KISQALI™ (ribociclib)

200 mg Film-coated tablets

Kisqali™

KISQALI™ 200 mg film-coated tablets

Description and composition

Pharmaceutical form

Film-coated tablet 200 mg

Light greyish violet, unscored, round, curved with beveled edges, debossed with "RIC" on one side and "NVR" on the other side.

Active substance

Each tablet containing 200 mg of ribociclib, as the succinate salt.

Excipients

Tablet core: Microcrystalline cellulose; low-substituted hydroxypropylcellulose; crospovidone (Type A); colloidal silicon dioxide; magnesium stearate.

Coating material: Polyvinyl alcohol (partially hydrolysed); titanium dioxide (E171); iron oxide black (E172); iron oxide red (E172); talc: lecithin (soy) (E322); xanthan gum.

Indications

Kisqali is indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

Kisqali is also indicated in combination with fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on endocrine therapy.

Dosage and administration

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

Dosage regimen

General target population

The recommended dose of Kisqali is 600 mg (3 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. Kisqali can be taken with or without food (see section Interactions).

When co-administered with Kisqali, refer to the full prescribing information for the recommended dose of the aromatase inhibitor to be used.

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

When co-administered with Kisqali, the recommended dose of fulvestrant is 500mg administered intramuscularly on days 1, 15 and 29, and once monthly thereafter. Please refer to the full prescribing information of fulvestrant.

Pre/peri-menopausal women treated with the combination of Kisqali plus an aromatase inhibitor should also receive a luteinizing hormone-releasing hormone (LHRH) agonist according to local clinical practice standards.

Dose modifications

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption, reduction, or discontinuation of Kisqali. If dose reduction is required, the recommended dose reduction guidelines for adverse drug reactions (ADRs) are listed in Table 1.

Table 1 Recommended Dose Modification Guidelines for Adverse Drug Reactions

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

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

Tables 2, 3, 4 and 5 summarize 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 sections Warnings and precautions, Adverse drug reactions).

Table 2 Dose Modification and Management for Hematological Toxicities

Neutropenia	**Grade 1 or 2** (ANC 1,000/mm^3 – <LLN)	**Grade 3** (ANC 500 - <1,000/mm^3)	**Grade 3 febrile* neutropenia**	**Grade 4** (ANC <500/mm^3)
	No dose adjustment is required.	Interrupt Kisqali until recovery to Grade ≤2. Resume Kisqali at the same dose level. If toxicity recurs at Grade 3, interrupt Kisqali dose until recovery to Grade ≤2, then resume Kisqali at the next lower dose level.	Interrupt Kisqali until recovery of neutropenia to Grade ≤2. Resume Kisqali at the next lower dose level.	Interrupt Kisqali until recovery to Grade ≤2. Resume Kisqali at the next lower dose level.
	Perform Complete Blood Counts (CBC) before initiating treatment with Kisqali. After initiating treatment with Kisqali, monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated.			

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

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

Table 3 Dose Modification and Management for Hepatobiliary toxicity

AST and/or ALT elevations from baseline*, without increase in total bilirubin above 2 x ULN	**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)**
	No dose adjustment is required.	Baseline at <Grade 2: Interrupt Kisqali until recovery to ≤baseline Grade, then resume Kisqali at same dose level. If Grade 2 recurs, resume Kisqali at next lower dose level. --- Baseline at Grade 2: No dose interruption.	Interrupt 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.			
Perform Liver Function Tests (LFTs) before initiating treatment with Kisqali. After initiating treatment with Kisqali, monitor LFTs 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 observed, more frequent monitoring is recommended.
***Baseline = prior to treatment initiation.* *Grading according to CTCAE Version 4.03 CTCAE=Common Terminology Criteria for Adverse Events.*

Table 4 Dose Modification and Management for QT prolongation

ECGs with QTcF >480 msec	1. Interrupt the Kisqali dose 2. If QTcF prolongation resolves to <481 msec, resume Kisqali at the next lower dose level; 3. If QTcF ≥481 msec recurs, interrupt the Kisqali dose until QTcF resolves to <481 msec; and then resume Kisqali at next lower dose level
ECGs with QTcF >500 msec	If QTcF greater than 500 msec: Interrupt Kisqali until QTcF reaches <481 msec then resume Kisqali at next lower dose level. If QTcF interval prolongation is greater than 500 msec or shows a greater than 60 msec change from baseline in combination with Torsade de Pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue Kisqali.
Assess ECG prior to initiation of treatment. After initiating treatment with Kisqali, repeat ECG 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 5 Dose Modification and Management for 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.	Interrupt Kisqali dose 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 hematological toxicities, 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

Concomitant use of Kisqali should be avoided with strong CYP3A inhibitors and an alternative concomitant medication should be considered with less potential for CYP3A inhibition. If a strong CYP3A inhibitor must be co-administered, the Kisqali dose should be reduced to 200 mg once daily If the strong inhibitor is discontinued, the Kisqali dose should be changed (after at least 5 half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor *(*see sections Warnings and precautions, Interactions and Clinical pharmacology).

Special populations

Renal impairment

Based on population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild or moderate renal impairment (see section Clinical pharmacology).

Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment, a starting dose of 200 mg is recommended. Kisqali has not been studied in breast cancer patients with severe renal impairment. (see section Clinical pharmacology).

Hepatic impairment

Based on a hepatic impairment study in healthy subjects and non-cancer subjects with impaired hepatic function, no dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). A dose adjustment is required in patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) and the starting dose of 400mg is recommended. Kisqali has not been studied in breast cancer patients with moderate and severe hepatic impairment (see section Clinical pharmacology).

Pediatric patients

There are limited data in pediatric patients and the safety and efficacy of Kisqali in this population has not been established.

Geriatric patients (65 years of age or older)

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

Method of administration

Kisqali should be taken 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). Tablets that are broken, cracked, or otherwise not intact should not be ingested.

Contraindications

Kisqali is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Neutropenia

In the 3 phase III clincial studies (MONALEESA-2 (A2301), MONALEESA-7 (E2301-NSAI) and MONALEESA-3 (F2301)), neutropenia was the most frequently reported adverse drug reaction (73.7%) and a Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 58.4% of patients receiving Kisqali plus any combination in the phase III clinical studies.

Among the patients who had Grade 2, 3 or 4 neutropenia in the phase III clinical studies, the median time to Grade 2, 3 or 4 neutropenia was 16 days. The median time to resolution of Grade ≥3 (to normalization or Grade <3) was 12 days in the Kisqali plus any combination treatment group. Severity of neutropenia is concentration dependent. Febrile neutropenia was reported in 1.4% of patients exposed to Kisqali in the phase III clinical studies. Physicians should inform patients to promptly report any fever (see section Adverse drug reactions).

A complete blood count (CBC) should be performed before initiating therapy with Kisqali. 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.

Based on the severity of the neutropenia, Kisqali may require dose interruption, reduction, or discontinuation as described in Table 2 Dose Modification and Management for Neutropenia (see section Dosage and administration).

In patients who develop Grade 1 or 2 neutropenia, no Kisqali dose adjustment is required. In patients who develop Grade 3 neutropenia without fever, the Kisqali dose should be interrupted until recovery to Grade ≤2 and then Kisqali should be resumed at the same dose level. If Grade 3 neutropenia without fever recurs, Kisqali dose should be interrupted until recovery, then Kisqali should be resumed at the next lower dose level.

In patients who develop Grade 3 febrile neutropenia (ANC 500 to <1,000/mm^3 with a single episode of fever >38.3°C (or) above 38°C for more than one hour and/or concurrent infection), or patients who develop Grade 4 neutropenia, Kisqali dose should be interrupted until recovery to Grade ≤2, then Kisqali should be resumed at the next lower dose level.

Hepatobiliary toxicity

In the phase III clinical studies, increases in transaminases were observed.

Grade 3 or 4 increases in ALT (9.7% vs. 1.5%) and AST (6.7% vs. 2.1%) were reported in the Kisqali plus any combination and placebo plus any combination arms respectively. Grade 4 increases in ALT (1.9% vs. 0.1%) and AST (1.1% vs. 0.1%) were reported in the Kisqali plus any combination treatment and placebo plus any combination treatment arms respectively

In the phase III clinical studies, 83.2% (89/107) of Grade 3 or 4 ALT or AST elevation events occurred within the first 6 months of treatment (see section Adverse drug reactions). 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 85 days for the Kisqali plus any combination treatment group . The median time to resolution (to normalization or Grade ≤2) was 22 days in the Kisqali plus any combination treatment group.

Concurrent elevations of ALT or AST greater than three times the upper limit of normal and of total bilirubin greater than two times the upper limit of normal, with normal alkaline phosphatase levels, and in the absence of cholestasis occurred in 6 patients (4 patients in Study A2301, whose levels recovered to normal within 154 days; and 2 patients in Study F2301, whose levels recovered to normal within 121 and 532 days, respectively, after discontinuation of Kisqali). There were no such cases reported in Study E2301.

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

Based on the severity of the transaminase elevations, Kisqali may require dose interruption, reduction, or discontinuation as described in Table 3 Dose modification and management – Hepatobiliary toxicity (see section Dosage and administration). Recommendations for patients who have elevated AST/ALT grade ≥3 at baseline have not been established.

The following dose modification and management guidelines are provided for hepatobiliary toxicity.:

- No Kisqali dose adjustment is required for Grade 1 (AST and/or ALT elevations of >ULN to 3 x ULN).
- In patients with a baseline of Grade <2 (AST and/or ALT elevations of <ULN to 3 x ULN), if Grade 2 (AST and/or ALT elevations of >3 to 5 x ULN) develops, Kisqali dose should be interrupted until values return to ≤baseline grade, then Kisqali should be resumed at the same dose level. If Grade 2 recurs, then Kisqali should be resumed at next lower dose level.
- In patients with baseline at Grade 2 (AST and/or ALT elevations of >3 to 5 x ULN), if Grade 2 continues, no Kisqali dose interruption is required.
- In patients who develop Grade 3 (ALT and/or AST elevations of >5 to 20 x ULN), Kisqali dose should be interrupted until values return to ≤baseline Grade, then Kisqali should be resumed at next lower dose level. If Grade 3 recurs, Kisqali should be discontinued.
- In patients who develop Grade 4 (ALT and/or AST elevations of >20 x ULN), Kisqali should be discontinued.

The following dose modification and management guidelines are provided for patients with concurrent elevations in AST and/or ALT together with an increase in total bilirubin (TB) increase, in the absence of cholestasis:

- In patients who develop total bilirubin >2 x ULN along with ALT and/or AST >3 x ULN, irrespective of baseline Grade, Kisqali should be discontinued.

QT interval prolongation

In the phase III clinical studies, in patients with advanced or metastatic breast cancer who received the Kisqali plus any combination partners, review of ECG data showed 14 patient (1.3%) had >500 msec post-baseline QTcF value , and 59 patients (5.6%) had a >60 msec QTcF interval increase from baseline. There were no reported cases of Torsade de Pointes.

In E2301 (MONALEESA-7), the observed mean QTcF increase from baseline was approximately more than 10 msecs higher in the tamoxifen plus placebo subgroup compared with NSAI plus placebo subgroup, suggesting that tamoxifen had a QTcF prolongation effect which can contribute to the QTcF observed in the ribociclib plus tamoxifen group (see section Clinical pharmacology – Cardiac electrophysiology). In the placebo arm, an increase of >60 msec from baseline occurred in 6/90 (6.7%) of the patients receiving tamoxifen, and in no patients receiving an NSAI. An increase of >60 msec from baseline in the QTcF interval was observed in 14/87 (16.1%) patients receiving ribociclib plus tamoxifen and in 18/245 (7.3%) of the patients receiving ribociclib plus an NSAI. Ribociclib is not indicated for concomitant use with tamoxifen.

The ECG should be assessed prior to initiation of treatment. Treatment with Kisqali should be initiated only in patients with QTcF values less than 450 msec . The ECG should be repeated at approximately Day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated.

Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorous, and magnesium) should be performed prior to initiation of treatment, at the beginning of the first 6 cycles, and then as clinically indicated. Any abnormality should be corrected before and during Kisqali therapy.

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

- long QT syndrome

- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias
- electrolyte abnormalities

Kisqali should be avoided with medicinal products known to prolong the QTc interval and/or strong CYP3A inhibitors as this may lead to clinically meaningful prolongation of the QTcF interval (see sections Dosage and administration, Interactions and Clinical pharmacology). Based on the findings in E2301, Kisqali is not recommended for use in combination with tamoxifen (see section Clinical pharmacology)

Based on the observed QT prolongation during treatment, Kisqali may require dose interruption, reduction, or discontinuation as described in Table 4 Dose Modification and Management-QT prolongation (see sections Dosage and administration, Adverse drug reactions and Clinical pharmacology).

In the event of ECGs with QTcF >480 msec:

- The treatment with Kisqali should be interrupted.
- If QTcF prolongation is resolved to <481, Kisqali should be resumed at the next lower dose level.
- If QTcF ≥481 msec recurs, Kisqali dose should be interrupted until QTcF resolves to <481 msec, then Kisqali should be resumed at the next lower dose level.

In the event of ECGs with QTcF >500 msec:

- The treatment with Kisqali should be interrupted.
- If QTcF prolongation resolved to <481 msec, Kisqali should be resumed at next lower dose level (see sections Dosage and administration, Adverse drug reactions and Clinical pharmacology).
- If QTcF interval prolongation to greater than 500 msec or has a greater than 60 msec change from baseline in combination with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, Kisqali should be permanently discontinued.

Reproductive toxicity

Based on animal findings and its mechanism of action, Kisqali can cause fetal harm when administered to a pregnant woman. Women of reproductive potential should be advised to use effective contraception during therapy with Kisqali and for at least 21 days after the last dose (see sections Pregnancy, lactation, females and males of reproductive potential).

Adverse drug reactions

Summary of the safety profile

The overall safety profile of Kisqali reported below is based on the pooled data set of 1065 patients who received Kisqali in combination with endocrine therapy (N=582 in combination with aromatase inhibitor, and N=483 in combination with fulvestrant), in double blind, placebo controlled phase III clinical studies (MONALEESA-2, MONALEESA-7-NSAI arm, MONALEESA-3) in HR-positive, HER2-negative advanced or metastatic breast cancer.

The median duration of exposure to Kisqali treatment across the pooled phase II studies dataset was 16.53 months with 61.7% patients exposed for ≥12 month.

Dose reductions due to adverse events (AEs), regardless of causality occurred in 37.3% of patients receiving Kisqali in phase III clinical studies regardless of the combination and in 3.4% of patients receiving placebo. Permanent discontinuations due to adverse events was reported in 7.0% of patients receiving Kisqali plus any combination and 2.9% in patients receiving placebo plus any combination. The most common AEs leading to permanent discontinuation of both Kisqali with any combination treatment partner were ALT increased (2.0%), AST increased (1.4%) and vomiting (0.8%).

In the pooled analysis of three phase III studies, on treatment deaths, were reported in 21 cases (2.0%) of patients treated with Kisqali plus any combination vs 16 cases (2.0%) of patients treated with placebo plus any combination treatment. Excluding the most frequent cause of death disease progression, three treatment related cause of deaths were reported in patients treated with Kisqali plus any combination treatment. Causes of death were acute respiratory distress syndrome (1 patient, 0.1%), acute respiratory failure (1 patient, 0.1%), and sudden death (in the setting of Grade 3 hypokalaemia and Grade 2 QT prolongation) (1 patient, 0.1%). The most common adverse drug reactions (ADRs) across the pooled phase III studies (reported at a frequency ≥20% and for which the rate for Kisqali exceeds the frequency for placebo) were infections, neutropenia, leukopenia, headache, cough, nausea, fatigue, diarrhoea, vomiting, constipation, alopecia and rash.

The most common Grade 3/4 ADRs in the pooled data (reported at a frequency ≥2% and for which the frequency for Kisqali exceeds the frequency for placebo) were infections, neutropenia, leukopenia, anaemia, abnormal liver function tests, lymphopenia, hypophosphataemia and vomiting.

Tabulated summary of adverse drug reactions based on pooled dataset from 3 phase III clinical studies

ADRs from the phase-III clinical studies (Table 6) 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).

Table 6 Adverse drug reactions based on pooled dataset from 3 phase III clinical studies

Adverse drug reactions	Kisqali N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kisqali N=1065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category All Grades
Infections and infestations					
Infections[1]	434 (40.8)	245 (30.0)	41 (3.8)	8 (1.0)	Very common
Blood and lymphatic system disorders					
Neutropenia	785 (73.7)	41 (5.0)	624 (58.6)	11 (1.3)	Very common
Leukopenia	314 (29.5)	24 (2.9)	165 (15.5)	4 (0.5)	Very common
Anaemia	200 (18.8)	51 (6.2)	30 (2.8)	12 (1.5)	Very common
Lymphopenia	95 (8.9)	18 (2.2)	56 (5.3)	5 (0.6)	Common

Adverse drug reactions	Kisqali N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kisqali N=1065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category All Grades
Thrombocytopenia	95 (8.9)	11 (1.3)	8 (0.8)	1 (0.1)	Common
Febrile neutropenia	15 (1.4)	2 (0.2)	15 (1.4)	2 (0.2)	Common
Eye disorders					
Lacrimation increased	59 (5.5)	9 (1.1)	0	0	Common
Dry eye	54 (5.1)	18 (2.2)	0	0	Common
Metabolism and nutrition disorders					
Decreased appetite	163 (15.3)	101 (12.3)	6 (0.6)	1 (0.1)	Very common
Hypocalcaemia	45 (4.2)	14 (1.7)	11 (1.0)	0	Common
Hypokalaemia	33 (3.1)	21 (2.6)	12 (1.1)	5 (0.6)	Common
Hypophosphatemia	34 (3.2)	11 (1.3)	22 (2.1)	7 (0.9)	Common
Nervous system disorders					
Headache	253 (23.8)	177 (21.6)	5 (0.5)	4 (0.5)	Very common
Dizziness	125 (11.7)	83 (10.1)	1 (0.1)	0	Very common
Vertigo	46 (4.3)	10 (1.2)	1 (0.1)	0	Common
Cardiac disorders					
Syncope	19 (1.8)	9 (1.1)	12 (1.1)	7 (0.9)	Common
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	132 (12.4)	81 (9.9)	15 (1.4)	7 (0.9)	Very common
Cough	218 (20.5)	132 (16.1)	0	0	Very common
Musculoskeletal and connective tissue disorders					
Back pain	211 (19.8)	153 (18.7)	20 (1.9)	7 (0.9)	Very common
Gastrointestinal disorders					
Nausea	475 (44.6)	219 (26.8)	15 (1.4)	4 (0.5)	Very common
Diarrhoea	317 (29.8)	176 (21.5)	16 (1.5)	5 (0.6)	Very common
Vomiting	284 (26.7)	128 (15.6)	21 (2.0)	3 (0.4)	Very common
Constipation	253 (23.8)	129 (15.8)	8 (0.8)	0	Very common
Stomatitis	122 (11.5)	53 (6.5)	3 (0.3)	1 (0.1)	Very common
Abdominal pain[2]	182 (17.1)	107 (13.1)	14 (1.3)	4 (0.5)	Very common
Dysgeusia	71 (6.7)	36 (4.4)	1 (0.1)	0	Common
Dyspepsia	88 (8.3)	35 (4.3)	1 (0.1)	0	Common
Hepatobiliary disorders					
Hepatotoxicity[3]	19 (1.8)	7 (0.9)	15 (1.4)	4 (0.5)	Common
Skin and subcutaneous tissue disorders					

Adverse drug reactions	Kisqali N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kisqali N=1065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category All Grades
Alopecia	256 (24.0)	97 (11.9)	0	0	Very common
Rash[4]	227 (21.3)	70 (8.6)	10 (0.9)	0	Very common
Pruritus	177 (16.6)	48 (5.9)	3 (0.3)	0	Very common
Erythema	43 (4.0)	8 (1.0)	2 (0.2)	0	Common
Dry skin	88 (8.3)	18 (2.2)	0	0	Common
Vitiligo	16 (1.5)	0	0	0	Common
General disorders and administration site conditions					
Fatigue	348 (32.7)	249 (30.4)	20 (1.9)	4 (0.5)	Very common
Peripheral oedema	147 (13.8)	71 (8.7)	1 (0.1)	0	Very common
Asthenia	145 (13.6)	103 (12.6)	7 (0.7)	3 (0.4)	Very common
Pyrexia	139 (13.1)	52 (6.4)	4 (0.4)	0	Very common
Dry mouth	74 (6.9)	44 (5.4)	1 (0.1)	0	Common
Oropharyngeal pain	67 (6.3)	33 (4.0)	0	0	Common
Investigations					
Abnormal liver function tests[5]	184 (17.3)	66 (8.1)	93 (8.7)	16 (2.0)	Very common
Blood creatinine increased	67 (6.3)	15 (1.8)	4 (0.4)	0	Common
Electrocardiogram QT prolonged	69 (6.5)	13 (1.6)	13 (1.2)	2 (0.2)	Common

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

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

[3]Hepatotoxicity: hepatocellular injury, drug induced liver injury, 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.

Laboratory abnormalities

Clinically relevant abnormalities of routine haematological or biochemical laboratory values from the dataset of 3 pooled phase III studies are presented in Table 7.

Table 7 Laboratory abnormalities based on pooled dataset from phase III clinical studies

Laboratory abnormalities	Kisqali N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kisqali N=1065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category (all Grades)
Hematological parameters					
Leukocyte count decreased	1002 (94.1)	243 (29.7)	336 (31.5)	8 (1.0)	Very common
Neutrophil count decreased	985 (92.5)	207 (25.3)	622 (58.4)	13 (1.6)	Very common
Haemoglobin decreased	698 (65.5)	309 (37.8)	36 (3.4)	13 (1.6)	Very common
Lymphocyte count decreased	649 (60.9)	209 (25.6)	163 (15.3)	30 (3.7)	Very common
Platelet count decreased	332 (31.2)	73 (8.9)	12 (1.1)	3 (0.4)	Very common
Biochemical parameters					
Alanine aminotransferase increased	466 (43.8)	291 (35.6)	103 (9.7)	12 (1.5)	Very common
Aspartate aminotransferase increased	498 (46.8)	308 (37.7)	71 (6.7)	17 (2.1)	Very common
Creatinine increased	409 (38.4)	107 (13.1)	7 (0.7)	1 (0.1)	Very common
Phosphorous decreased	165 (15.5)	66 (8.1)	44 (4.1)	8 (1.0)	Very common
Potassium decreased	95 (8.9)	68 (8.3)	17 (1.6)	9 (1.1)	Common
Gamma glutamyl transferase increased	357 (48.8)	220 (45.1)	53 (7.3)	47 (9.6)	Very common
Albumin decreased	112 (10.5)	45 (5.5)	1 (0.1)	1 (0.1)	Very common
Glucose serum decreased	184 (17.3)	100 (12.2)	1 (0.1)	1 (0.1)	Very common
Bilirubin increased	54 (5.1)	44 (5.4)	9 (0.8)	9 (1.1)	Common

Description of selected adverse drug reactions

Neutropenia

Neutropenia was most frequently reported by laboratory findings in the phase III studies. Based on its severity, neutropenia was managed by laboratory monitoring, dose interruption and/or dose modification. Treatment discontinuation due to neutropenia was low (0.8%) in patients receiving Kisqali plus any combination partner (see sections Dosage and administration and Warnings and precautions).

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 vs the placebo plus any combination arms (23.2% vs 16.5%, respectively), with more Grade 3/4 adverse events reported in the patients treated with Kisqali plus any combination treatment (11.4% vs. 5.4%, respectively). Dose interruptions and/or adjustments due to hepatobiliary toxicity events were reported in 10.4% of Kisqali treated patients, primarily due to ALT increased (6.9%) and/or AST increased (6.1%). Discontinuation of treatment with Kisqali due to abnormal

liver function tests, hepatotoxicity were 2.3% and 0.4% respectively (see section Warnings and precautions).

QT prolongation

In the phase III clinical studies, 8.4% of patients in the Kisqali arm and 3.2% in the placebo arm had at least one event of QT interval prolongation (including ECG QT prolonged, syncope). Dose interruptions-adjustments were reported in 2.3% of Kisqali treated patients due to electrocardiogram QT prolonged and syncope.

A central analysis of ECG data (average of triplicate) showed 52 patients (4.9%) and 11 patient (1.4%) with at least one post-baseline QTcF >480 m sec for the Kisqali treatment arm and the placebo arm respectively. Among the patients who had QTcF prolongation of >480 m secs, the median time to onset is 15 days, regardless of combination and these changes were reversible with dose interruption and/or dose reduction (see sections Dosage and administration, Warnings and precautions and Clinical pharmacology).

Interactions

Ribociclib is primarily metabolized by CYP3A and is a time-dependent inhibitor of CYP3A *in vivo*. Therefore, medicinal products which can influence CYP3A enzyme activity may alter the pharmacokinetics of ribociclib.

Medicinal products that may increase ribociclib plasma concentrations

Co-administration of a strong CYP3A4 inhibitor (ritonavir) increased ribociclib exposure in healthy subjects by 3.21-fold. Concomitant use of strong CYP3A inhibitors including but not limited to clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole (see section Warnings and precautions) should be avoided. Alternative concomitant medications with less potential to inhibit CYP3A should be considered and patients should be monitored for ADRs (see sections Dosage and administration, Warnings and precautions and Clinical Pharmacology).

If co-administration of Kisqali with a strong CYP3A inhibitor cannot be avoided, Kisqali dose should be reduced to 200mg. However, there are no clinical data with this dose adjustment (see section Dosage and administration). If the strong inhibitor is discontinued, the Kisqali dose should be resumed (after at least 5 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 patients, therefore close monitoring for ADRs is recommended. In the event of Kisqali related toxicity, dose should be modified (see section Dosage and administration), or treatment should be interrupted until toxicity is resolved (see sections Dosage and administration and Clinical Pharmacology).

Patients should be instructed to avoid grapefruits or grapefruit juice, all of which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib.

Medicinal products that may decrease ribociclib plasma concentrations

Co-administration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of ribociclib in healthy subjects by 89%. Avoid concomitant use of strong CYP3A inducers, including but not limited to phenytoin, rifampin, carbamazepine and St John's Wort *(Hypericum perforatum)*. An alternate

concomitant medication with no or minimal potential to induce CYP3A should be considered (see sections Warnings and precautions and Clinical pharmacology).

Medicinal products that may have their plasma concentrations altered by ribociclib

Co-administration of midazolam (CYP3A4 substrate) with multiple doses of Kisqali (400mg) increased the midazolam exposure by 280% (3.80-fold) in healthy subjects, compared with administration of midazolam alone. Simulations using physiologically-based PK (PBPK) models suggested that Kisqali given at the clinically relevant dose of 600mg is expected to increase the midazolam AUC by 5.2-fold. Therefore caution is recommended when Kisqali is administered with CYP3A substrates with a narrow therapeutic index. 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 has the potential to increase their exposure (see section Clinical pharmacology).

Co-administration of caffeine (CYP1A2 substrate) with multiple doses of Kisqali (400 mg) increased 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) (see section Clinical pharmacology).

Medicinal products that are substrates of transporters

In vitro evaluations indicated that ribociclib has a low potential to inhibit the activities of drug transporters P-gp, OAT1/3, OATP1B1/B3, and OCT1 at clinically relevant concentrations. Ribociclib may inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations (see section Clinical pharmacology).

Drug-food interactions

Kisqali can be administered with or without food (see section Dosage and method of administration).

Compared to the fasted state, oral administration of a single 600mg dose of Kisqali film-coated tablet with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib (C_{max} GMR: 1.00; 90% CI: 0.898, 1.11; AUC_{inf} GMR: 1.06; 90% CI: 1.01, 1.12 (see section Clinical pharmacology).

Gastric pH elevating medications

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

Anticipated interactions

Anti-arrhythmic medicines and other medicinal products that may prolong the QT interval: Co-administration of Kisqali should be avoided with medicinal products with known potential to prolong the QT interval such as anti-arrhythmic medicines. Concomitant use of anti-arrhythmic medicines (including but not limited to amiodarone, disopyramide, procainamide, quinidine, and sotalol), 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 ondansetron (i.v), should be avoided (see section Warnings and precautions). Kisqali is not recommended for use in combination with tamoxifen (See section Warnings and precautions).

Pregnancy, lactation, females and males of reproductive potential

Pregnancy

Risk summary

Based on animal data and its mechanism of action, it is possible that Kisqali can cause fetal harm when administered to a pregnant woman.

The patient should be advised of the risk to a fetus if Kisqali is used during pregnancy or if the patient becomes pregnant while taking this medicinal product.

There are no adequate and well-controlled studies in pregnant women. Reproductive studies in rats and rabbits have demonstrated ribociclib induced embryotoxicity, fetotoxocity and teratogenicity. Following prenatal exposure, increased incidences of post-implantation loss and reduced fetal weights were observed in rats and ribociclib was teratogenic in rabbits as evidenced by increased incidences of fetal abnormalities (malformations and external, visceral and skeletal variants) at exposures lower than or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600mg/day based on AUC. There are no available human data informing the drug-associated risk.

Data

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ribociclib up to 1,000mg/kg/day and 60mg/kg/day, respectively, during the period of organogenesis.

In rats, 1,000mg/kg/day was lethal in the maternal animals. At 300mg/kg/day, a slight, non-adverse trend towards reduced maternal body weight gain and fetal toxicity evidenced by reduced fetal weights accompanied by skeletal changes were considered to be transitory and/or related to the lower fetal weights. There were no effects upon embryo-fetal mortality or adverse effects on fetal morphology at 50 or 300mg/kg/day. The no-observed-adverse-effect level (NOAEL) for maternal toxicity was considered to be 300mg/kg/day. The no-observed-effect-level (NOEL) for embryo-fetal development was considered to be 50mg/kg/day.

In rabbits at doses ≥30mg/kg/day, there were adverse effects on embryo-fetal development as evidenced by increased incidences of fetal abnormalities (malformations and external, visceral and skeletal variants) and fetal growth (lower fetal 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 60mg/kg), extra/rudimentary 13^{th} ribs and misshapen hyoid bone and reduced number of phalanges in the pollex. There was no evidence of embryo-fetal mortality. The no-observed-effect level (NOEL) for maternal toxicity was considered to be at least 30mg/kg/day and the NOEL for the embryo-fetal development was 10mg/kg/day.

At 300mg/kg/day in rats and 30mg/kg/day in rabbits, the maternal systemic exposure (AUC) were 13,800ng*hr/mL and 36,700ng*hr/mL, lower than or at 1.5 times, the one achieved in patients at the highest recommended dose of 600mg/day.

Lactation

Risk summary

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breastfed child or the effects of ribociclib on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse reactions in nursing infants from Kisqali, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is recommended that women taking Kisqali should not breastfeed for at least 21 days after the last dose.

Data

Animal data

In lactating rats administered a single dose of 50mg/kg, exposure to ribociclib was 3.56 fold higher in milk than in maternal plasma.

Females and males of reproductive potential

Based on animal studies, Kisqali can cause fetal harm when administered to a pregnant woman (see section Non clinical safety data).

Pregnancy testing

For females of reproductive potential the pregnancy status should be verified prior to initiating treatment with Kisqali.

Contraception

Females of reproductive potential should be advised that animal studies have been performed showing ribociclib to be harmful to the developing fetus. Sexually active females of reproductive potential should use effective contraception (methods that result in < 1 % pregnancy rates) when using Kisqali during treatment and for 21 days after stopping treatment with Kisqali.

Infertility

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

A fertility study in male rats has not been performed, however atrophic changes in testes were reported in repeated dose toxicity studies in rats and dogs at exposures that were less or equal to the human exposure at the highest recommended daily dose of 600mg/day based on AUC (see section Non clinical safety data). There are no clinical data available regarding the effects of Kisqali on fertility. Based on animal studies, Kisqali may impair fertility in males of reproductive potential.

Overdosage

There is limited experience with reported cases of Kisqali overdose in humans. General symptomatic and supportive measures should be initiated in all cases of overdosage where necessary.

Clinical pharmacology

Pharmacotherapeutic group, ATC

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

Mechanism of action (MOA)

Ribociclib is a selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signaling 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 tumor regressions which correlated with inhibition of pRb phosphorylation at well tolerated doses.

In vivo studies using patient-derived estrogen positive breast cancer xenograft models combination of ribociclib and antiestrogens (i.e. letrozole) resulted in superior inhibition of tumor growth compared to each drug alone. Tumor regrowth was delayed for 33 days after stopping dosing. Additionally, in vivo antitumor activity of combination of ribociclib with fulvestrant was assessed in immune-deficient mice bearing the ZR751 ER+ human breast cancer xenografts. The combination of ribociclib and fulvestrant resulted in complete tumor growth inhibition.

Pharmacodynamics (PD)

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

In cell-based assays, ribociclib inhibits CDK4/6-dependent pRb phosphorylation with an average IC_{50} of 0.06 micro molar (26ng/mL). Ribociclib halts G1 to S phase cell cycle progression measured by flow cytometry with an average IC_{50} of 0.11 micro molar (47.8ng/mL). Ribociclib also inhibits cellular proliferation measured by bromodeoxyuridine (BrdU) uptake with an IC_{50} of 0.8 micro molar (34.8ng/mL). The similar IC_{50} values obtained from the target modulation, cell cycle and proliferation assays confirms that the blockade of the pRb phosphorylation by ribociclib directly leads to G1 to S phase arrest and subsequent inhibition of cellular proliferation. 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.

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 1,200mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval. The estimated QTcF mean change from baseline for Kisqali 600mg dose in combination with NSAI or fulvestrant was 22.00 ms (90% CI: 20.56, 23.44) and 23.7ms (90% CI: 22.31, 25.08) respectively, at the geometric mean C_{max} at steady-state compared to 34.7 ms (90% CI: 31.64, 37.78) in combination with tamoxifen (see section Warnings and precautions).

Pharmacokinetics (PK)

The pharmacokinetics of ribociclib were investigated in patients with advanced cancer following oral daily doses of 50mg to 1,200mg. Healthy subjects received single oral doses ranging of 400 or 600mg or repeated daily oral doses (8 days) of 400mg.

Absorption

Following oral administration of Kisqali to patients with advanced solid tumors or lymphomas peak plasma levels (C_{max}) of ribociclib were achieved between 1 and 4 hours (time to reach maximum concentration, T_{max}). Ribociclib exhibited slightly over-proportional increases in exposure (C_{max} and AUC) across the dose range tested (50 to 1,200mg). 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: 0.972 to 6.40).

Food effect:

Compared to the fasted state, oral administration of a single 600mg dose of ribociclib film-coated tablet formulation with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib (C_{max} GMR: 1.00; 90% CI: 0.898, 1.11; AUC_{inf} GMR: 1.06; 90% CI: 1.01, 1.12) (see section Interactions).

Distribution

Binding of ribociclib to human plasma proteins *in vitro* was approximately 70% and independent of concentration (10 to 10,000ng/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 1,090 L based on the population pharmacokinetic analysis.

Biotransformation/metabolism

In vitro and *in vivo* studies indicated ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600mg 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 (43.5%). The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide), each representing an estimated 9.39%, 8.60%, and 7.78% of total radioactivity, and 21.6%, 19.8%, and 17.9% of ribociclib exposure, respectively. Clinical activity (pharmacological and safety) of ribociclib was primarily due to parent drug, with negligible contribution from circulating metabolites.

Ribociclib was extensively metabolized with the unchanged drug accounting for 17.3% and 12.1% in feces and urine, respectively. Metabolite LEQ803 was a significant metabolite in excreta and represented approximately 13.9% and 3.74% of the administered dose in feces and urine, respectively. Numerous other metabolites were detected in both feces 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 600mg in patients with advanced cancer. The geometric mean 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 600mg across studies in healthy subjects.

Ribociclib is eliminated mainly via the feces, with a small contribution from 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; feces was the major route of excretion (69.1%), with 22.6% of the dose recovered in the urine.

Linearity/non-linearity

Ribociclib exhibited slightly over-proportional increases in exposure (C_{max} and AUC) across the dose range of 50mg to 1,200mg 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 600mg dose cohort.

Special populations

Renal impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment. Based on a population pharmacokinetic analysis that included 438 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/1.73m^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 (see section Dosage and administration).

The effect of renal impairment on the pharmacokinetics of ribociclib was also assessed in a renal impairment study that included 7 subjects with normal renal function (eGFR ≥90 mL/min/1.73 m2), 7 subjects with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m2), and 3 subjects with end stage renal disease (ESRD) (eGFR <15 mL/min/1.73 m2) at single ribociclib dose of 400mg/day. The geometric mean AUC_{inf} (geometric %CV, n) of 5570ng*hr/mL (22.8%, 7), 10900ng*hr/mL (38.1%, 7), 13600ng*hr/mL (20.9%, 3) and C_{max} (geometric %CV, n) of 356ng/mL (15%, 7), 538ng/mL (43.3%, 7), 593ng/mL (11.3%, 3) was observed in subjects with normal renal function, severe renal impairment and ESRD, respectively. In subjects with severe renal impairment AUC_{inf} increased by 1.96 fold, and C_{max} increased by 1.51 fold compared to subjects with normal renal function.

Based on this study, a starting dose of 200mg is recommended for patients with severe renal impairment (see section Dosage and administration).

Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A); a dose adjustment is required in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) and a starting dose of 400mg is recommended (see section Dosage and administration). Based on a pharmacokinetic trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib (see section Dosage and 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}) hepatic impairment. Based on a population pharmacokinetic analysis that included 160 patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib, further supporting the findings from the dedicated hepatic impairment study (see section Dosage and administration).

Effect of age, weight, gender and race

The population pharmacokinetic 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.

Geriatric use

Of 334 patients who received Kisqali in the phase III study (MONALEESA 2, in ribocilib plus letrozole arm), 150 patients (44.9%) were ≥65 years of age and 35 patients (10.5%) were ≥75 years of age. Of 484 patients who received Kisqali in the phase III study (MONALEESA 3, in ribociclib plus fulvestrant arm), 226 patients (46.7%) were ≥65 years of age and 65 patients (13.4%) were ≥75 years of age. No overall differences in safety or effectiveness of Kisqali were observed between these patients and younger patients (see section Dosage and administration).

Interactions

Strong CYP3A inhibitors: A drug interaction study in healthy subjects was conducted with ritonavir (strong CYP3A inhibitor). Compared to ribociclib alone, ritonavir (100mg b.i.d for 14 days) increased ribociclib C_{max} and AUC_{inf} by 1.7-fold and 3.2-fold, respectively, following a single 400mg ribociclib dose. 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. Simulations using physiologically-based pharmacokinetic modeling (PBPK) suggested that a moderate CYP3A4 inhibitor (erythromycin) may increase C_{max} and AUC of ribociclib 400mg single dose by 1.3-fold and 1.9-fold, respectively (see sections Dosage and administration, Warnings and precautions and Interactions).

Strong CYP3A inducers: A drug interaction study in healthy subjects was conducted with rifampicin (strong CYP3A4 inducer). Compared to ribociclib alone, rifampicin (600mg daily for 14 days) decreased ribociclib C_{max} and AUC_{inf} by 81% and 89%, respectively, following a single 600mg ribociclib dose. LEQ803 C_{max} increased 1.7-fold and AUC_{inf} decreased by 27%, respectively. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease ribociclib single dose C_{max} and AUC by 37% and 60%**,** respectively (see section Interactions).

Cytochrome P450 enzymes (CYP3A4 and CYP1A2 substrates): A drug interaction study in healthy subjects was conducted as a cocktail study with midazolam (sensitive CYP3A4 substrate) and caffeine (sensitive CYP1A2 substrate). Compared to midazolam and caffeine alone, multiple doses of ribociclib (400mg once daily for 8 days) increased midazolam C_{max} and AUC_{inf} by 2.1-fold and 3.8-fold, respectively. Simulations using PBPK suggested that at a 600mg ribociclib dose, midazolam C_{max} and AUC may increase 2.4-fold and 5.2-fold, respectively. The effect of multiple doses of ribociclib on caffeine was minimal, with C_{max} decreasing by 10% and AUC_{inf} increasing slightly by 20%. Simulations using PBPK suggested only weak inhibitory effects on CYP1A2 substrates at a 600mg ribociclib dose (see section Interactions).

Ribociclib exhibited no capacity to inhibit CYP2E1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, and showed no apparent time-dependent inhibition of CYP1A2, CYP2C9, and CYP2D6 at

clinically relevant concentrations. No induction of CYP1A2, CYP2B6, CYP2C9 or CYP3A4 was observed *in vitro* at clinically relevant concentrations. (see section Interactions).

Gastric pH-elevating agents: 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 was not observed in population pharmacokinetic analysis nor in simulations using PBPK models (see sections Dosage and administration and Interactions).

Letrozole: Data from clinical trials in patients with breast cancer and population PK analysis indicated no drug interaction between ribociclib and letrozole following co-administration of the drugs.

Anastrozole: Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and anastrazole following coadministration of the drugs.

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

Tamoxifen: Data from a clinical trial in patients with breast cancer indicated that tamoxifen exposure was increased approximately 2 fold following coadministration of ribociclib and tamoxifen.

Effect of ribociclib on transporters: *In vitro* evaluations indicated that Kisqali has a low potential to inhibit the activities of drug transporters P-gp, OATP1B1/B3, OCT1, MATE2K at clinically relevant concentrations. Kisqali may inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations (see section Interactions).

Effect of transporters on ribociclib: Based on *in vitro* data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of ribociclib at therapeutic doses. Ribociclib is not a substrate for hepatic uptake transporters OATP1B1/1B3 or OCT-1 *in vitro* (see section Interactions).

Clinical studies

Study CLEE011A2301 (MONALEESA-2)

Kisqali was evaluated in a randomized, double-blind, placebo-controlled, multicenter phase III clinical study in the treatment of postmenopausal women with HR 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 randomized in a 1:1 ratio to receive either Kisqali 600mg 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%))] vs No [n=376 (56%))]). Demographics and baseline disease characteristics were balanced and comparable between study arms. Kisqali was given orally at a dose of 600mg daily for 21 consecutive days followed by 7 days off treatment in combination with letrozole 2.5mg once daily for 28 days. Patients were not allowed to cross over from placebo to Kisqali during the study or after disease progression.

Patients enrolled in this study had a median age of 62 years (range 23 to 91). 44.2% patients were of age 65 years and older, including 69 patients (10.3%) of age 75 years and older. The patients included were Caucasian (82.2%), Asians (7.6%), and Black (2.5%). All patients had an ECOG performance status of 0 or 1. A total of 43.6% of patients had received chemotherapy in the neoadjuvant or adjuvant setting and 51.8% had received antihormonal therapy in the neo/adjuvant setting prior to study entry. 34.1% of

patients had de novo metastatic disease. 20.7% of patients had bone only disease and 59.0% of patients had visceral disease.

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 Tumors (RECIST v1.1), based on the investigator assessment in the full population (all randomized patients) and confirmed by a blinded independent central radiological assessment.

The efficacy results (29 January 2016 cut-off) 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 [HR] = 0.556 with 95% CI: 0.429, 0.720, one sided stratified log-rank test p-value 0.00000329), with an estimated 44% reduction in risk of progression for patients treated with the combination of reduction in Kisqali plus letrozole. The results for PFS based on the blinded independent central radiological assessment were consistent with the primary efficacy results based on the investigator's assessment (hazard ratio: 0.592 with 95% CI: (0.412, 0.852). The one-sided stratified log-rank test p-value was 0.002.

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

Overall survival (OS) was a key secondary endpoint. At the time of primary PFS analysis, overall survival was not mature with 11% of events.

A more mature update of efficacy data (02 January 2017 cutoff) is provided in Table 8 and Figure 1. 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 CLEE011A2301 primary efficacy results (PFS) based on investigator radiological assessment (02 January 2017 cutoff)

	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 Kaplan-Meier plot of PFS based on Investigator assessment – Study A2301 (Full analysis set 02 January 2017 cut-off)

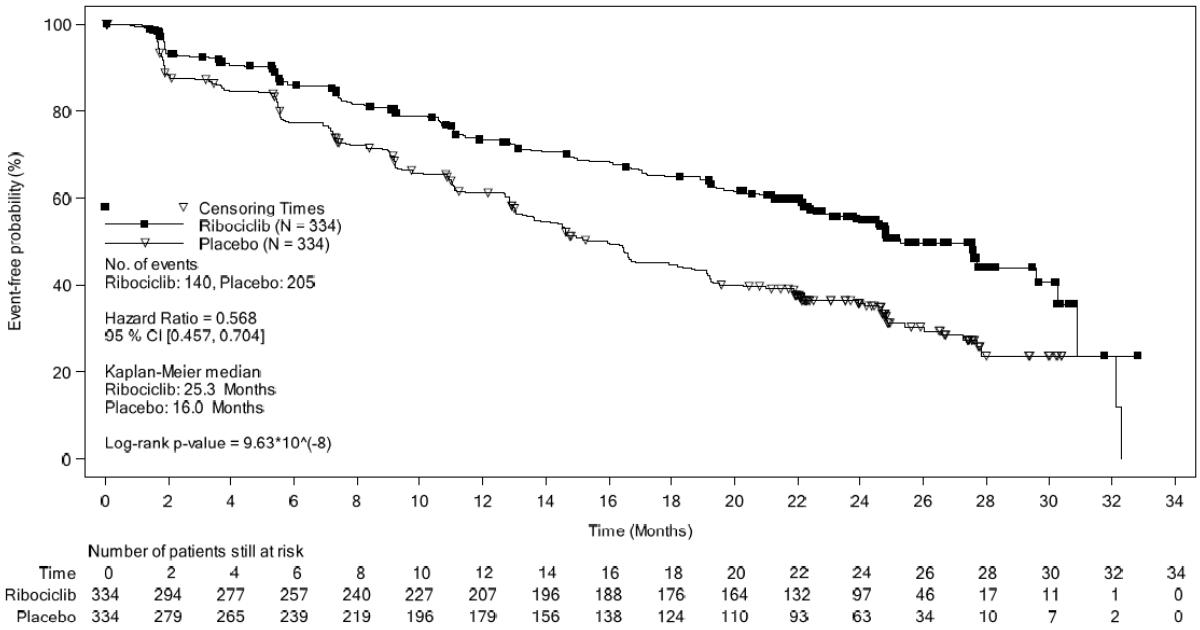
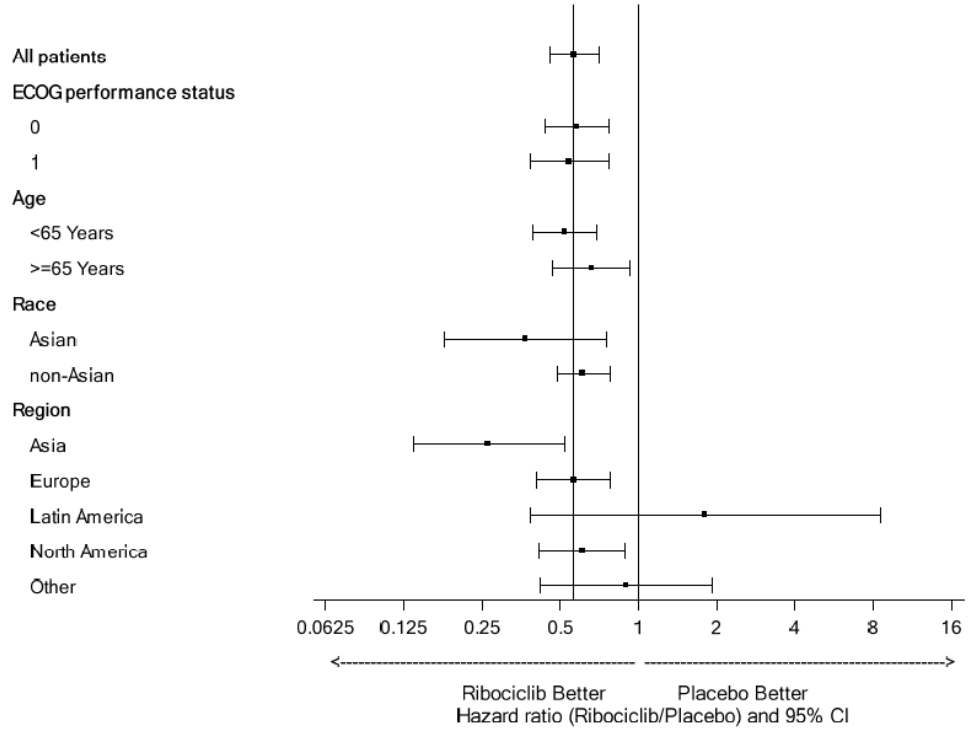
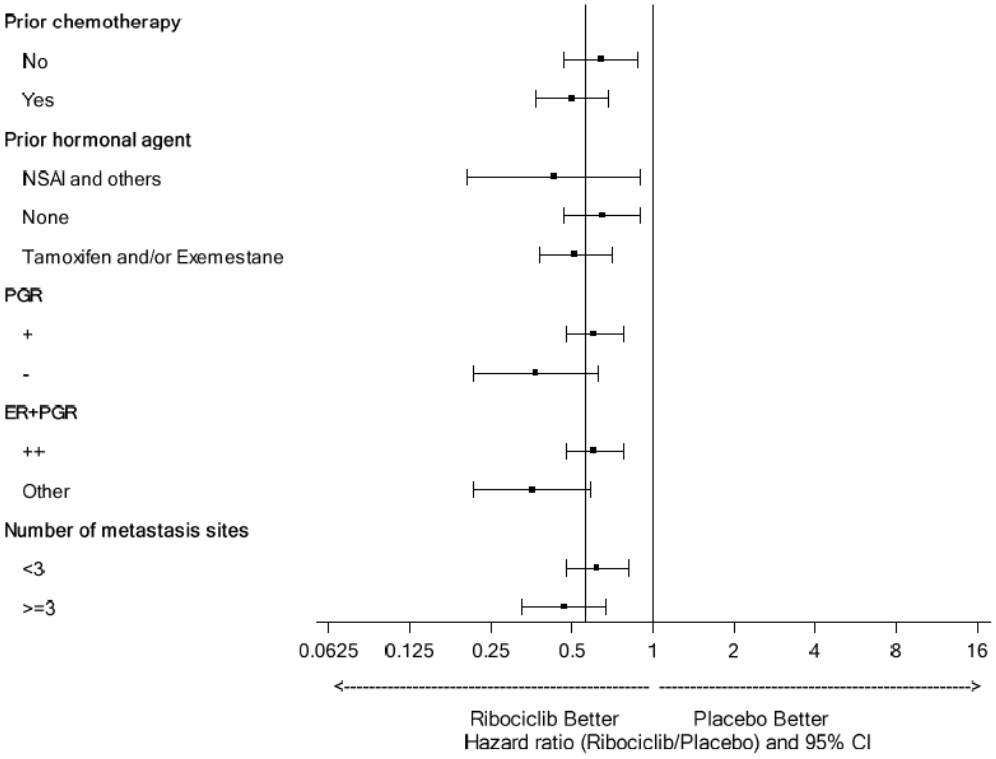
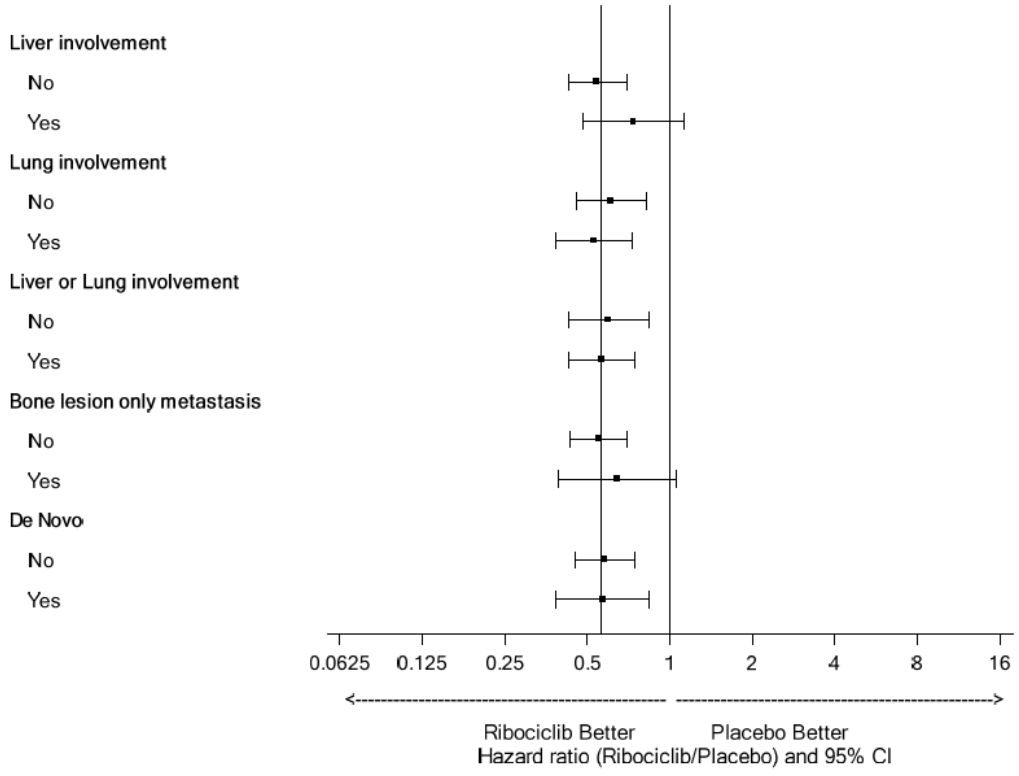
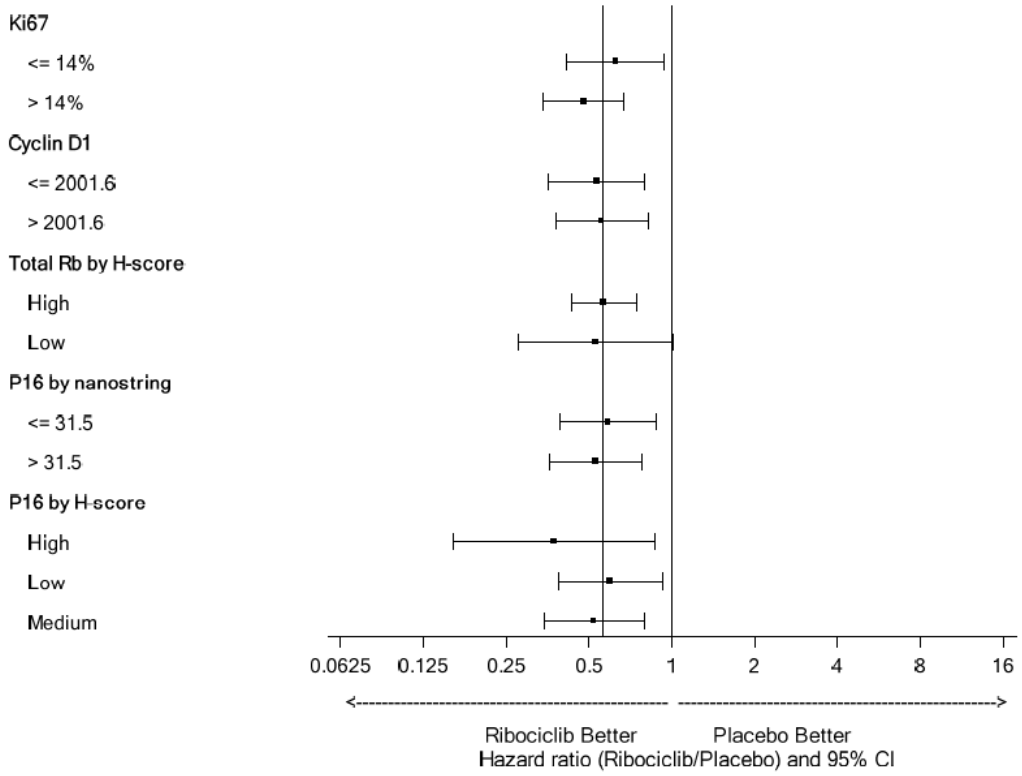


Figure 2 Forest plot of PFS based on Investigator review – Study A2301 (Full analysis set) (02 January 2017 cut-off)




Prior chemotherapy
No
Yes
Prior hormonal agent
NSAI and others
None
Tamoxifen and/or Exemestane
PGR
+
-
ER+PGR
++
Other
Number of metastasis sites
<3
>=3
0.0625
0.125
0.25
0.5
1
2
4
8
16
Ribociclib Better
Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI


Liver involvement
No
Yes
Lung involvement
No
Yes
Liver or Lung involvement
No
Yes
Bone lesion only metastasis
No
Yes
De Novo
No
Yes
0.0625
0.125
0.25
0.5
1
2
4
8
16
Ribociclib Better
Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI



A series of pre-specified subgroup PFS analyses was performed (02 January 2017 cut-off) based on prognostic factors and baseline characteristics to investigate the internal consistency of treatment effect (Figure 2). A reduction in the risk of disease progression or death in favour of the ribociclib plus letrozole arm was observed in all individual patient subgroups of age, race, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone-only metastatic disease. This was evident for patients with liver and/or lung disease (HR of 0.561 [95% CI: 0.424, 0.743], median progression-free survival [mPFS] 24.8 months versus 13.4 months respectively for ribociclib and placebo arm, the same for next) or without liver and/or lung disease (HR of 0.597 [95% CI: 0.426, 0.837], mPFS 27.6 months versus 18.2 months).

Updated results (02 January 2017 cut-off) for overall response and clinical benefit rates are displayed in Table 9.

Table 9 CLEE011A2301 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 CLEE011F2301 (MONALEESA-7)

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

MONALEESA-7 was a randomized, double-blind, placebo-controlled study of KISQALI plus either a non-steroidal aromatase inhibitor (NSAI) or tamoxifen and goserelin versus placebo plus either a NSAI or tamoxifen and goserelin conducted in pre/perimenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior endocrine therapy for advanced disease.

A total of 672 patients were randomized to receive KISQALI plus NSAI or tamoxifen plus goserelin (n= 335) or placebo plus NSAI or tamoxifen plus goserelin (n= 337), stratified according to the presence of liver and/or lung metastases, prior chemotherapy for advanced disease and endocrine combination partner (tamoxifen and goserelin vs NSAI and goserelin). NSAI (letrozole 2.5 mg or anastrozole 1 mg) or tamoxifen 20 mg or were given orally once daily on a continuous daily schedule, goserelin was administered as a sub-cutaneous injection 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. The major efficacy outcome measure for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Patients enrolled in MONALEESA-7 had a median age of 44 years (range 25 to 58) and were primarily Caucasian (58%), Asian (29%), or Black (3%). Nearly all patients (99%) had an ECOG performance status of 0 or 1. Of the 672 patients, 33% had received chemotherapy in the adjuvant vs. 18% in the neoadjuvant setting and 40% had received endocrine therapy in the adjuvant vs 0.7% in the neoadjuvant setting prior to study entry. Forty percent (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, and endocrine combination partner.

The efficacy results from a pre-specified subgroup analysis of 495 patients who had received KISQALI or placebo with NSAI plus goserelin are summarized in Table 10 and Figure 3. Consistent results were observed in stratification factor subgroups of disease site and prior chemotherapy for advanced disease. Overall survival data were immature with 13% deaths.

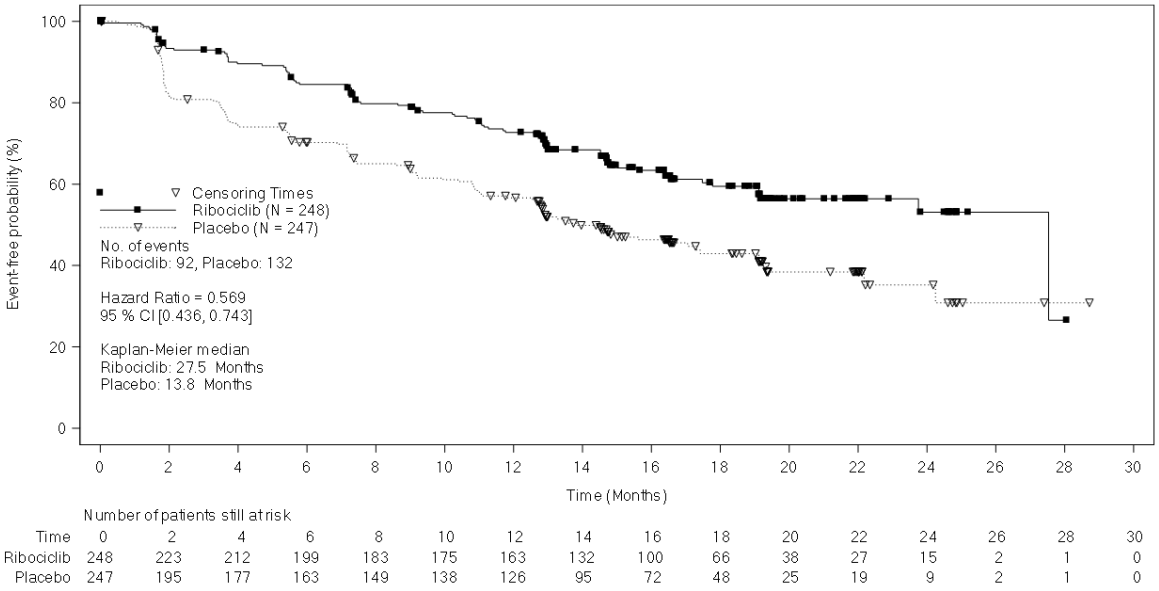
Table 10: Efficacy Results – MONALEESA-7 (NSAI, Investigator Assessment)

Patients with measurable disease (95% CI)	50.5 (43.4, 57.6)	36.2 (29.5, 42.9)

NR = not reached
* Based on confirmed responses

	KISQALI + NSAI + goserelin	**Placebo + NSAI + goserelin**
Progression-free survival	**N = 248**	**N = 247**
Events (n, %)	92 (37.1%)	132 (53.4%)
Median (months, 95% CI)	27.5 (19.1, NR)	13.8 (12.6, 17.4)
Hazard Ratio (95% CI)	0.569 (0.436, 0.743)	
Overall Response Rate*	**N=192**	**N=199**

Figure 3 Kaplan-Meier Progression Free Survival Curves – MONALEESA-7 (NSAI, Investigator Assessment)



Study CLEE011E2301 (MONALEESA-3)

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

MONALEESA-3 was a randomized double-blind, placebo-controlled, multi-centre phase III clinical study in the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment.

A total of 726 female patients were randomized in a 2:1 ratio to receive KISQALI 600 mg and fulvestrant (n= 484) or placebo and fulvestrant (n= 242), stratified according to the presence of liver and/or lung metastases and prior endocrine therapy for advanced or metastatic disease. 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. The major efficacy outcome measure for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Patients enrolled in this study had a median age of 63 years (range 31 to 89). Of the patients enrolled, 47% were 65 years and older, including 14% age 75 years and older. The patients enrolled were primarily Caucasian (85%), Asian (9%), and Black (0.7%). 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). Forty three percent (43%) of patients had received chemotherapy in the adjuvant vs. 13% in the neoadjuvant setting and 59% had received endocrine therapy in the adjuvant vs. 1% in the neoadjuvant setting prior to study entry. Twenty one percent (21%) of patients had bone only disease and 61% had visceral disease. Demographics and baseline disease characteristics were balanced and comparable between study arms.

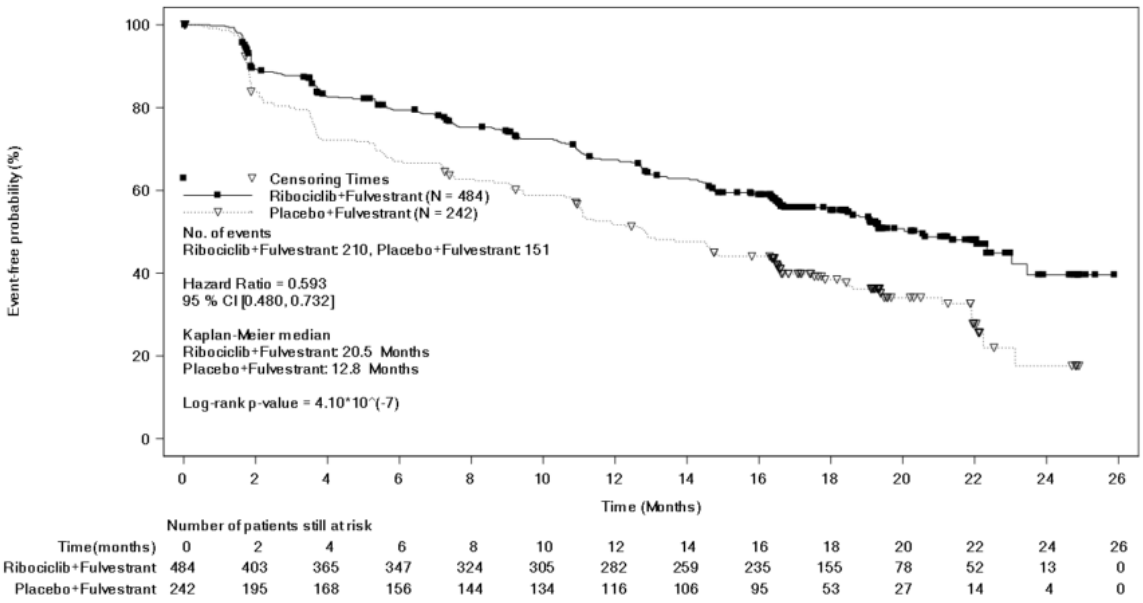
The efficacy results from MONALEESA-3 are summarized in Table 11 and Figure 4. Consistent results were observed in stratification factor subgroups of disease site and prior endocrine treatment for advanced disease. At the time of the PFS analysis, 17% of patients had died, and overall survival data were immature.

Table 11: Efficacy Results – MONALEESA-3 (Investigator Assessment, Intent-to-Treat Population)

	KISQALI + Fulvestrant	**Placebo + Fulvestrant**
Progression-free survival	**N = 484**	**N = 242**
Events (n, %)	210 (43.4%)	151 (62.4%)
Median (months, 95% CI)	20.5 (18.5, 23.5)	12.8 (10.9, 16.3)
Hazard Ratio (95% CI)	0.593 (0.480 to 0.732)	
p-value[a]	<0.0001	
Overall Response Rate*	**N=379**	**N=181**
Patients with measurable disease (95% CI)	40.9 (35.9, 45.8)	28.7 (22.1, 35.3)

[a] p-value is obtained from the one-sided log-rank
* Based on confirmed responses

Figure 4 Kaplan-Meier Progression



Non-clinical safety data

Ribociclib was evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity, and phototoxicity studies.

Safety pharmacology

Ribociclib did not have effects on CNS or respiratory functions . *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 600mg. As well, there is potential to induce incidences of 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) in rats up to 26 weeks duration and dogs up to 39 weeks duration, 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. These effects can be linked to a direct anti-proliferative effect on the testicular germ cells resulting in atrophy of the seminiferous tubules. 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

See section Pregnancy, lactation, females and males of reproductive potential.

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 mutagenic potential of ribociclib.

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 ribociclib causes photosensitization in patients is considered very low.

Carcinogenesis

No carcinogenesis studies have been conducted with ribociclib.

Pharmaceutical information

Incompatibilities

Not applicable.

Storage

See folding box.

Kisqali should not be used after the date marked “EXP” on the pack.

Kisqali must be kept out of the sight and reach of children.

Instructions for use and handling

Not applicable.

Manufacturer:

See folding box.

Presentation:

PCTFE/PVC (Polychlorotrifluoroethylene/Polyvinyl chloride) Aclar blisters with aluminium foil containing 14 or 21 film-coated tablets.

Kisqali 200mg: 1 x 21s, 3 x 14s and 3 x 21s

Not all presentations may be available locally.

Information issued: July 2018.SIN

Novartis Pharma AG, Basel, Switzerland