam.

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

Substances that are substrates of transporters

In vitro evaluations indicated that ribociclib has a potential to inhibit the activities of drug transporters P-gp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1 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.

Drug-food interactions

Kisqali can be administered with or without food (see sections 4.2 and 5.2).

Medicinal products that elevate gastric pH

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 study; however, altered ribociclib absorption was not observed in population pharmacokinetic and non–compartmental pharmacokinetic analyses.

Drug-drug interaction between ribociclib and letrozole

Data from a clinical study in patients with breast cancer and population pharmacokinetic analysis indicated no drug interaction between ribociclib and letrozole following co-administration of these medicinal products.

Drug-drug interaction between ribociclib and anastrozole

Data from a clinical study in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and anastrozole following co-administration of these medicinal products.

Drug-drug interaction between ribociclib and fulvestrant

Data from a clinical study in patients with breast cancer indicated no clinically relevant effects of fulvestrant on ribociclib exposure following co-administration of these medicinal products.

Drug-drug interaction between ribociclib and tamoxifen

Data from a clinical study in patients with breast cancer indicated that tamoxifen exposure was increased approximately 2-fold following co-administration of ribociclib and tamoxifen.

Drug-drug interactions between ribociclib and oral contraceptives

Drug-drug interaction studies between ribociclib and oral contraceptives have not been conducted (see section 4.6)

Anticipated interactions

Anti-arrhythmic medicinal products and other medicinal products that may prolong the QT interval
Co-administration of Kisqali with medicinal products with a known potential to prolong the QT interval such as anti-arrhythmic medicinal products (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine and sotalol), and other medicinal products that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, ciprofloxacin, levofloxacin, azithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and intravenous ondansetron) should be avoided (see section 4.4). Kisqali is also not recommended to be used in combination with tamoxifen (see sections 4.1, 4.4 and 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Pregnancy status should be verified prior to starting treatment with Kisqali.

Women of childbearing potential who are receiving Kisqali should use effective contraception (e.g. double-barrier contraception) during therapy and for at least 21 days after stopping treatment with Kisqali.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Based on findings in animals, ribociclib can cause foetal harm when administered to a pregnant woman (see section 5.3). Kisqali is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breast-fed infant or the effects of ribociclib on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Patients receiving Kisqali should not breast-feed for at least 21 days after the last dose.

Fertility

There are no clinical data available regarding effects of ribociclib on fertility. Based on animal studies, ribociclib may impair fertility in males of reproductive potential (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common ADRs and the most common grade 3/4 ADRs (reported at a frequency ≥20%) in the pooled dataset for which the frequency for Kisqali plus any combination exceeds the frequency for placebo plus any combination were neutropenia, infections, nausea, fatigue, diarrhoea, leukopenia, vomiting, headache, constipation, alopecia, cough, rash, back pain, anaemia, abnormal liver function tests.

The most common grade 3/4 ADRs (reported at a frequency of ≥2%) in the pooled dataset for which the frequency for Kisqali plus any combination exceeds the frequency for placebo plus any combination were neutropenia, leukopenia, abnormal liver function tests, lymphopenia, infections, back pain, anaemia, fatigue, hypophosphataemia and vomiting.

Dose reduction due to adverse events, regardless of causality, occurred in 39.5% of patients receiving Kisqali in the phase III clinical studies regardless of the combination and permanent discontinuation was reported in 8.7% of patients receiving Kisqali and any combination in the phase III clinical studies.

In addition, the safety of Kisqali in combination with letrozole was evaluated in men (n=39) in an open-label, multicenter clinical study (COMPLEEMENT-1) for the treatment of patients with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease. The median duration of exposure to Kisqali was 20.8 months (range: 0.5 to 30.6 months).
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.

Tabulated list of adverse reactions

The overall safety evaluation of Kisqali is based on the pooled dataset from 1,065 patients who received Kisqali in combination with endocrine therapy (N=582 in combination with an aromatase inhibitor and N=483 in combination with fulvestrant) and who were included in the randomised, double-blind, placebo-controlled phase III clinical studies (MONALEESA-2, MONALEESA-7 NSAI subgroup and MONALEESA-3) in HR-positive, HER2-negative advanced or metastatic breast cancer.

Additional ADRs were identified post-marketing.

The median duration of exposure to study treatment across the pooled phase III studies dataset was 19.2 months, with 61.7% patients exposed ≥12 months.

Adverse drug reactions from the phase III clinical studies (Table 7) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data).

Table 7 Adverse drug reactions observed in the three phase III clinical studies and during post-marketing experience

Adverse drug reaction	Frequency
Infections and infestations	
Infections[1]	Very common
Blood and lymphatic system disorders	
Neutropenia, leukopenia, anaemia, lymphopenia Thrombocytopenia, febrile neutropenia	Very common Common
Metabolism and nutrition disorders	
Decreased appetite Hypocalcaemia, hypokalaemia, hypophosphataemia	Very common Common
Nervous system disorders	
Headache, dizziness Vertigo	Very common Common
Eye disorders	
Lacrimation increased, dry eye	Common
Cardiac disorders	
Syncope	Common
Respiratory, thoracic and mediastinal disorders	
Cough, dyspnoea, Interstitial lung disease (ILD)/pneumonitis*	Very common Not known
Gastrointestinal disorders	
Nausea, diarrhoea, vomiting, constipation, abdominal pain[2], stomatitis, dyspepsia Dysgeusia	Very common Common
Hepatobiliary disorders	
Hepatotoxicity[3]	Common
Skin and subcutaneous tissue disorders	
Alopecia, rash[4], pruritus Dry skin, erythema, vitiligo Toxic epidermal necrolysis (TEN)*	Very common Common Not known
Musculoskeletal and connective tissue disorders	
Back pain	Very common

General disorders and administration site conditions	
Fatigue, peripheral oedema, pyrexia, asthenia Oropharyngeal pain, Dry mouth	Very common Common
Investigations	
Abnormal liver function tests[5] Blood creatinine increased, electrocardiogram QT prolonged	Very common Common
[1] Infections: urinary tract infections, respiratory tract infections, gastroenteritis, sepsis (<1%). [2] Abdominal pain: abdominal pain, abdominal pain upper. [3] Hepatotoxicity: hepatic cytolysis, hepatocellular injury, drug-induced liver injury (<1%), hepatotoxicity, hepatic failure, autoimmune hepatitis (single case). [4] Rash: rash, rash maculopapular, rash pruritic. [5] Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased. * Adverse reactions reported during post-marketing experience. These are derived from spontaneous reports for which it is not always possible to reliably establish frequency or a causal relationship to exposure to the medicinal product.	

Description of selected adverse drug reactions

Neutropenia
Neutropenia was the most frequently reported adverse drug reaction (75.4%) and a grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 62.0% of patients receiving Kisqali plus any combination in the phase III studies.

Among the patients who had grade 2, 3 or 4 neutropenia, the median time to onset was 17 days, for those patients who had an event. The median time to resolution of grade ≥3 (to normalisation or grade <3) was 12 days in the Kisqali plus any combination arms following treatment interruption and/or reduction and/or discontinuation. Febrile neutropenia was reported in about 1.7% of patients exposed to Kisqali in the phase III studies. Patients should be instructed to report any fever promptly.

Based on its severity, neutropenia was managed by laboratory monitoring, dose interruption and/or dose modification. Treatment discontinuation due to neutropenia was low (0.8%) (see sections 4.2 and 4.4).

Hepatobiliary toxicity
In the phase III clinical studies, hepatobiliary toxicity events occurred in a higher proportion of patients in the Kisqali plus any combination arms compared with the placebo plus any combination arms (27.3% versus 19.6%, respectively), with more grade 3/4 adverse events reported in the patients treated with Kisqali plus any combination (13.2% versus 6.1%, respectively). Increases in transaminases were observed. Grade 3 or 4 increases in ALT (11.2% versus 1.7%) and AST (7.8% versus 2.1%) were reported in the Kisqali and placebo arms, respectively. Concurrent elevations in ALT or AST greater than three times the upper limit of normal and total bilirubin greater than two times the upper limit of normal, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 patients (4 patients in Study A2301 [MONALEESA-2], whose levels recovered to normal within 154 days and 2 patients in Study F2301 [MONALEESA-3], whose levels recovered to normal in 121 and 532 days, respectively, after discontinuation of Kisqali). There were no such cases reported in Study E2301 (MONALEESA-7).

Dose interruptions and/or adjustments due to hepatobiliary toxicity events were reported in 12.3% of Kisqali plus any combination treated patients, primarily due to ALT increased (7.9%) and/or AST increased (7.3%). Discontinuation of treatment with Kisqali plus any combination due to abnormal liver function tests or hepatotoxicity occurred in 2.4% and 0.3% of patients respectively (see sections 4.2 and 4.4).

In the phase III clinical studies, 70.9% (90/127) of grade 3 or 4 ALT or AST elevation events occurred within the first 6 months of treatment. Among the patients who had grade 3 or 4 ALT/AST elevation, the median time to onset was 92 days for the Kisqali plus any combination arms. The median time to resolution (to normalisation or grade ≤2) was 21 days in the Kisqali plus any combination arms.

QT prolongation

In study E2301 (MONALEESA-7), the observed mean QTcF increase from baseline was approximately 10 msec higher in the tamoxifen plus placebo subgroup compared with the NSAI plus placebo subgroup, suggesting that tamoxifen alone had a QTcF prolongation effect which can contribute to the QTcF values observed in the Kisqali plus tamoxifen group. In the placebo arm, a QTcF interval increase of >60 msec from baseline occurred in 6/90 (6.7%) patients receiving tamoxifen and in no patients receiving a NSAI (see section 5.2). A QTcF interval increase of >60 msec from baseline was observed in 14/87 (16.1%) patients receiving Kisqali plus tamoxifen and in 18/245 (7.3%) patients receiving Kisqali plus a NSAI. Kisqali is not recommended to be used in combination with tamoxifen (see section 5.1).

In the phase III clinical studies 9.3% of patients in the Kisqali plus aromatase inhibitor or fulvestrant arms and 3.5% in the placebo plus aromatase inhibitor or fulvestrant arms had at least one event of QT interval prolongation (including ECG QT prolonged and syncope). Review of ECG data showed 15 patients (1.4%) had >500 msec post-baseline QTcF value, and 61 patients (5.8%) had a >60 msec increase from baseline in QTcF intervals. There were no reported cases of torsade de pointes. Dose interruptions/adjustments were reported in 2.9% of Kisqali plus aromatase inhibitor or fulvestrant treated patients due to electrocardiogram QT prolonged and syncope.

The analysis of ECG data showed 55 patients (5.2%) and 12 patients (1.5%) with at least one >480 msec post-baseline QTcF for the Kisqali plus aromatase inhibitor or fulvestrant arms and the placebo plus aromatase inhibitor or fulvestrant arms, respectively. Amongst the patients who had QTcF prolongation >480 msec, the median time to onset was 15 days regardless of the combination and these changes were reversible with dose interruption and/or dose reduction (see sections 4.2, 4.4 and 5.2).

Patients with renal impairment

In the three pivotal studies, 341 patients with mild renal impairment and 97 patients with moderate renal impairment were treated with ribociclib. No patient with severe renal impairment was enrolled (see section 5.1). There was a correlation between the degree of renal impairment at baseline and blood creatinine values during the treatment. Slightly increased rates of QT prolongation and thrombocytopenia were observed in patients with mild or moderate renal impairment. For monitoring and dose adjustment recommendations for these toxicities see sections 4.2. and 4.4.

4.9 Overdose

There is only limited experience with reported cases of overdosage with Kisqali. In the event of an overdose, symptoms such as nausea and vomiting may occur. In addition, haematological (e.g. neutropenia, thrombocytopenia) toxicity and possible QTc prolongation may occur. General supportive care should be initiated in all cases of overdosage as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE42

Mechanism of action

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

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

In vivo studies using patient-derived oestrogen receptor-positive breast cancer xenograft model combinations of ribociclib and antioestrogens (i.e. letrozole) resulted in superior tumour growth inhibition with sustained tumour regression and delayed tumour regrowth after stopping dosing compared to each substance alone. Additionally, *in vivo* antitumour activity of ribociclib in combination with fulvestrant was assessed in immune-deficient mice bearing the ZR751 ER+ human breast cancer xenografts and the combination with fulvestrant resulted in complete tumour growth inhibition.

When tested in a panel of breast cancer cell lines with known ER status, ribociclib demonstrated to be more efficacious in ER+ breast cancer cell lines than in the ER- ones. In the preclinical models tested so far, intact pRb was required for ribociclib activity.

Cardiac electrophysiology

Serial, triplicate 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. A pharmacokinetic-pharmacodynamic analysis included a total of 997 patients treated with ribociclib at doses ranging from 50 to 1200 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval. The estimated QTcF mean change from baseline for 600 mg Kisqali in combination with NSAI or fulvestrant was 22.0 msec (90% CI: 20.56, 23.44) and 23.7 msec (90% CI: 22.31, 25.08), respectively at the geometric mean C_{max} at steady-state compared to 34.7 msec (90% CI: 31.64, 37.78) in combination with tamoxifen (see section 4.4).

Clinical efficacy and safety

Study CLEE011A2301 (MONALEESA-2)

Kisqali was evaluated in a randomised, double-blind, placebo-controlled, multicentre phase III clinical study in the treatment of postmenopausal women with hormone receptor-positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease in combination with letrozole versus letrozole alone.

A total of 668 patients were randomised in a 1:1 ratio to receive either Kisqali 600 mg and letrozole (n=334) or placebo and letrozole (n=334), stratified according to the presence of liver and/or lung metastases (Yes [n=292 (44%)]) versus No [n=376 (56%)]). Demographics and baseline disease characteristics were balanced and comparable between study arms. Kisqali was given orally at a dose of 600 mg daily for 21 consecutive days followed by 7 days off treatment in combination with letrozole 2.5 mg once daily for 28 days. Patients were not allowed to cross over from placebo to Kisqali during the study or after progression of disease.

Patients enrolled in this study had a median age of 62 years (range 23 to 91). 44.2% patients were older than 65 years, including 69 patients older than 75 years. The patients included were Caucasian (82.2%), Asian (7.6%), and Black (2.5%). All patients had an ECOG performance status of 0 or 1. In the Kisqali arm 43.7% of patients had received chemotherapy in the neoadjuvant or adjuvant setting and 52.4% had received antihormonal therapy in the neoadjuvant or adjuvant setting prior to study entry. 34.1% of patients were *de novo*. 20.7% of patients had bone-only disease and 59.0% of patients had visceral disease. Patients with prior (neo)adjuvant therapy with anastrozole or letrozole must have completed this therapy at least 12 months before study randomisation.

The primary endpoint for the study was met at the planned interim analysis conducted after observing 80% of targeted progression-free survival (PFS) events using Response Evaluation Criteria in Solid Tumours (RECIST v1.1), based on the investigator assessment in the full population (all randomised patients), and confirmed by a blinded independent central radiological assessment.

The efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Kisqali plus letrozole compared to patients receiving placebo plus letrozole in the full analysis set (hazard ratio of 0.556, 95% CI: 0.429, 0.720, one sided stratified log-rank test p-value 0.00000329) with clinically meaningful treatment effect.

The global health status/QoL data showed no relevant difference between the Kisqali plus letrozole arm and the placebo plus letrozole arm.

A more mature update of efficacy data (02 January 2017 cut-off) is provided in Tables 8 and 9.

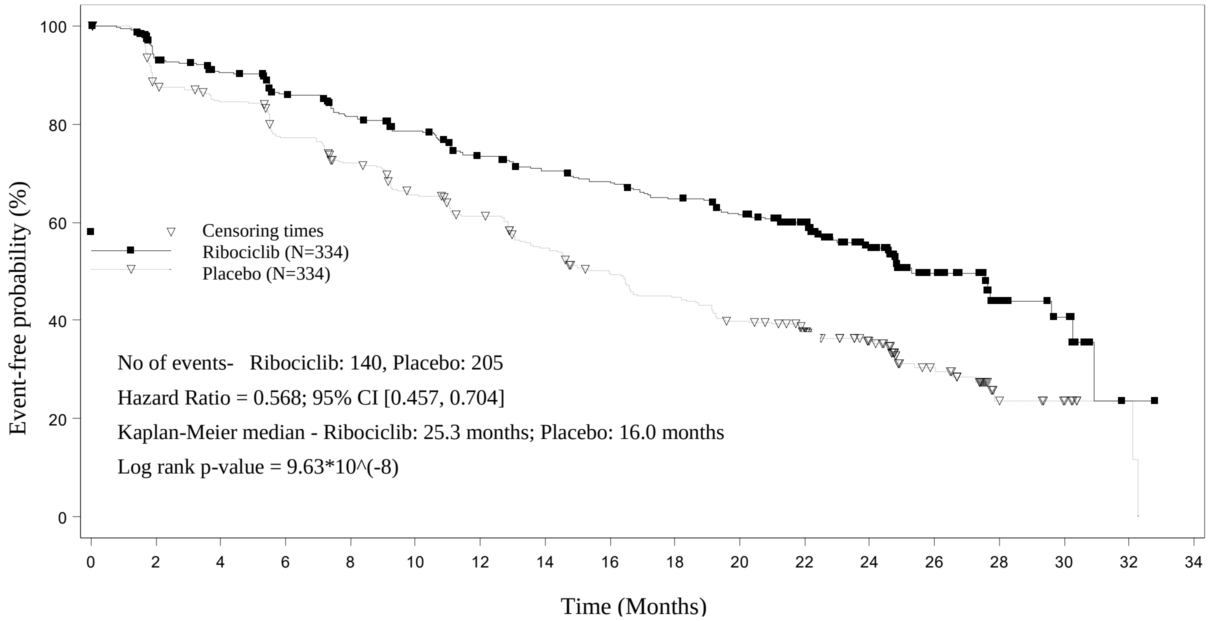
Median PFS was 25.3 months (95% CI: 23.0, 30.3) for ribociclib plus letrozole treated patients and 16.0 months (95% CI: 13.4, 18.2) for patients receiving placebo plus letrozole. 54.7% of patients receiving ribociclib plus letrozole were estimated to be progression-free at 24 months compared with 35.9% in the placebo plus letrozole arm.

There was no statistically significant difference in overall survival (OS) between the Kisqali plus letrozole arm and the placebo plus letrozole arm (HR 0.746 [95% CI: 0.517, 1.078]). OS data remain immature.

Table 8 MONALEESA-2 - Efficacy results (PFS) based on investigator radiological assessment (02 January 2017 cut-off)

	Updated analysis (02 January 2017 cut-off)	
	Kisqali plus letrozole N=334	**Placebo plus letrozole N=334**
Progression-free survival		
Median PFS [months] (95% CI)	25.3 (23.0-30.3)	16.0 (13.4-18.2)
Hazard ratio (95% CI)	0.568 (0.457-0.704)	
p-value[a]	9.63×10^{-8}	
CI=confidence interval; N=number of patients; [a]p-value is obtained from the one-sided stratified log-rank test.		

Figure 1 MONALEESA-2 - Kaplan-Meier plot of PFS based on investigator assessment02 January 2017 cut-off)



Number of patients still at risk

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

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

Updated results for overall response and clinical benefit rates are displayed in Table 9.

Table 9 MONALEESA-2 - Efficacy results (ORR, CBR) based on investigator assessment(02 January 2017 cut-off)

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

[a] ORR: Overall response rate = proportion of patients with complete response + partial response
[b] CBR: Clinical benefit rate = proportion of patients with complete response + partial response (+ stable disease or non-complete response/Non-progressive disease ≥24 weeks)
[c] p-values are obtained from one-sided Cochran-Mantel-Haenszel chi-square test

Study CLEE011E2301 (MONALEESA-7)
Kisqali was evaluated in a randomised, double-blind, placebo-controlled, multicentre phase III clinical study in the treatment of pre- and perimenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer in combination with a NSAI or tamoxifen plus goserelin versus placebo in combination with a NSAI or tamoxifen plus goserelin. Patients in MONALEESA-7 had not received prior endocrine treatment in the advanced breast cancer setting.

A total of 672 patients were randomised in a 1:1 ratio to receive either Kisqali 600 mg plus NSAI/tamoxifen plus goserelin (n=335) or placebo plus NSAI/tamoxifen plus goserelin (n=337), stratified according to: the presence of liver and/or lung metastases (Yes [n=344 (51.2%)] versus No [n=328 (48.8%)]), prior chemotherapy for advanced disease (Yes [n=120 (17.9%)] versus No [n=552 (82.1%)]), and endocrine combination partner (NSAI and goserelin [n=493 (73.4%)] versus tamoxifen and goserelin [n=179 (26.6%)]). Demographics and baseline disease characteristics were balanced and comparable between study arms. Kisqali was given orally at a dose of 600 mg daily for 21 consecutive days followed by 7 days off treatment in combination with NSAI (letrozole 2.5 mg or anastrozole 1 mg) or tamoxifen (20 mg) orally once daily for 28 days, and goserelin (3.6 mg) subcutaneously every 28 days, until disease progression or unacceptable toxicity. Patients were not allowed to cross over from placebo to Kisqali during the study or after disease progression. Switching the endocrine combination partners was also not permitted.

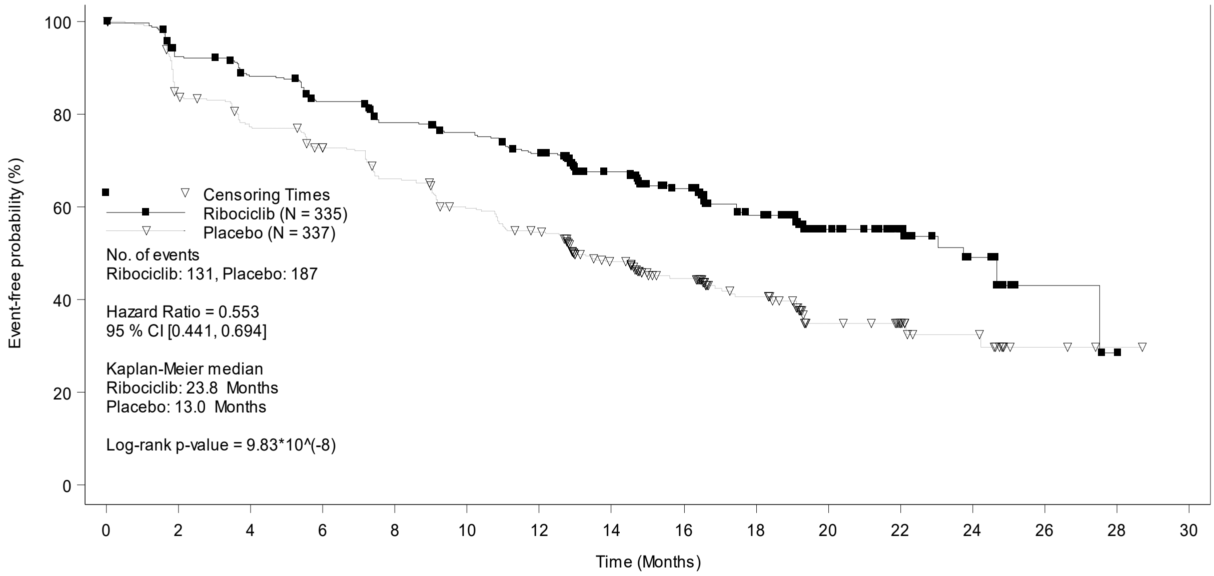
Patients enrolled in this study had a median age of 44 years (range 25 to 58) and 27.7% of patients were younger than 40 years old. The majority of patients included were Caucasian (57.7%), Asian (29.5%) or Black (2.8%) and nearly all patients (99.0%) had a baseline ECOG performance status of 0 or 1. Prior to study entry, of these 672 patients, 14% of patients had received prior chemotherapy for metastatic disease, 32.6% of patients had received chemotherapy in the adjuvant and 18.0% in the neoadjuvant setting; 39.6% had received endocrine therapy in the adjuvant setting and 0.7% in the neoadjuvant setting. In study E2301 40.2% of patients had *de novo* metastatic disease, 23.7% had bone-only disease, and 56.7% had visceral disease.

The study met the primary endpoint at the primary analysis conducted after 318 progression-free survival (PFS) events based on the investigator assessment using RECIST v1.1 criteria in the full analysis set (all randomised patients). The primary efficacy results were supported by PFS results based on blinded independent central radiological assessment. The median follow-up time at the time of primary PFS analysis was 19.2 months.

In the overall study population, the efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Kisqali plus NSAI/tamoxifen plus goserelin compared to patients receiving placebo plus NSAI/tamoxifen plus goserelin (hazard ratio of 0.553, 95% CI: 0.441, 0.694, one-sided stratified log-rank test p-value 9.83×10^{-8}) with clinically meaningful treatment effect. Median PFS was 23.8 months (95% CI: 19.2, NE) for Kisqali plus NSAI/tamoxifen plus goserelin treated patients and 13.0 months (95% CI: 11.0, 16.4) for patients receiving placebo plus NSAI/tamoxifen plus goserelin.

Distribution of PFS is summarised in the Kaplan-Meier curve for PFS in Figure 2.

Figure 2 MONALEESA-7 - Kaplan-Meier plot of PFS in overall population based on investigator assessment



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Ribociclib	335	301	284	264	245	235	219	178	136	90	54	40	20	3	1	0
Placebo	337	273	248	230	207	183	165	124	94	62	31	24	13	3	1	0

The results for PFS based on the blinded independent central radiological assessment of a randomly selected subset of approximately 40% of randomised patients were supportive of the primary efficacy results based on the investigator's assessment (hazard ratio of 0.427; 95% CI: 0.288, 0.633).

At the time of the primary PFS analysis overall survival, data were not mature with 89 (13%) of deaths (HR 0. 916 [95% CI: 0.601, 1.396]).

Overall response rate (ORR) per investigator assessment based on RECIST v1.1 was higher in the Kisqali arm (40.9%; 95% CI: 35.6, 46.2) compared to the placebo arm (29.7%; 95% CI: 24.8, 34.6, p=0.00098). The observed clinical benefit rate (CBR) was higher in Kisqali arm (79.1%; 95% CI: 74.8:83.5) compared to placebo arm (69.7%; 95% CI: 64.8:74.6, p=0.002).

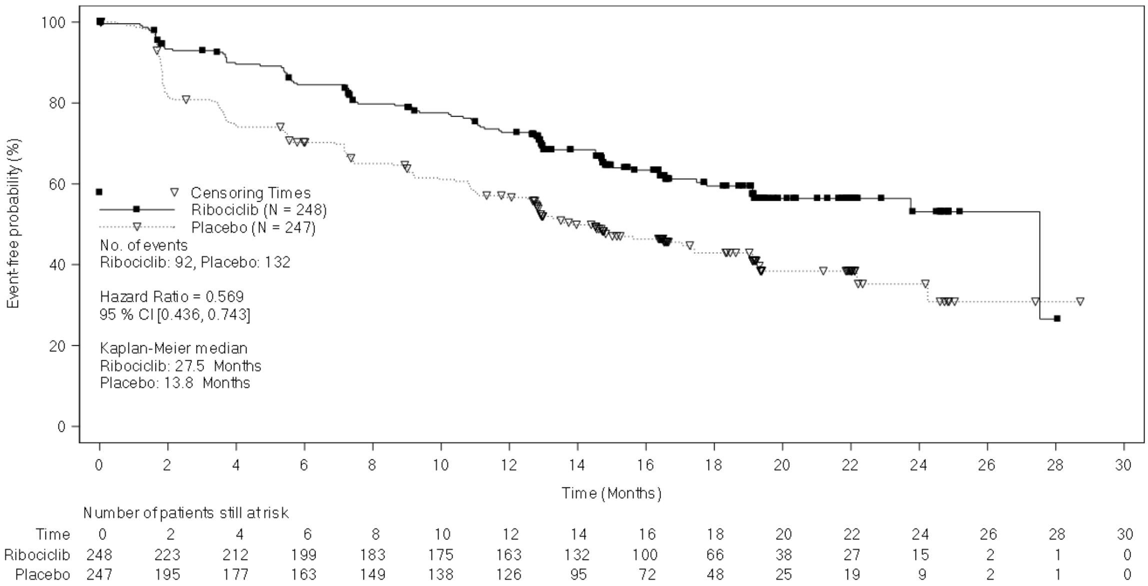
In the pre-specified subgroup analysis of 495 patients who had received Kisqali or placebo in combination with NSAI plus goserelin, the median PFS was 27.5 months (95% CI: 19.1, NE) in the Kisqali plus NSAI subgroup and 13.8 months (95% CI: 12.6, 17.4) in the placebo plus NSAI subgroup [HR: 0.569; 95% CI: 0.436, 0.743]. Efficacy results are summarised in Table 10 and the Kaplan-Meier curves for PFS are provided in Figure 3.

Table 10 MONALEESA-7 - Efficacy results (PFS) in patients who received NSAI

	Kisqali plus NSAI plus goserelin N=248	**Placebo plus NSAI plus goserelin N=247**
Progression free survival[a]		
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)	

CI=confidence interval; N=number of patients; NE = Not estimable.
[a] – PFS based on investigator radiological assessment

Figure 3 MONALEESA-7 – Kaplan-Meier plot of PFS based on investigator assessment in patients who received NSAI



Efficacy results for overall response rate (ORR) and clinical benefit rate (CBR) per investigator assessment based on RECIST v1.1 are provided in Table 11.

Table 11 MONALEESA-7 - Efficacy results (ORR, CBR) based on investigator assessment in patients who received NSAI

Analysis	Kisqali plus NSAI plus goserelin (%, 95% CI)	Placebo plus NSAI plus goserelin (%, 95% CI)
Full analysis set	**N=248**	**N=247**
Overall response rate (ORR)[a]	39.1 (33.0, 45.2)	29.1 (23.5, 34.8)
Clinical benefit rate (CBR)[b]	80.2 (75.3, 85.2)	67.2 (61.4, 73.1)
Patients with measurable disease	**N=192**	**N=199**
Overall response rate[a]	50.5 (43.4, 57.6)	36.2 (29.5, 42.9)
Clinical benefit rate[b]	81.8 (76.3, 87.2)	63.8 (57.1, 70.5)
[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)		

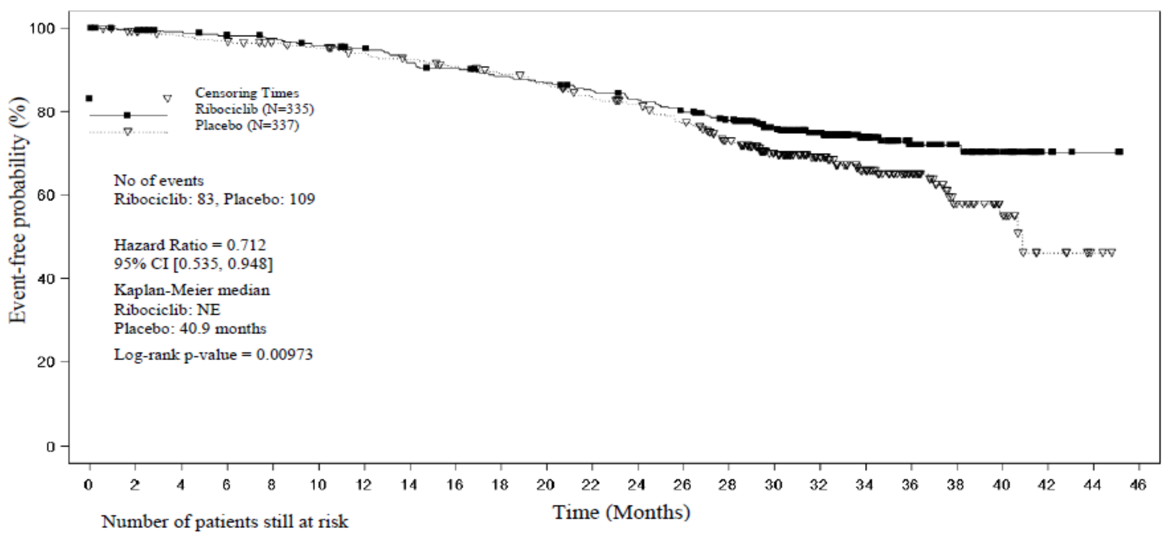
Results in the Kisqali plus NSAI subgroup were consistent across subgroups of age, race, prior adjuvant/ neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone-only metastatic disease.
A more mature update of overall survival data (30 November 2018 cut-off) is provided in Table 12 and Figures 4 and 5.

In the second OS analysis the study met its key secondary endpoint demonstrating a statistically significant improvement in OS.

Table 12 MONALEESA-7 - Efficacy results (OS)

	Updated analysis (30 November 2018 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; [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 (interactive response technology).		

Figure 4 MONALEESA-7 – Kaplan-Meier plot of final OS analysis (30-Nov-2018 cut-off)

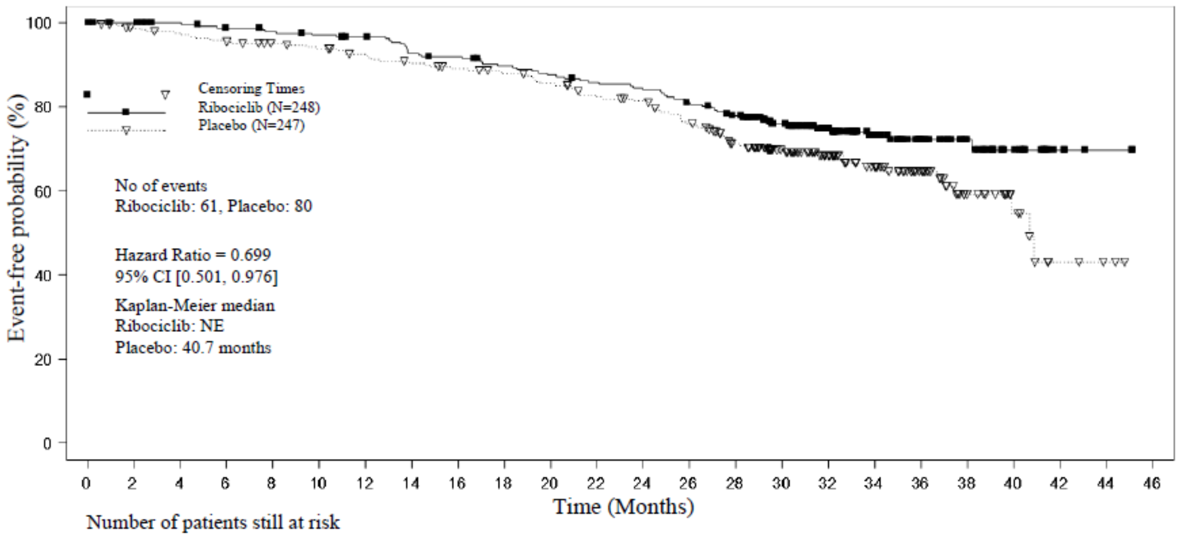


Number of patients still at risk

Time (months)	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 5 MONALEESA-7 – Kaplan-Meier plot of final OS analysis in patients who received NSAI (30-Nov-2018 cut-off)



Number of patients still at risk

Time (months)	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, the probability of progression on next-line therapy or death (PFS2) in patients who received prior ribociclib in the study was lower compared to patients in the placebo arm with an HR of 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) for the ribociclib arm. Similar results were observed for the NSAI subgroup, with an HR of 0.660 (95% CI: 0.503, 0.868) and a median PFS2 of 32.3 months (95% CI: 26.9, 38.3) in the placebo arm versus not reached (95% CI: 39.4, NE) in the ribociclib arm.

Study CLEE011F2301 (MONALEESA-3)
Kisqali was evaluated in a 2:1 randomised double-blind, placebo-controlled, multicentre phase III clinical study in 726 postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer who had received no or only one line of prior endocrine treatment, in combination with fulvestrant versus fulvestrant alone.

Patients enrolled in this study had a median age of 63 years (range 31 to 89). 46.7% of patients were of age 65 years and older, including 13.8% patients of age 75 years and older. The patients included were Caucasian (85.3%), Asian (8.7%) or Black (0.7%) 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 whom 19.1% had *de novo* metastatic disease). Prior to study entry 42.7% of patients had received chemotherapy in the adjuvant and 13.1% in the neoadjuvant setting, while 58.5% had received endocrine therapy in the adjuvant and 1.4% in the neoadjuvant setting and 21% had received prior endocrine therapy in the advanced breast cancer setting. In study F2301 21.2% had bone-only disease and 60.5% had visceral disease.

Primary analysis
The study met the primary endpoint at the primary analysis conducted after 361 progression-free survival (PFS) events based on the investigator assessment and using RECIST v1.1 criteria in the full analysis set (all randomised patients, 03 November 2017 cut-off). The median follow-up time at the time of primary PFS analysis was 20.4 months.

The primary efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Kisqali plus fulvestrant compared to patients receiving placebo plus fulvestrant in the full analysis set (hazard ratio of 0.593, 95% CI: 0.480, 0.732, one-sided stratified log-rank test p-value

4.1×10^{-7}), with an estimated 41% reduction in relative risk of progression or death in favour of the Kisqali plus fulvestrant arm.

The primary efficacy results were supported by a random central audit of 40% imaging subset by a blinded independent central radiological assessment (hazard ratio of 0.492; 95% CI: 0.345, 0.703).

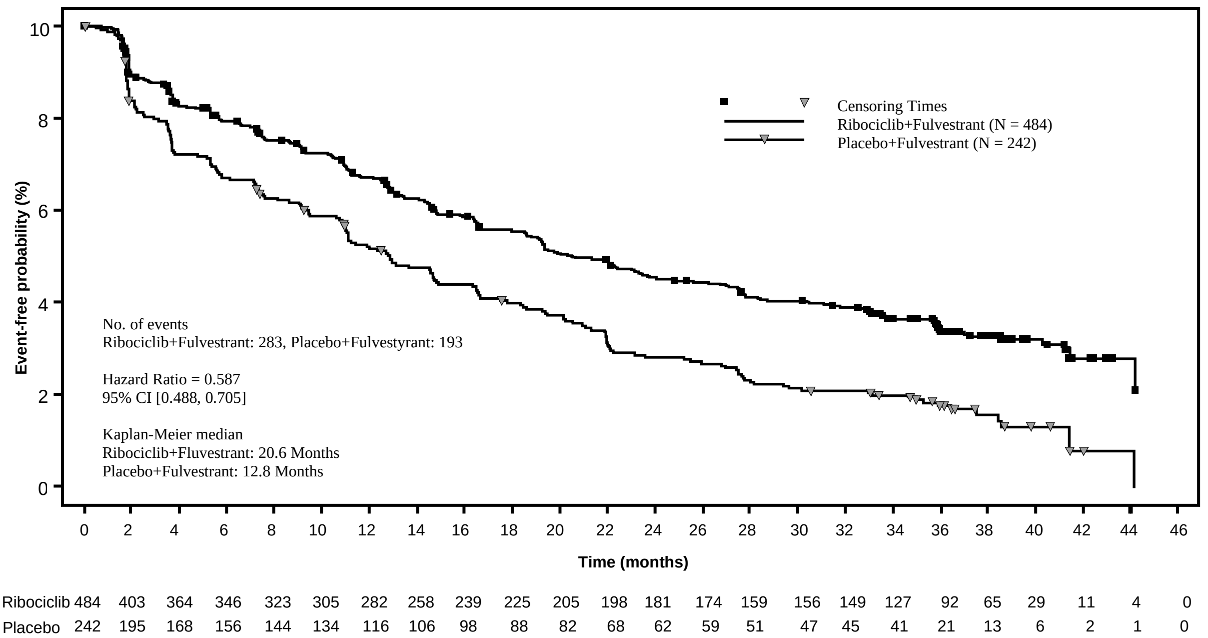
A descriptive update of PFS was performed at the time of the second OS interim analysis, and the updated PFS results on the overall population and the subgroups based on prior endocrine therapy are summarised in Table 13 and the Kaplan-Meier curve is provided in Figure 6.

Table 13 MONALEESA-3 - (F2301) - Updated PFS results based on investigator assessment (03-Jun-2019 cut-off)

	Kisqali plus fulvestrant N=484	Placebo plus fulvestrant N=242
Progression free survival overall study population		
Number of events- n [%]	283 (58.5)	193 (79.8)
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)	
First-line setting subgroup[a]	**Kisqali plus fulvestrant n=237**	**Placebo plus fulvestrant 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 early relapse subgroup[b]	**Kisqali plus fulvestrant n=237**	**Placebo plus fulvestrant 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
[a] patients with *de novo* advanced breast cancer with no prior endocrine therapy, and patients who relapsed after 12 months of (neo)adjuvant endocrine therapy completion.
[b] patients whose disease relapsed during adjuvant therapy or within 12 months of (neo)adjuvant endocrine therapy completion, and patients who had progression after one line of endocrine therapy for advanced disease.

Figure 6 MONALEESA-3 (F2301) – Kaplan-Meier plot of PFS based on investigator assessment (FAS) (03-Jun-2019 cut-off)



Efficacy results for overall response rate (ORR) and clinical benefit rate (CBR) per investigator assessment based on RECIST v1.1 are provided in Table 14.

Table 14 MONALEESA-3 - Efficacy results (ORR, CBR) based on investigator assessment (03-Nov-2017 cut-off)

Analysis	**Kisqali plus fulvestrant (%, 95% CI)**	**Placebo plus fulvestrant (%, 95% CI)**
Full analysis set	**N=484**	**N=242**
Overall response rate (ORR)[a]	32.4 (28.3, 36.6)	21.5 (16.3 , 26.7)
Clinical benefit rate (CBR)[b]	70.2 (66.2 , 74.3)	62.8 (56.7, 68.9)
Patients with measurable disease	**N=379**	**N=181**
Overall response rate[a]	40.9 (35.9 , 45.8)	28.7 (22.1, 35.3)
Clinical benefit rate[b]	69.4 (64.8 , 74.0).	59.7 (52.5 , 66.8)

[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)

Hazard ratios based on pre-specified subgroup analysis of the patients treated with Kisqali plus fulvestrant showed consistent benefit across different subgroups including age, prior treatment (early or advanced), prior adjuvant/neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone-only metastatic disease.

OS Analysis
In the pre-specified second OS interim analysis, the study met its secondary endpoint, demonstrating a statistically significant improvement in OS.

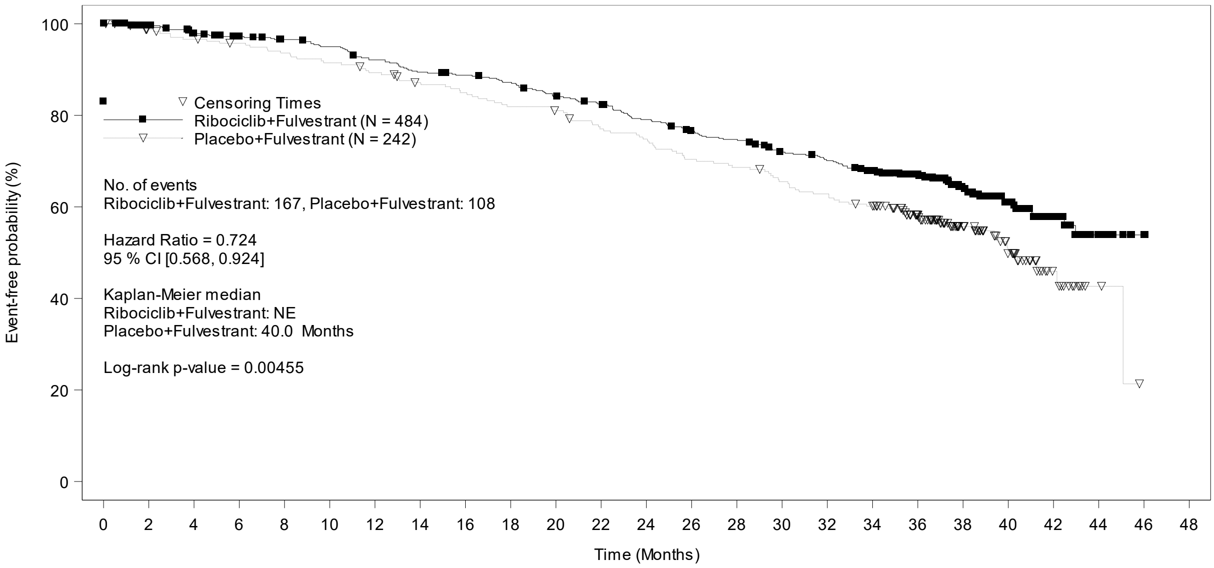
The results from this final OS analysis on the overall study population and the subgroups analysis are provided in Table 15 and Figure 7.

Table 15 MONALEESA-3 (F2301) efficacy results (OS) (03-Jun-19 cut-off)

	Kisqali plus fulvestrant	**Placebo plus fulvestrant**
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)[a]	0.724 (0.568, 0.924)	
p value[b]	0.00455	
First line setting subgroup	**n=237**	**n=128**
Number of events - n [%]	63 (26.6)	47 (36.7)
HR (95% CI)[c]	0.700 (0.479, 1.021)	
Second-line setting or early relapse subgroup	**n=237**	**n=109**
Number of events - n [%]	102 (43.0)	60 (55.0)
HR (95% CI)[c]	0.730 (0.530, 1.004)	

NE = Not estimable
[a]Hazard ratio is obtained from the Cox PH model stratified by lung and/or liver metastasis, previous endocrine therapy.
[b]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.
[c] Hazard ratio is obtained from the unstratified Cox PH model.

Figure 7 MONALEESA-3 (F2301) Kaplan Meier plot of OS (full analysis set [FAS]) (03-Jun-2019 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

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)

Kisqali was evaluated in an open-label, single arm, multicenter 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, 38.5% were 65 years and older, including 10.3% aged 75 years and older. The male patients enrolled were Caucasian (71.8%), Asian (7.7%), and Black (2.6%), with 17.9% unknown. Nearly all male patients (97.4%) 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 (69.2% each). Table 16 summarizes the efficacy results in male patients.

Table 16 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)

Elderly patients
Of all patients who received Kisqali in studies MONALEESA-2 and MONALEESA-3, representative proportions of patients were ≥65 years and ≥75 years of age (see section 5.1). No overall differences in safety or effectiveness of Kisqali were observed between these patients and younger patients (see section 4.2).

Patients with renal impairment
In the three pivotal studies (MONALEESA-2, MONALEESA-3 and MONALEESA-7), 510 (53.8%) patients with normal renal function, 341 (36%) patients with mild renal impairment and 97 (10.2%) patients with moderate renal impairment were treated with ribociclib. No patient with severe renal impairment was enrolled. PFS results were consistent in patients with mild and moderate renal impairment who received ribociclib at the starting dose of 600 mg as compared to those with normal renal function. The safety profile was generally consistent across renal cohorts (see section 4.8).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Kisqali in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Absorption

The absolute bioavailability of ribociclib is not known.

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

Food effect
Compared to the fasted state, oral administration of a single 600 mg dose of ribociclib film-coated tablets with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib.

Distribution

Binding of ribociclib to human plasma proteins *in vitro* was approximately 70% and was independent of concentration (10 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 apparent volume of distribution at steady state (Vss/F) was 1090 L based on population pharmacokinetic analysis.

Biotransformation

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

Ribociclib was extensively metabolised, with unchanged drug accounting for 17.3% and 12.1% of the dose in faeces and urine, respectively. Metabolite LEQ803 was a significant metabolite in excreta and represented approximately 13.9% and 3.74% of the administered dose in faeces and urine, respectively. Numerous other metabolites were detected in both faeces and urine in minor amounts (≤2.78% of the administered dose).

Elimination

The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63% CV) and the geometric mean apparent oral clearance (CL/F) was 25.5 l/hr (66% CV) at steady state at 600 mg in patients with advanced cancer. The geometric mean apparent plasma terminal half-life ($T_{1/2}$) of ribociclib ranged from 29.7 to 54.7 hours and the geometric mean CL/F of ribociclib ranged from 39.9 to 77.5 l/hr at 600 mg across studies in healthy subjects.

Ribociclib and its metabolites are eliminated mainly via faeces, with a small contribution of the renal route. In 6 healthy male subjects, following a single oral dose of [^{14}C] ribociclib, 91.7% of the total administered radioactive dose was recovered within 22 days; faeces was the major route of excretion (69.1%), with 22.6% of the dose recovered in urine.

Linearity/non-linearity

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

Special populations

Renal impairment
The effect of renal function on the pharmacokinetics of ribociclib was assessed in a renal impairment study that included 14 healthy subjects with normal renal function (absolute Glomerular Filtration Rate [aGFR] ≥90 ml/min), 8 subjects with mild renal impairment (aGFR 60 to <90 ml/min), 6 subjects with moderate renal impairment (aGFR 30 to<60 ml/min), 7 subjects with severe renal impairment (aGFR 15 to <30 ml/min) and 3 subjects with end-stage renal disease (ESRD) (aGFR <15 ml/min) at a single ribociclib dose of 400 mg.

AUC_{inf} increased 1.6-fold, 1.9-fold and 2.7-fold and C_{max} increased 1.8-fold, 1.8-fold and 2.3-fold in subjects with mild, moderate and severe renal impairment, relative to the exposure in subjects with normal renal function. Since the efficacy and safety studies of ribociclib included a large proportion of patients with mild renal impairment (see section 5.1), data from the subjects with moderate or severe renal impairment in the renal impairment study were also compared with pooled data for the subjects with normal renal function and mild renal impairment. Compared to the pooled data for the subjects with normal renal function and mild renal impairment, AUC_{inf} increased 1.6-fold and 2.2-fold and C_{max} increased 1.5-fold and 1.9-fold in subjects with moderate and severe renal impairment, respectively. A

fold difference for subjects with ESRD was not calculated due to the small number of subjects., but results indicate a similar or somewhat larger increase in ribociclib exposure compared to subjects with severe renal impairment.
The effect of renal function on the pharmacokinetics of ribociclib was also assessed in cancer patients included in efficacy and safety studies where patients were given the 600 mg start dose (see section 5.1). In a sub-group analysis of pharmacokinetic data from studies in cancer patients following oral administration of 600 mg ribociclib as a single dose or repeat doses, AUC_{inf} and C_{max} of ribociclib in patients with mild (n=57) or moderate (n=14) renal impairment were comparable to the AUC_{inf} and C_{max} in patients with normal renal function (n=86) suggesting no clinically meaningful effect of mild or moderate renal impairment on ribociclib exposure.

Hepatic impairment
Based on a pharmacokinetic study in non-cancer subjects with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib (see section 4.2). 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}) hepatic impairment (see section 4.2).

Based on a population pharmacokinetic analysis that included 160 breast cancer patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib, further supporting the findings from the dedicated hepatic impairment study. Ribociclib has not been studied in breast cancer patients with moderate or severe hepatic impairment.

Effect of age, weight, gender and race
Population pharmacokinetic analysis showed that there are no clinically relevant effects of age, body weight or gender on the systemic exposure of ribociclib that would require a dose adjustment. Data on differences in pharmacokinetics due to race are too limited to draw conclusions.

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 CYP2C9, CYP2C19 and CYP3A4 via PXR. Therefore, Kisqali is unlikely to affect substrates of these enzymes. *In vitro* data are not sufficient to exclude a potential of ribociclib to induce CYP2B6 via CAR.

Effect of transporters on ribociclib
Ribociclib is a substrate for P-gp *in vitro*, but based on mass balance data inhibition of P-gp or BCRP is unlikely to affect ribociclib exposure at therapeutic doses. Ribociclib is not a substrate for hepatic uptake transporters OATP1B1, OATP1B3 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 P-gp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1 and BSEP. Ribociclib did not inhibit OAT1, OAT3 or MRP2 at clinically relevant concentrations *in vitro*.

5.3 Preclinical safety data

Safety pharmacology

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

Repeated-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 any dose up to 300 mg/kg/day (which is likely at an exposure lower than or equal to patients' clinical exposure at the highest recommended dose of 600 mg/day based on AUC).

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

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

Genotoxicity

Genotoxicity studies in bacterial *in vitro* systems and in mammalian *in vitro* and *in vivo* systems with and without metabolic activation did not reveal any evidence for a genotoxic potential of ribociclib.

Carcinogenesis

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

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

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

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

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

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

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Crospovidone type A
Low-substituted hydroxypropylcellulose
Magnesium stearate
Colloidal anhydrous silica

Film coating

Iron oxide black (E172)
Iron oxide red (E172)
Soya lecithin (E322)
Polyvinyl alcohol (partially hydrolysed)
Talc
Titanium dioxide (E171)
Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PCTFE (polyvinylchloride/polychlorotrifluoroethylene) or PA/alu/PVC (polyamide/aluminium/polyvinylchloride) blisters containing 14 or 21 film-coated tablets.

Unit packs containing 21, 42 or 63 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis (Thailand) Limited

8. MARKETING AUTHORISATION NUMBER(S)

1C 15019/61 (N)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 April 2018

10. DATE OF REVISION OF THE TEXT

May 2022