PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrKISQALI®

ribociclib (as ribociclib succinate)

Tablets, 200 mg, oral

Protein kinase inhibitor, L01XE42

Anti-neoplastic agent

Novartis Pharmaceuticals Canada Inc.
385, Bouchard Blvd.
Dorval, Quebec,
H9S 1A9
www.novartis.ca

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RECENT MAJOR LABEL CHANGES

Section 7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis	July 2021
Section 8, 8.1 Adverse Reaction Overview, 8.2 Clinical Trial Adverse Reactions, 8.4 Less Common Clinical Trial Adverse Reactions.	July 2021
Section 16, NON-CLINICAL TOXICOLOGY, Carcinogenicity	July 2021

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

KISQALI® (ribociclib tablets) is indicated in combination with:

- an aromatase inhibitor 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, as initial endocrine-based therapy;

  In pre/perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone releasing hormone (LHRH) agonist.

- 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.

1.1 Pediatrics

Pediatrics (≤ 18 years of age):
There are limited data in pediatric patients and the safety and efficacy of KISQALI in this population have not been established.

1.2 Geriatrics

Geriatrics (≥ 65 years of age):
Of 334 patients who received KISQALI plus letrozole in the pivotal phase III study A2301, 150 patients (44.9%) were ≥ 65 years of age; no major differences in safety of KISQALI were observed between patients < 65 and ≥ 65 years of age. Of 484 patients who received KISQALI plus fulvestrant in the phase III study F2301, 226 patients (46.7%) were ≥65 years of age and 65 patients (13.4%) were ≥75 years of age. No major differences in safety of KISQALI were observed between these patients and younger patients (see 4 DOSAGE AND ADMINISTRATION).

2 CONTRAINDICATIONS

- Patients with hypersensitivity to this drug or to any ingredient in the formulation. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION and PACKAGING section.
- Patients with untreated congenital long QT syndrome, a QTcF interval of ≥450 msec at baseline, and those who are at significant risk of developing QTc prolongation (see 7 WARNINGS and PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- QT interval prolongation (see 7 WARNINGS AND PRECAUTIONS)
- Hepatotoxicity (see 7 WARNINGS AND PRECAUTIONS)

- Neutropenia (see 7 WARNINGS AND PRECAUTIONS)
- KISQALI (ribociclib tablets) should be administered by health professionals experienced with anti-cancer agents

4 DOSAGE AND ADMINISTRATION

4.1 Dosing considerations

Treatment of pre- or peri-menopausal women with KISQALI combination should include an LHRH agonist according to local clinical practice standards.

Dose adjustment is required in patients with moderate and severe hepatic impairment (see 4.2 Recommended Dose and Dosage Adjustments, and 10 CLINICAL PHARMACOLOGY.)

Dose adjustment is required in patients with severe renal impairment (see 4.2 Recommended Dose and Dosage Adjustments, and 10 CLINICAL PHARMACOLOGY).

Concomitant use of KISQALI should be avoided with strong CYP3A inhibitors. KISQALI dose adjustment is required if a strong CYP3A inhibitor must be co-administered (see 4.2 Recommended Dose and Dosage Adjustments, and 10 CLINICAL PHARMACOLOGY).

4.2 Recommended Dose and Dosage Adjustment

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

Recommended dose

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 10 CLINICAL PHARMACOLOGY and Drug-Food Interactions sections).

For dosing and co-administration of KISQALI with an aromatase inhibitor refer to the applicable Product Monograph for detailed conditions of use.

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

When co-administered with KISQALI, the recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15 and 29, and once monthly thereafter. Refer to the Product Monograph for fulvestrant for detailed conditions of use.

Dose Adjustments for Adverse Drug Reactions

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption, reduction, or permanent 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

	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 200 mg/day is required, discontinue the treatment.*

Tables 2, 3, 14, 5 and 6 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 **7** WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS sections).

Table 2 Dose modification and management for neutropenia

Neutropenia	**Grade 1 or 2** (ANC[1] 1,000/mm^3 – <LLN[2])	**Grade 3** (ANC[1] <1,000/mm^3)	**Grade 3 febrile* neutropenia**	**Grade 4** (ANC[1] <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, and as clinically indicated.			

**Grade 3 neutropenia with a single episode of fever >38.3˚C or a sustained temperature above 38˚C for more than one hour*
Grading according to CTCAE Version 4.03 CTCAE=Common Terminology Criteria for Adverse Events.
[1]: absolute neutrophil count
[2]: lower limit of normal

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 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, and monitor periodically as clinically indicated. If Grade ≥2 abnormalities are observed, more frequent monitoring, for example, twice weekly, 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 interval >480 ms	1. Interrupt the KISQALI dose 2. If QTcF interval prolongation resolves to <481 ms, resume KISQALI at the next lower dose level 3. If QTcF interval ≥481 ms recurs, interrupt the KISQALI dose until QTcF interval resolves to <481 ms; and then resume KISQALI at next lower dose level
ECGs with QTcF interval >500 ms	If QTcF interval is greater than 500 ms, interrupt KISQALI until QTcF interval reaches <481 ms then resume KISQALI at next lower dose level

Torsade de Pointes, polymorphic ventricular tachycardia, unexplained syncope, or signs/symptoms of serious arrhythmia	Permanently discontinue KISQALI
Assess ECG prior to initiation of treatment. After initiating treatment with KISQALI, repeat ECGs on Day 14 of the first cycle, at the beginning of Cycle 2, at regular intervals thereafter during steady-state treatment (e.g., at approximately day 14 of the cycle), and whenever clinically indicated. In case of QTc prolongation at any given time during treatment, more frequent ECG monitoring is recommended. Serum electrolytes (including potassium, calcium, phosphorous and magnesium) should be assessed prior to initiation of treatment, at regular intervals in later cycles, and whenever clinically indicated with abnormalities corrected prior to commencement/ resumption of treatment.	

Table 5 Dose modification and management for ILD/Pneumonitis

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

Grading according to CTCAE Version 4.03.

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

ILD = Interstitial Lung Disease

Table 6 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 neutropenia, hepatobiliary toxicity, QT interval prolongation and ILD/Pneumonitis.*
Grading according to CTCAE Version 4.03. CTCAE=Common Terminology Criteria for Adverse Events.

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

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 low 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 elimination half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor *(*see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS section).

Special populations

Patients with hepatic impairment:

Based on a hepatic impairment study in healthy subjects and non-cancer subjects with impaired hepatic function, no adjustment of the starting dose 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 400 mg is recommended (see 10 CLINICAL PHARMACOLOGY section). However, in the Phase III trial, the efficacy and safety of KISQALI have not been studied in breast cancer patients with moderate and severe hepatic impairment; initiate KISQALI treatment in these patients only when perceived benefit outweighs potential risk.

Refer to the appropriate Product Monograph for the aromatase inhibitor, fulvestrant or the LHRH agonist for dose modifications related to hepatic impairment.

Patients with renal impairment:

KISQALI has not been studied in breast cancer patients with severe renal impairment. Based on population pharmacokinetic analysis, and data from cancer patients in clinical trials, no adjustment of the starting dose is necessary in patients with mild or moderate renal impairment.

Based on a renal impairment study in non-cancer subjects with severe renal impairment and normal renal function, a starting dose of 200 mg is recommended for patients with severe renal impairment. Caution should be used in patients with severe renal impairment with close monitoring for signs of toxicity. (see 10 CLINICAL PHARMACOLOGY section); initiate KISQALI treatment in these patients only when perceived benefit outweighs potential risk.

Pediatrics (< 18 years of age): There are limited data in pediatric patients and the safety and efficacy of KISQALI in this population have not been established.

Geriatrics (≥ 65 years of age): No adjustment of the starting dose is required in patients over 65 years of age.

4.3 Administration

KISQALI and aromatase inhibitors or fulvestrant should be taken at approximately the same time each day, preferably in the morning. 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.

4.4 Missed Dose

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

5 OVERDOSAGE

There is limited experience with reported cases of KISQALI overdose in humans. Patients should be

closely monitored for adverse drug reactions. General symptomatic and supportive measures, such as ECG monitoring, should be initiated in all cases of overdosage.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablet 200 mg ribociclib (as ribociclib succinate) *Strength:* Each tablet contains 200 mg ribociclib (as ribociclib succinate) *Medicinal ingredient:* ribociclib succinate	No clinically relevant non-medicinal ingredients: Excipients *Tablet core:* Colloidal silicon dioxide; crospovidone (Type A); low-substituted hydroxypropylcellulose; magnesium stearate; microcrystalline cellulose; *Coating material:* Iron oxide black (E172); iron oxide red (E172); lecithin (soy) (E322); polyvinyl alcohol (partially hydrolysed); talc; titanium dioxide (E171); xanthan gum.

COMPOSITION:

KISQALI (ribociclib tablets) is a light greyish violet film-coated tablet, unscored, round, curved with beveled edge, debossed with "RIC" on one side and "NVR" on the other side.

PACKAGING:

KISQALI (ribociclib tablets) is supplied in unit dose blisters in the following pack sizes: 21, 42 and 63 tablets.

KISQALI TABLETS	
Package Size	Package Configuration
Pack of 63:	Blister pack containing 21 tablets (3 tablets for 600mg dose). 3 Blister packs per outer container
Pack of 42 :	Blister pack containing 14 tablets (2 tablets for 400 mg dose). 3 Blister packs per outer container
Pack of 21:	Blister pack containing 21 tablets (1 tablet for 200mg dose). 1 Blister pack per outer container

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis

In the 2 year rat carcinogenicity study, increase incidence of adenocarcinoma in the uterus/cervix and follicular tumors in the thyroid glands of males have been observed.

These effects may be related to prolonged hypoprolactinemia secondary to CDK4 inhibition of lactotrophic cell function in the pituitary gland, altering the hypothalamus-pituitary-gonadal axis. Considering important differences between rodents and humans with regard to synthesis and role of prolactin, it is not certain whether this mode of action is expected to have consequences in humans (see 16, NON-CLINICAL TOXICOLOGY section)

Cardiovascular

QT interval prolongation

KISQALI has shown a concentration-dependent prolongation of the QTc interval, with the mean increase from baseline of approximately 19.6 msec (90% CI 18.0, 21.2) during steady-state treatment at 2 hours post-dosing on Day 15 in the phase III A2301 clinical trial (see 10 ACTION AND CLINICAL PHARMACOLOGY section). One event of sudden death (0.3%) occurred during treatment with KISQALI plus letrozole in the phase III clinical trial (A2301) in a patient with Grade 2 QT prolongation and Grade 3 hypokalemia. No cases of sudden death were reported in studies E2301 or F2301. In the pooled phase III clinical studies, in patients with advanced or metastatic breast cancer who received the KISQALI plus any combination partners, 14 patients (1.3%) had >500 ms post-baseline QTcF value, and 59 patients (5.6%) had a >60 msec QTcF interval increase from baseline.

ECG assessments during steady-state were collected on Cycle 1 Day 15 in the three phase III clinical studies and were also collected on Cycle 3 Day 15 in study E2301 and Cycle 2 Day 15 in study F2301.

QTc prolongation can lead to an increased risk of ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of Torsade de Pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de Pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, Torsade de Pointes can progress to ventricular fibrillation and sudden cardiac death.

Risk factors for Torsade de Pointes in the general population include, but are not limited to, the following: female gender, age ≥ 65 years, baseline prolongation of the QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid hemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

Treatment with KISQALI is contraindicated in patients with untreated congenital long QT syndrome; baseline prolongation of the QTc interval; and patients at risk of developing QTc prolongation (for example, uncontrolled, significant cardiac disease including but not limited to, recent myocardial

infarction, congestive heart failure, unstable angina and bradyarrhythmias). Treatment with KISQALI should be avoided in patients with uncorrected hypokalemia, hypomagnesemia, or hypocalcemia. Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to initiation or continuation of KISQALI treatment.

Particular care should be exercised when administering KISQALI to patients who are suspected to be at an increased risk of experiencing Torsade de Pointes during treatment with a QTc-prolonging drug.

Assess electrocardiography (ECG) before initiating KISQALI and repeat at approximately Day 14 of the first cycle, at the beginning of the second cycle, at regular intervals thereafter during steady-state treatment (at approximately Day 14 of the cycle) and whenever clinically indicated. QTc prolongation is expected to be maximal during days 8 – 21 of the 28-day cycle. Assess serum electrolytes prior to the initiation of KISQALI treatment, at regular intervals in later cycles, and whenever clinically indicated.

More frequent ECG and serum electrolyte monitoring may be required based on a patient's individual risk factors, and in the event of QTc prolongation and/or serum electrolyte imbalance (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 4 DOSAGE AND ADMINISTRATION sections).

KISQALI should be avoided in combination with other medicinal products known to prolong the QTc interval and/or strong CYP3A inhibitors as this may lead to further prolongation of the QTcF interval (see 4 DOSAGE AND ADMINISTRATION, 9 DRUG INTERACTIONS and 10 CLINICAL PHARMACOLOGY sections). Use caution when KISQALI is in combination with agents known to cause bradycardia (e.g., beta-blockers, non-dyhydropyridine calcium channel blockers, clonidine, and digoxin.)

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 4 DOSAGE AND ADMINISTRATION, 8 ADVERSE REACTIONS and **10** CLINICAL PHARMACOLOGY sections).

When drugs that prolong the QTc interval are prescribed, health professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug. Patients should be advised to contact their health professional immediately to report any new chest pain or discomfort, changes in heart beat, palpitations, dizziness, lightheadedness, fainting, or changes in or new use of other medications.

Increased QTc Prolongation with Concomitant Use of Tamoxifen

KISQALI is not indicated for use in combination with tamoxifen and combined treatment is not recommended (see 10 PHARMACOLOGY, Cardiac Electrophysiology). In E2301 (MONALEESA-7), the observed mean QTcF interval increase from baseline in the tamoxifen 20 mg/day plus placebo subgroup was approximately 14-18 msec at steady-state on C3/D15 (i.e., Day 71) compared with approximately 2-3 msec in the NSAI plus placebo population, suggesting that tamoxifen had a QTcF interval prolongation effect which contributed to the QTcF interval prolongation observed in the KISQALI plus tamoxifen group (see 10 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 20 mg/day, and in no patients (0/245) receiving an NSAI**.** An increase of >60 msec from baseline in the QTcF interval was observed in 14/87 (16.1%) of patients receiving KISQALI plus

tamoxifen and in 18/245 (7.3%) of patients receiving KISQALI plus an NSAI.

Tamoxifen exposure (C_{max} and AUC_{0-24h}) was increased approximately 2-fold following co-administration of ribociclib and tamoxifen (see 9 DRUG INTERACTIONS).]

Driving and operating machinery

Fatigue and syncope have been reported with the use of KISQALI. Patients should exercise caution when driving or operating machinery while taking KISQALI.

Hematologic

Neutropenia

In the pooled phase III clinical studies , neutropenia was the most frequently reported adverse drug reaction (73.7%) and a Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 58.4% of patients receiving KISQALI plus any combination.

Among the patients who had Grade 2, 3 or 4 neutropenia in the pooled 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 8 ADVERSE DRUG REACTIONS section).

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 and 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 4 DOSAGE AND ADMINISTRATION section).

Other Hematologic Parameters

Decreases in lymphocytes, leukocytes, hemoglobin and platelets were observed in patients treated with KISQALI. Grade 3 or 4 leukopenia was reported in 15.5% of patients in the KISQALI arm in the pooled phase III studies. (see 8 ADVERSE REACTIONS).

In clinical trials with KISQALI, anemia and leukopenia were usually managed with temporary KISQALI interruption and/or dose reduction. Monitor complete blood count prior to the start of KISQALI therapy, every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 4 DOSAGE AND ADMINISTRATION sections).

Hepatic/Biliary/Pancreatic

Hepatobiliary toxicity

In the pooled 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 AEs reported in patients treated with KISQALI plus any combination (11.4% vs. 5.4%, respectively. Dose interruptions and/or adjustments due to hepatotobiliary 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 and hepatotoxicity occurred in 2.3% and 0.4% of patients respectively.

Of the six patients in KISQALI plus fulvestrant group who met biochemical criteria of Hy's Law, two were confirmed. KISQALI was discontinued in both of these cases and these patients subsequently recovered after discontinuation.

In the pooled phase III clinical studies, increases in transaminases were observed. Grade 3 or 4 increases in alanine aminotransferase (ALT, 9.7% vs. 1.5%) and aspartate aminotransferase (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 and placebo plus any combination arms respectively.

Concurrent elevations of ALT or AST greater than three times the upper limit of normal (ULN) and of total bilirubin greater than two times the ULN, with normal ALP levels, and in the absence of cholestasis (consistent with the definition of drug-induced liver injury) occurred in 6 (0.6%) 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

In the pooled 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 8 ADVERSE REACTIONS section). 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.

Liver function tests (LFTs) should be performed before initiating therapy with KISQALI. The LFTs should be monitored every 2 weeks for the first 2 cycles at the beginning of each of the subsequent 4 cycles, and as clinically indicated. In the event of Grade ≥ 2 LFT abnormality, more frequent monitoring is required (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 4 DOSAGE AND ADMINISTRATION sections).

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 4 DOSAGE AND ADMINISTRATION section). Recommendations for patients who have elevated AST/ALT Grade ≥3 at baseline have not been established.

Monitoring and Laboratory Tests

- ***Complete blood count (CBC):*** 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 and as clinically indicated.
- ***Liver function test (LFT):*** LFT should be performed before initiating therapy with KISQALI. LFT should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated (for example, repeating liver enzyme and serum bilirubin twice weekly may be required in case of liver enzyme or bilirubin increase requiring dose interruption).
- ***Electrocardiography (ECG):*** Assess ECGs prior to initiating treatment, during Cycle 1 at approximately Day 14, at the beginning of Cycle 2, at regular intervals thereafter during steady-state treatment (at approximately Day 14 of the cycle), and whenever clinically indicated. Treatment with KISQALI should be initiated only in patients with QTcF value less than 450

msec. QTc prolongation is expected to be maximal during steady-state treatment between days 8 and 21 of the 28-day cycle. More frequent ECG monitoring is recommended whenever clinically indicated, for example in case of QTc prolongation during treatment or if the patient has underlying risk factors for Torsade de Pointes or is receiving concomitant treatment with drugs that prolong the QTc interval. Repeat ECGs should be performed if there are any symptoms that may be related to QT prolongation (e.g. palpitations or syncope), or in the event of electrolyte imbalances.

- ***Electrolytes:*** Monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed prior to initiation of treatment, at regular intervals during steady-state treatment in later cycles, and whenever clinically indicated. Any abnormality should be corrected before the initiation or continuation of KISQALI therapy.

Reproductive Health: Female and Male Potential

Based on animal studies and the mechanism of action of ribociclib, 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 16 NON-CLINICAL TOXICOLOGY section).

- **Fertility**

  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 (see 16 NON-CLINICAL TOXICOLOGY section).

Respiratory

Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis has been reported with CDK4/6 inhibitors including KISQALI. In the three phase III clinical studies (MONALEESA-2 (A2301), MONALEESA-7 (E2301-NSAI) and MONALEESA-3 (F2301)), ILD (any grade 0.3%, including 0.1% grade 3) was reported in the KISQALI - treated group, with no cases in the placebo treated group. Pneumonitis was reported in both the KISQALI and the placebo treated groups (any grade 0.4%, with no Grade 3/4 in either treatment group).

Based on the severity of the ILD/pneumonitis, which may be fatal, patients may require treatment interruption, dose reduction or permanent discontinuation as described in Table 5 (see 4 DOSAGE AND ADMINISTRATION).

Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. In patients who develop grade 1 ILD/pneumonitis, no dose adjustment is required. Appropriate medical therapy and monitoring should be initiated as clinically indicated. In patients who developed grade 2 ILD/pneumonitis, the treatment with KISQALI should be interrupted until recovery to grade ≤1, and then KISQALI can be resumed at the next lower dose level. For Grade 3 or 4 ILD/pneumonitis KISQALI should be permanently discontinued (see 4 DOSAGE AND ADMINISTRATION).

Skin

Severe cutaneous reactions

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

Thromboembolic events

In the pooled phase III clinical studies, thromboembolic events occurred in 37 patients (3.5%) in the KISQALI plus any combination, compared with 19 (2.3%) in the placebo plus any combination. Pulmonary embolism was reported in 14 patients (1.3%) receiving KISQALI plus any combination and 10 patients (1.2%) receiving placebo plus any combination.

Patients at risk of thromboembolic events should be closely monitored while receiving KISQALI.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies using KISQALI in pregnant women. Ribociclib showed fetotoxicity and teratogenicity at doses which did not show maternal toxicity in rats and rabbits (see 16 NON-CLINICAL TOXICOLOGY section). It is possible that KISQALI can cause fetal harm when administered to a pregnant woman.

Female patients of reproductive potential should have a pregnancy test prior to initiation of treatment with KISQALI. 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 KISQALI.

7.1.2 Breast-feeding

Ribociclib and its metabolites readily passed into the milk of lactating rats. It is not known if ribociclib is excreted in human milk. There are no data on the effects of ribociclib on the breastfed child or the effects of ribociclib on milk production.

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 (see 16 NON-CLINICAL TOXICOLOGY section).

7.1.3 Pediatrics

Pediatrics (≤ 18 years of age): There are limited data in pediatric patients and the safety and efficacy of KISQALI in this population have not been established.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Of 334 patients who received KISQALI plus letrozole in the phase III study A2301, 150 patients (44.9%) were ≥65 years of age. Of 484 patients who received KISQALI plus fulvestrant in the phase III study F2301, 226 patients (46.7%) were ≥65 years of age and 65 patients (13.4%) were ≥75 years of age. No major differences in safety of KISQALI were observed between these patients and patients <65 years of age (see 4 DOSAGE AND ADMINISTRATION section).

7.1.5 Hepatic Impairment:

Based on a pharmacokinetic trial in subjects with hepatic impairment (Child-Pugh Class), mild hepatic impairment (Child-Pugh Class A) had no effect on the exposure of ribociclib; no initial dose reduction is required for patients with mild hepatic impairment at baseline.

In the Phase III study, the efficacy and safety of KISQALI have not been studied in patients with moderate or severe hepatic impairment [defined as breast cancer patients with ALT or AST ≥ 5 x ULN or total serum bilirubin ≥ ULN (with the exception of documented Gilbert's Syndrome), as these patients were excluded according to the protocol eligibility criterion]. Treatment decision should be based on individual benefit/risk assessment for patients with moderate and severe hepatic impairment. If treatment is required, the starting dose should be reduced to 400 mg and patients should be closely monitored (see 10 CLINICAL PHARMACOLOGY and 4 DOSE AND ADMINISTRATION sections).

7.1.6 Renal Impairment:

KISQALI has not been studied in breast cancer patients with severe renal impairment.

Based on population pharmacokinetic analysis, and data from cancer patients in clinical trials; no starting dose adjustment is necessary for patients with mild or moderately impaired renal function and patients should be closely monitored (see 10 CLINICAL PHARMACOLOGY and 4 DOSE AND ADMINISTRATION sections).

Based on a renal impairment study in non-cancer subjects with severe renal impairment and normal renal function, a starting dose of 200 mg is recommended for patients with severe renal impairment.

Caution should be used in patients with severe renal impairment with close monitoring for signs of toxicity. Treatment decision should be made based on individual benefit/risk assessment for patients with severe renal impairment. (see 10 CLINICAL PHARMACOLOGY).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

The median duration of exposure to KISQALI treatment across the pooled phase III studies dataset was 16.53 months with 61.7% patients exposed for >12 months.

The most common adverse drug reactions (ADRs) across the pooled phase III studies (reported at a frequency of ≥20% and exceeding the frequency for placebo) were neutropenia, leukopenia, nausea, diarrhea, vomiting, constipation, infections/infestations, fatigue, alopecia, rash, headache, cough and back pain.

The most common Grade 3/4 ADRs in the pooled data (reported at a frequency of ≥2% and exceeding the frequency for placebo) were neutropenia, leukopenia, lymphopenia, anemia, abnormal liver function tests, dry mouth, oropharyngeal pain, infections/infestations, hypophosphatemia and vomiting. Dose reductions of KISQALI or placebo 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. No dose reduction was allowed for NSAI or fulvestrant in the phase III studies. Permanent discontinuation of KISQALI or placebo due to AEs,

regardless of causality occurred in 14.6% n KISQALI plus any combination versus 4.4% in placebo plus any combination; The most common AEs leading to permanent discontinuation of KISQALI with any combination partner were ALT increased (2.0%), AST increased (1.4%) and vomiting (0.8%).

In the pooled studies, ILD was reported in 3 patients (0.3%) and pneumonitis was reported in 4 patients (0.4%) in the ribociclib arm (N=1065). In the placebo arm, ILD was not reported, and pneumonitis was reported in 3 patients (0.4%) (N= 818). A clinical review of these cases revealed various confounders (e.g. chemotherapy, radiotherapy, concomitant treatment with drugs known to cause ILD/pneumonitis, lung metastases, lung infection), and there was no conclusive evidence that ribociclib, as a direct agent, may cause ILD/pneumonitis.

In the pooled analysis of three phase III studies, on-treatment deaths were reported in 21 patients (2.0%) treated with KISQALI plus any combination versus 16 patients (2.0%) treated with placebo plus any combination treatment. Excluding the most frequent causes of death, disease progression, 3 treatment-related causes of death were reported in patients treated with KISQALI plus any combination treatment. Causes of death were acute respiratory distress syndrome 1 (0.1%), acute respiratory failure 1 (0.1%), and sudden death (in a patient who had Grade 3 hypokalaemia and Grade 2 QT prolongation that improved to Grade 1 on the same day, both reported 10 days before the event) 1 (0.1%).

In Study F2301, on-treatment deaths, regardless of causality, were reported in 7 patients (1.4%) due to the underlying malignancy and 6 patients (1.2%) due to other causes while on treatment with KISQALI plus fulvestrant. Causes of death included one pulmonary embolism, one acute respiratory distress syndrome, one cardiac failure, one pneumonia, one hemorrhagic shock, and one ventricular arrhythmia. Seven patients (2.9%) died due to the underlying malignancy and 1 patient (0.4%) died due to pulmonary embolism while on placebo plus fulvestrant.

QT interval prolongation

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

A central analysis of ECG data (average of triplicate) showed 52 patients (4.9%) and 11 patients (1.4%) with at least one post-baseline QTcF interval >480 m sec for the KISQALI treatment arm and the placebo arms respectively. In study A2301, ECG assessments during steady-state treatment were collected only on Cycle 1, Day 15. Among the patients who had QTcF prolongation of >480 msecs, the median time to onset was 15 days regardless of the combination and these changes were reversible with dose interruption and/or dose adjustment (see 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY sections).

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 occurred in 8 of 1065 (0.8%) patients receiving KISQALI plus any combination partner. Dose interruptions due to neutropenia occurred in 434 of 1065 (40.8%) patients and led to dose reductions in 196 of 1065 (18.4%) of the patients receiving KISQALI plus letrozole (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS sections).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

ADRs from the phase III clinical studies (Table 7, 8 and 9) are listed by MedDRA system organ class (MedDRA version 18.1). 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.

Table 7 Adverse drug reactions observed in ≥ 10% and ≥ 2% higher than Placebo Arm in the phase III clinical study A2301

System Organ Class	KISQALI plus Letrozole N=334		Placebo plus Letrozole N=330	
	All grades	Grades 3/4	All grades	Grades 3/4
Adverse drug reactions	**%**	**%**	**%**	**%**
Blood and lymphatic system disorders				
Neutropenia	74	59	5	1
Leukopenia	33	21	4	<1
Anemia	19	1	5	1
Lymphopenia	11	7	2	1
Gastrointestinal disorders				
Nausea	52	2	29	1
Diarrhea	35	1	22	1
Vomiting	29	4	16	1
Constipation	25	1	19	0
Stomatitis	12	<1	7	0
Abdominal pain	11	1	8	0

System Organ Class	KISQALI plus Letrozole N=334		Placebo plus Letrozole N=330	
	All grades	Grades 3/4	All grades	Grades 3/4
Adverse drug reactions	**%**	**%**	**%**	**%**
General disorders and administration site conditions				
Fatigue	37	2	30	1
Peripheral edema	15	0	10	0
Asthenia	13	1	12	1
Pyrexia	13	<1	6	0
Infections				
Urinary tract infection	13	1	9	0
Investigations				
Abnormal liver function tests[1]	18	10	6	2
Metabolism and nutrition disorders				
Decreased appetite	19	2	15	<1
Musculoskeletal and connective tissue disorders				
Back pain	20	2	18	<1
Nervous system disorders				
Headache	22	<1	19	<1
Insomnia	12	<1	9	0

System Organ Class	KISQALI plus Letrozole N=334		Placebo plus Letrozole N=330	
	All grades	Grades 3/4	All grades	Grades 3/4
Adverse drug reactions	**%**	**%**	**%**	**%**
Respiratory, thoracic and mediastinal disorders				
Dyspnea	12	1	9	1
Skin and subcautaneous tissue disorders				
Alopecia	33	0	16	0
Rash[2]	20	1	8	0
Pruritus	15	1	6	0

[1]Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.
[2]Rash: rash, rash maculopapular.

Table 8 Adverse Drug Reactions Observed in ≥ 10% and ≥ 2% higher than Placebo Arm in the phase III clinical Study E2301 (NSAI)

System Organ Class	KISQALI plus NSAI plus goserelin N=248			Placebo plus NSAI plus goserelin N=247		
Adverse drug reactions	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Blood and lymphatic system disorders						
Neutropenia	80	56	12	8	3	< 1
Leukopenia	33	15	< 1	4	< 1	0
Anemia	20	4	0	9	2	0
Thrombocytopenia[1]	10	0	<1	2	0	<1
Gastrointestinal disorders						
Nausea	32	0	0	24	0	0
Vomiting	20	<1	0	18	0	0

Constipation	17	0	0	13	0	0
Stomatitis	13	0	0	9	< 1	0
Abdominal Pain	11	1	0	8	<1	0
General disorders and administration site conditions						
Pyrexia	18	< 1	0	7	<1	0
Asthenia	14	0	0	11	<1	0
Pain in extremity	15	0	0	10	1	0
Infections and Infestations						
Infections[2]	40	2	0	30	< 1	0
Investigations						
Abnormal liver function tests[3]	19	6	0	13	3	0
Musculoskeletal and connective tissue disorders						
Arthralgia	37	< 1	0	29	1	0
Respiratory, thoracic and mediastinal disorders						
Cough	18	0	0	11	0	0
Skin and subcutaneous tissue disorders						
Alopecia	21	0	0	14	0	0
Rash	19	< 1	0	10	0	0
Pruritus	11	0	0	5	0	0

Grading according to CTCAE 4.03 (Common Terminology Criteria for Adverse Events)
[1]Thrombocytopenia: thrombocytopenia, platelet count decreased
[2] Infections: urinary tract infections; respiratory tract infections; gastroenteritis.
[3] Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased

Table 9 Adverse Drug Reactions Observed in ≥ 10% and ≥ 2% higher than Placebo Arm in phase III clinical Study F2301

System Organ Class	KISQALI + fulvestrant N = 483			Placebo + fulvestrant N = 241		
Adverse drug reactions	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Blood and lymphatic system disorders						
Neutropenia	71	49	8	3	1	0

Leukopenia	29	13	<1	0.8	0	0
Anemia	19	4	0	7	3	0
Gastrointestinal disorders						
Nausea	47	2	0	31	1	0
Diarrhea	32	1	0	22	1	0
Vomiting	28	2	0	14	0	0
Constipation	26	1	0	13	0	0
Abdominal pain	19	2	0	14	1	0
Stomatitis	12	1	0	5	0	0
Dyspepsia	11	0	0	6	0	0
General disorders and administration site conditions						
Edema peripheral	16	0	0	8	0	0
Asthenia	15	<1	0	13	<1	0
Pyrexia	15	<1	0	7	0	0
Infections and Infestations						
Infections[1]	47	5	<1	34	3	0
Investigations						
Abnormal liver function tests[2]	17	8	2	10	2	0
Metabolism and nutrition disorders						
Decreased appetite	18	<1	0	12	0	0
Nervous system disorders						
Headache	24	0	1	21	0	<1
Dizziness	15	<1	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	25	0	0	17	0	0
Dyspnea	17	1	<1	14	2	0
Skin and subcutaneous tissue disorders						
Alopecia	20	0	0	5	0	0
Pruritus	21	<1	0	7	0	0
Rash	26	1	0	7	0	0

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

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

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

8.3 Less common clinical trial adverse reactions

Other clinically significant adverse drug reactions in Study A2301 reported in < 10% of patients and with higher incidences reported in the KISKALI plus letrozole arm (all grades) are presented below:

Blood and lymphatic system disorders: thrombocytopenia (9%), febrile neutropenia (2%)

Eye disorders: lacrimation increased (7%), dry eye (6%)

Cardiac disorders: syncope (3%)

Gastrointestinal disorders: dysgeusia (9%), dyspepsia (7%)

Hepatobiliary disorders: hepatotoxicity[#] (2%)

Investigations: blood creatinine increased (7%), weight decreased (6%), electrocardiogram QT prolonged (5%)

Metabolism and nutrition disorders: hypocalcemia (5%), hypokalemia (5%), hypophosphatemia (4%)

Respiratory, thoracic and mediastinal disorders: epistaxis (5%), pulmonary embolism (1%)

Skin and subcautanous tissue disorders: erythema (5%)

[#]Hepatotoxicity: hepatocellular injury, drug-induced liver injury, hepatotoxicity, hepatic failure (single non-fatal case), autoimmune hepatitis (single case).

Other clinically significant adverse drug reactions in Study E2301 reported in < 10% of patients and with higher incidences reported in the Kisqali plus NSAI arm (all grades) are presented below:

Blood and lymphatic system disorders: febrile neutropenia (3%)

Eye disorders: lacrimation increased (5%), dry eye (4%)

Gastrointestinal disorders: oropharyngeal pain (9%), dyspepsia (7%)

Investigations: electrocardiogram QT prolonged (9%)

Metabolism and nutrition disorders: hypocalcemia (2%)

Skin and subcutaneous tissue disorders: dry skin (9%), vitiligo (3%)

Other clinically significant adverse drug reactions in Study F2301 reported in < 10% of patients and with higher incidences reported in the Kisqali plus fulvestrant arm (all grades) are presented below:

Blood and lymphatic system disorders: thrombocytopenia (9%)

Cardiac disorders: syncope (2%)

Ear and labyrinth disorders: vertigo (6%)

Eye disorders: dry eye (6%), lacrimation increased (5%)

Gastrointestinal disorders: dysgeusia (7%), dry mouth (5%)

Investigations: electrocardiogram QT prolonged (6%)

Metabolism and nutrition disorders: hypocalcemia (5%)

Skin and subcutaneous tissue disorders: dry skin (8%), erythema (5%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Clinically relevant abnormalities of routine hematological or biochemical laboratory values from the phase III studies, are presented in Tables 10, 11 and 12.

Table 10 Laboratory abnormalities observed in the phase III clinical study A2301

Laboratory abnormalities	KISQALI plus Letrozole N=334 %		Placebo plus Letrozole N=330 %	
	All grades	Grades 3/4	All grades	Grades 3/4
	%	%	%	%
Leukocyte count decreased	93	34	29	2
Neutrophil count decreased	93	60	24	1
Hemoglobin decreased	57	2	26	1
Lymphocyte count decreased	51	14	22	4
Platelet count decreased	29	1	6	<1
Alanine aminotransferase increased (ALT)	46	10	36	1
Aspartate aminotransferase increased (AST)	44	7	32	2
Creatinine increased	20	1	6	0
Phosphorous decreased	13	5	4	1
Potassium decreased	11	1	7	1
Bilirubin increased	5	1	3	<1

Table 11 Laboratory Abnormalities Observed in ≥ 10% of Patients in the phase III clinical Study E2301

Laboratory abnormalities	KISQALI + NSAI + goserelin N = 248			Placebo + NSAI + goserelin N = 247		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
HEMATOLOGY						
Leukocyte count decreased	94	37	2	33	< 1	< 1
Neutrophil count decreased	92	56	11	29	3	0
Hemoglobin decreased	85	3	0	54	< 1	0
Lymphocyte count decreased	59	17	2	21	3	< 1
Platelet count decreased	29	< 1	0	10	0	< 1
CHEMISTRY						
Alanine aminotransferase increased	41	7	0	33	2	< 1
Aspartate aminotransferase increased	44	6	0	38	1	< 1
Creatinine increased	11	0	0	2	0	0
Phosphorous decreased	16	2	0	15	< 1	< 1
Potassium decreased	15	< 1	< 1	15	< 1	< 1
Gamma-glutamyl transferase increased	44	7	2	43	9	1
Glucose serum decreased	13	< 1	<1	11	< 1	0

Table 12 Laboratory Abnormalities Observed in ≥ 10% of Patients in the phase III clinical Study F2301

Laboratory abnormalities	KISQALI + fulvestrant N = 483			Placebo + fulvestrant N = 241		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
HEMATOLOGY						
Leukocyte count decreased	95	28	1	28	<1	0
Neutrophil count decreased	93	48	8	23	1	0
Hemoglobin decreased	63	6	0	36	3	0
Lymphocyte count decreased	73	17	2	38	5	<1
Platelet count decreased	35	1	1	12	0	0
CHEMISTRY						
Creatinine increased	67	1	<1	35	<1	0

Laboratory abnormalities	KISQALI + fulvestrant N = 483			Placebo + fulvestrant N = 241		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gamma-glutamyl transferase increased	56	8	1	50	9	2
Aspartate aminotransferase increased	55	6	2	47	3	0
Alanine aminotransferase increased	48	9	3	39	2	0
Glucose serum decreased	24	0	0	20	0	0
Phosphorous decreased	19	5	0	9	1	0
Albumin decreased	12	0	0	8	0	0

8.5 Post-Market Adverse Reactions

The following ADR is derived from post-marketing experience with KISQALI via spontaneous case reports and literature cases. As this reaction is reported voluntarily from a population of uncertain size, it is not possible to reliably estimate its frequency which is therefore categorized as not known.

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

Skin and subcutaneous tissue disorders	
	Toxic epidermal necrolysis (TEN)

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

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

9.2 Drug-Drug Interactions

Concomitant use of KISQALI and tamoxifen resulted in approximately a 2-fold increase in tamoxifen exposure and increased QTc prolongation. Avoid concomitant use of tamoxifen and drugs known to prolong QT interval, such as anti-arrhythmic medicines (see below).

Concomitant use of KISQALI and CYP3A inhibitors and inducers may respectively increase and decrease exposure to ribociclib. Co-administration of KISQALI and a strong CYP3A inhibitor or a strong CYP3A inducer should be avoided (see below).

Concomitant use of KISQALI and a CYP3A4 substrate may increase the exposure to the substrate. Co-

administration of KISQALI and a CYP3A substrate with a narrow therapeutic index should be avoided; if avoidance is not possible, the dose of the substrate may need to be reduced (see below).

Drugs that may increase ribociclib plasma concentrations

CYP3A inhibitors: 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, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole should be avoided.

Alternative concomitant medications with a low potential to inhibit CYP3A should be considered and patients should be monitored for ADRs *(*see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS sections).

If co-administration of KISQALI with a strong CYP3A inhibitor cannot be avoided, the KISQALI dose should be reduced to 200 mg. However, there are no clinical data with this dose adjustment (see 4 DOSAGE AND ADMINISTRATION). If the strong inhibitor is discontinued, the KISQALI dose should be resumed (after at least 5 elimination half-lives of the CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Due to inter-patient variability (see 10 CLINICAL PHARMACOLOGY), 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 interruption or reduction may be required until toxicity has resolved *(*see 4 DOSAGE AND ADMINISTRATION section).

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.

Drugs that may decrease ribociclib plasma concentrations

CYP3A inducers: 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 7 WARNINGS AND PRECAUTIONS section).

Drugs that may have their plasma concentrations altered by ribociclib

CYP3A4 substrates: 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 PK (PBPK) 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 co-administration of KISQALI with a CYP3A substrates with a narrow therapeutic index should be avoided. If avoidance is not possible, 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.

CYP1A2 substrates: 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).

Anti-arrhythmic medicines and other medicinal products that may prolong the QT interval

QTc interval prolongation has been reported in patients treated with KISQALI. The concomitant administration of KISQALI with other medicinal products known to prolong the QT interval or induce Torsade de Pointes should be avoided.

While the patient is using KISQALI, other QTc-prolonging drugs should be discontinued and alternative concomitant drugs that do not prolong the QTc interval should be chosen. When it is not feasible to avoid concomitant use of drugs known to prolong the QTc interval, obtain ECGs and electrolytes prior to the start of treatment, after initiation of any drug known to prolong QTc interval, and monitor periodically as clinically indicated during treatment.

Drugs that have been associated with QTc interval prolongation and/or Torsade de Pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc interval prolongation and/or Torsade de Pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone)
- Class 1C antiarrhythmics (e.g., flecainide, propafenone)
- antipsychotics (e.g., olanzapine, chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone)
- antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants [e.g., amitriptyline, imipramine, maprotiline])
- opioids (e.g., methadone)
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, azithromycin, tacrolimus)
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin)
- pentamidine
- antimalarials (e.g., quinine, chloroquine)
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole)
- domperidone
- anagrelide
- ivabradine
- 5-hydroxytryptamine (5-HT)3 receptor antagonists (e.g., ondansetron)
- tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, ceritinib, vandetanib)
- arsenic trioxide
- histone deacetylase inhibitors (e.g., vorinostat)
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)

Tamoxifen

KISQALI is not indicated for use in combination with tamoxifen and combined use is not recommended because of increased QTc prolongation (See 7 WARNINGS AND PRECAUTIONS; 10 CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). Data from a clinical trial in patients with breast cancer indicated that tamoxifen exposure (C_{max} and AUC_{0-24h}) was increased approximately 2-fold following co-administration of ribociclib and tamoxifen.

Drugs that affect electrolytes

Use of KISQALI with drugs that can decrease electrolyte levels should be avoided to the extent possible. Such drugs include, but are not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high-dose corticosteroids; and proton pump inhibitors.

Drugs that reduce heart rate

Avoid using KISQALI concomitantly with drugs that reduce heart rate (e.g., beta-blockers, digitialis glycosides, non-dihydropyridine calcium channel blockers, cholinesterase inhibitors, alpha2-adrenoceptor agonists, I_f inhibitors and sphingosine-1 phosphate receptor modulators).

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval, inhibit CYP3A, or decrease electrolytes, as well as for older drugs for which these effects have recently been established.

Gastric pH elevating medications

Ribociclib exhibited 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.

Effect of ribociclib on transporters

Ribociclib may inhibit Breast Cancer Resistance Protein (BCRP), Organic Cation Transporter 2 (OCT2), Multidrug and Toxic Compound Extrusion Protein-1 (MATE1), and human Bile Salt Export Pump (BSEP) at clinically relevant concentrations. Patients should be closely monitored when co-administered with ribociclib and substrates of these transporters.

In vitro evaluations indicated that ribociclib has a low potential to inhibit the activities of drug transporters P-glycoprotein (P-gp), Organic Anion Transporter 1 /3 (OAT1/3), Organic anion transporting polypeptides B1/B3 (OATP1B1/B3), Organic Cation Transporter 1 (OCT1), Multidrug and Toxic Compound Extrusion Protein 2K (MATE2K) and Multidrug resistance-associated protein 2 (MRP2) at clinically relevant concentrations.

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*.

Effect of ribociclib on CYP enzymes

In vitro, ribociclib did not inhibit CYP2E1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Ribociclib was a reversible inhibitor of CYP1A2 and CYP3A4/5 and a time-dependent inhibitor of CYP3A4/5 at clinically relevant concentrations. No induction of CYP1A2, CYP2B6, CYP2C9 or CYP3A4 was observed *in vitro* at clinically relevant concentrations.

Co-administration with Letrozole

Data from a clinical trial in patients with breast cancer and population PK analysis indicated no drug interaction between ribociclib and letrozole following co-administration of the drugs. (See Table 14, Pharmacokinetics).

Co-administration with Exemestane: Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and exemestane following coadministration of the drugs.

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

Co-administration with 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.

Co-administration with Goserelin: No formal examination of the potential drug interaction with goserelin was done. The metabolism of goserelin is not CYP-mediated; rather hydrolysis of C-terminal amino acids is the major clearance mechanism. Based on the available information, goserelin is not expected to affect the metabolism of nor be affected by co-administered drugs. It is not clear if all molecules in this drug class would have no potential for drug interaction with ribociclib.

9.3 Drug-Food Interactions

KISQALI can be administered with or without food (see 4 DOSAGE AND ADMINISTRATION).

Compared to the fasted state, oral administration of a single 600 mg 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 10 CLINICAL PHARMACOLOGY section).

KISQALI should not be administered with grapefruit, grapefruit juice, or grapefruit-containing products, all of which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's wort (*Hypericum perforatum*) is an inducer of CYP3A4/5 that may decrease ribociclib plasma concentrations and should be avoided.

9.5 Drug-Laboratory Test Interactions

Interactions between KISQALI and laboratory tests have not been studied.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ribociclib is an 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) (see 16 NON-CLINICAL TOXICOLOGY, DETAILED PHARMACOLOGY, Pharmacodynamics section).

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 *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. Additionally, *in vivo* antitumor activity of combination of ribociclib with fulvestrant was assessed in immune-deficient mice bearing human breast cancer xenografts. The combination of ribociclib and fulvestrant resulted in complete tumor growth inhibition.

10.2 Pharmacodynamics

Cardiac electrophysiology

In the phase III clinical trial CLEE011A2301, the phase Ib/II trial CLEE011X2107, and the phase III trial CLEE011E2301 in patients with HR+, HER2-negative breast cancer, ribociclib 600 mg was administered once daily for 21consecutive days followed by 7-day planned break (28-day cycle, 3 weeks on/1 week off). In CLEE011E2301 and CLEE011X2107, QTcF interval prolongation occurred that was maximal during steady-state treatment (day 8-21) (Table 13).

Table 13 Mean QTc change from baseline observed in Studies CLEE011A2301 and CLEE011X2107

Study	Treatment	Cycle/Day	Time (h)	n	Mean Change from Baseline QTc (msec)	90% CI
CLEE011A2301	Ribociclib 600 mg + Letrozole 2.5 mg	C1/D15	0	308	13.5	12.1, 14.9
			2	277	19.6	18.0, 21.2
	Placebo + Letrozole 2.5 mg	C1/D15	0	313	1.7	0.5, 2.8
			2	307	1.8	0.7, 3.0
CLEE011X2107	Ribociclib 600 mg + Letrozole 2.5 mg	C1/D1	2	46	5.9	3.3, 8.6
			4	46	12.3	9.4, 15.3
		C1/D8	0	46	10.6	7.4, 13.7
			4	46	19.3	15.5, 23.1
		C1/D15	0	46	11.5	7.4, 15.6
			2	42	23.0	19.1, 26.9
			4	42	21.5	17.1, 25.9
			8	43	20.3	16.5, 24.1
		C1/D21	0	43	14.3	11.1, 17.5
			2	39	21.7	17.6, 25.8
			4	40	24.6	18.9, 30.3

In Study CLEE011E2301, the magnitude of the QTc prolongation effect was greater when KISQALI was administered in combination with tamoxifen than when KISQALI was administered in combination with NSAI. The QTc prolongation effects of tamoxifen and KISQALI appeared to be approximately additive. Because of the lengthy elimination half-life values of tamoxifen and its active metabolite, only the Cycle

3 data are expected to represent steady-state effects, with mean changes from baseline QTc of 27.6-32.6 msec in the KISQALI plus tamoxifen group and 13.7-17.6 msec in the placebo plus tamoxifen group KISQALI is not indicated for use in combination with tamoxifen and combined use is not recommended (see 9 DRUG INTERACTIONS-Tamoxifen).

Ribociclib also appears to decrease heart rate. In study CLEE011X2107 (Arm 1; N=47), the mean change from baseline in heart rate was -5.5 bpm (90% CI: -7.3, -3.7, n=42) at 2 h post-dosing on C1D15 and -7.1 bpm (90% CI -8.8, -5.3) at 2 h post-dosing on C1D21.

In study CLEE011A2301 (N=334), the mean change from baseline in heart rate on C1D15 at 2 h post-dose was -2.2 bpm (90% CI -3.2, -1.2; n=277) in the ribociclib plus letrozole arm and 1.7 bpm (90% CI: 0.8, 2.7, N=307) in the placebo plus letrozole arm.

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 1,200 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval. The estimated QTcF interval mean change from baseline for KISQALI 600 mg dose in combination with NSAI or fulvestrant was 22.00 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 7 WARNING AND PRECAUTIONS).

10.3 Pharmacokinetics

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

Table 14 Summary of Ribociclib Pharmacokinetic Parameters

	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (hr•ng/mL)	$T_{1/2}$,acc (h)	CL/F (L/h)
Multiple doses (C1, D18/21) 600 mg (study X2101) Pooled[1]	n=57 1820 (62.4)	n=57 2.40 (0.683, 7.82)	n=54 23800 (66.0)	n=49 32.0 (63.2)	n=53 25.5 (65.7)
Multiple doses (C1 D21) 600 mg (study X2107)	n=28 1720 (44.6)	n=28 2.11 (1.05, 7.67)	n=23 23290 (52.2)	n=18 30.4 (38.7)	n=20 26.5 (53.2)

C: cycle; D: day; n: number of patients with cancer with corresponding evaluable PK parameters; PK: pharmacokinetics.

Data are presented as geometric mean (CV% geo mean) for all parameters except for T_{max} which is presented as median (range)

[1] Pooled data from patients with cancer receiving intermittent schedule (3 weeks on 1 week off) and patients with cancer with continuous dosing (once daily for 28 days)

Absorption

Following oral administration of ribociclib 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 1,200 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: 0.972 to 6.40)

Compared to the fasted state, oral administration of a single 600 mg 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 9 DRUG INTERACTIONS, Drug-Food Interaction section).

Distribution:

Binding of ribociclib to human plasma proteins *in vitro* was approximately 70% and independent of concentration (10 to 10,000 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 1,090 L based on the population pharmacokinetic analysis. In rats with intact blood brain barriers, there was relatively low brain penetration by ribociclib following oral administration and intracarotid injection.

Metabolism:

In vitro and *in vivo* studies indicated that ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of [^{14}C]ribociclib to humans, the primary metabolic pathways for ribociclib involved oxidation [dealkylation, C and/or N-oxygenation, oxidation (-2H)] and combinations thereof. Phase II conjugates of ribociclib phase I metabolites involved N-acetylation, 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. The pharmacological effects of ribociclib are considered to be 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% of the dose 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 600 mg in patients with advanced cancer. The geometric mean half-life ($T_{1/2}$) of ribociclib ranged from 29.7 to 54.7 hours and the geometric mean CL/F of ribociclib ranged from 39.9 to 77.5 L/hr at 600 mg across studies in healthy subjects.

Ribociclib is eliminated mainly via 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.

Special Populations and Conditions

- **Pediatrics (< 18 years of age):** There are limited data in pediatric patients and the pharmacokinetics of ribociclib in this population has not been established.
- **Geriatrics (≥ 65 years of age):** Of 334 patients who received KISQALI plus letrozole in the phase III study A2301 (MONALEESA 2), 150 patients (44.9%) were ≥65 years of age. Of 484 patients who received KISQALI plus fulvestrant in the phase III study F2301 (MONALEESA 3), 226 patients (46.7%) were ≥65 years of age and 65 patients (13.4%) were ≥75 years of age No major differences in safety of KISQALI were observed between these patients and younger patients (see 4 DOSAGE AND ADMINISTRATION).
- **Effect of age, weight, gender and race:** 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. Two of 42 patients in the MONALEESA3 study (F2301), who had population pharmacokinetic simulated exposure and had age 65 or older as well as weight less than 59 kg, had Grade 3 or 4 pulmonary toxicity, in the context of progression of underlying malignancy.
- **Hepatic Impairment:** Based on a pharmacokinetic trial in subjects with hepatic impairment (Child-Pugh Class), mild hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in subjects 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 (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1 to ≤1.5 xULN and AST any value), mild hepatic impairment had no effect on the exposure of ribociclib.
- **Renal Impairment:** The effect of renal function on the pharmacokinetics of ribociclib was assessed in a renal impairment study in non-cancer subjects that included 14 subjects with normal renal function (Absolute Glomerular Filtration Rate (aGFR) ≥90 mL/min), 8 subjects with mild renal impairment (aGFR 60 to <90 mL/min), 6 subjects with moderate renal impairment (aGFR 30 to <60 mL/min), 7 subjects with severe renal impairment (aGFR 15 to <30 mL/min), and 3 subjects with end stage renal disease (ESRD) (aGFR <15 mL/min) at single oral ribociclib dose of 400 mg.

  The geometric means AUC_{inf} (geometric %CV, n) for the following cohorts were: normal renal function 4100 ng*hr/mL (53.2%, 14), mild renal impairment 6650 ng*hr/mL (36.4%, 8), moderate renal impairment 7960 ng*hr/mL (45.8%, 6), severe renal impairment 10900 ng*hr/mL (38.1%, 7), and ESRD 13600 ng*hr/mL (20.9%, 3). The C_{max} (geometric %CV, n) values

for the cohorts were: normal 234 ng/mL (58.5%, 14), mild 421 ng/mL (31.6%, 8), moderate 419 ng/mL (30.3%, 6), severe 538 ng/mL (43.3%, 7), and ESRD 593 ng/mL (11.3%, 3).

Based on a 2.67- and 2.30-fold increase in AUC_{inf} and C_{max}, respectively, in subjects with severe renal impairment versus those with normal renal function, a starting dose of 200 mg ribociclib is recommended for patients with severe renal impairment (see 4 DOSAGE AND ADMINISTRATION).

The effect of renal function on the pharmacokinetics of ribociclib was also assessed in cancer patients in clinical trials. Based on a population pharmacokinetic analysis that included 77 cancer patients with normal renal function [estimated glomerular filtration rate (eGFR) ≥90 mL/min/1.73 m2], 76 patients with mild renal impairment (eGFR 60 to <90 mL/min/1.73 m2) and 35 patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m2), mild and moderate renal impairment had no clinically meaningful effect on the exposure of ribociclib. Similar findings were reported in a subgroup pharmacokinetic analysis based on three of the clinical trials in cancer patients treated with ribociclib 600 mg daily.

Both the population and subgroup PK analyses suggest that no starting dose adjustment is necessary in patients with mild or moderate renal impairment (see 4 DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL

KISQALI should not be stored above 30°C.

Store in original package to protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: ribociclib succinate

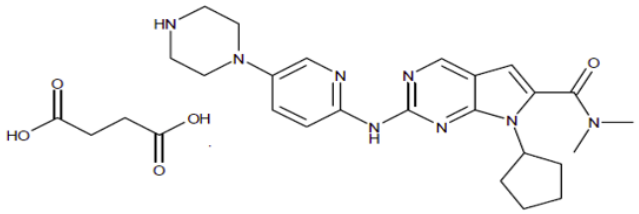
Chemical name: Butanedioic acid—7-cyclopentyl-*N*,*N*-dimethyl-2-{[5-(piperazin-1-yl) pyridin-2-yl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (1/1)

Molecular formula and molecular mass: Free base: $C_{23}H_{30}N_8O$

Succinate salt: $C_{23}H_{30}N_8O.C_4H_6O_4$

552.64 g/mole (salt form) [free base: 434.55 g/mol]

Structural formula:



Physicochemical properties:

Physical Description: Light yellow to yellowish brown crystalline powder

Solubility: The solubility of ribociclib succinate drug substance is pH-dependent, with high solubility in acidic media and low solubility in neutral media.

In acidic conditions, ribociclib succinate has a solubility > 2.4 mg/mL, but at pH 6.8 ribociclib freeform precipitates and the solubility decreases to 0.8 mg/mL. Ribociclib succinate is therefore considered to have low solubility according to the Biopharmaceutics Classification System (BCS).

pH: The pH of a 1.0% m/V solution of ribociclib succinate drug substance in water is 5.19.

pKa: The drug substance is an anhydrous succinate salt of ribociclib with pKa values of 5.3 and 8.5.

Partition Coefficient/Distribution Coefficient:

Distribution coefficients were measured for ribociclib succinate drug substance at different pH at 37 °C. The different values as function of the pH are reported below.

Distribution coefficient:

Media	pH (measured)	Distribution coefficient, D	Log D (measured)
n-octanol / pH 1 (0.1 N HCl)	0.93	0.00290	-2.57
n-octanol / pH 5.5 (acetate buffer)	5.57	0.471	-.033
n-octanol / pH 7.5 (phosphate buffer)	7.45	71.9	1.85

Melting point: Ribociclib succinate drug substance shows melting followed by decomposition at about 205 °C (by DSC).

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Study CLEE011A2301 (MONALEESA-2)

Table 15 - Summary of patient demographics for MONALEESA-2

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age (Range)	Gender
LEE011 A2301	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	Route of Administration: Oral Dosage: Ribociclib (600 mg once daily, on Days 1-21 of a 28- day cycle) plus letrozole (2.5 mg once daily in a 28- day cycle) Placebo (daily, on Days 1-21 of a 28-day cycle) plus letrozole (2.5 mg once daily in a 28-day cycle) Duration: Until disease progression, unacceptable toxicity, death, or study treatment discontinuation for any other reason. The median duration of exposure to the study treatment was similar in both treatment groups: 13.0 months in the ribociclib plus letrozole group (range: 0 to 23 months) and 12.4 months (range: 0 to 22 months) in the placebo plus letrozole group	A total of 668 patients with advanced breast cancer Ribociclib plus Letrozole: 334 female patients Placebo plus Letrozole: 330 female patients 4 patients in Placebo plus Letrozole never treated	Ribociclib plus letrozole Mean= 61.4 (23-91)years of age Placebo plus letrozole All patients 61.9 (29-88) years of age	Post-menopausal women

Study CLEE011A2301 was a randomized, double-blind, placebo-controlled, multicenter phase III clinical study of KISQALI plus letrozole versus placebo plus letrozole for the treatment of postmenopausal women with HR positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease.

A total of 668 patients were randomized 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. 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 disease progression.

Patients enrolled in this study had a median age of 62 years (range 23 to 91) with 44.2% 65 years of age and older, including 69 patients (10.3%) of age 75 years and older. 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. 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. Patients with CNS metastases documented at baseline were not permitted in this study.

Study CLEE011E2301 (MONALEESA-7)

Table 16- Summary of patient demographics for MONALEESA-7

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age (Range)	Gender
LEE011 E2301	A Phase III randomized, double-blind, placebo-controlled study comparing ribociclib plus goserelin plus either tamoxifen or a NSAI (letrozole or anastrozole), (henceforth ribociclib arm) versus placebo plus goserelin plus either tamoxifen or a NSAI (letrozole or anastrozole) (henceforth placebo arm), in premenopausal women with HR-positive, HER2-	Route of Administration: Oral Dosage Ribociclib arm: Ribociclib (600 mg orally once daily, on Days 1-21 of a 28-Day cycle) plus goserelin (3.6 mg subcutaneous implant on Day 1 of 28-day Cycle) plus either tamoxifen (20 mg orally once daily) or a NSAI (either letrozole 2.5 mg orally once daily or anastrozole 1 mg orally once daily). Dosage Placebo arm: Placebo (orally daily, on Days 1-21 of a 28-day cycle) plus goserelin (3.6 mg subcutaneous implant on Day 1 of 28-day Cycle) plus either tamoxifen (20 mg orally once daily) or a NSAI (letrozole 2.5 mg orally once daily or anastrozole 1 mg orally once daily). Duration of treatment: until	Total of 672 Randomized 1:1 335 patients in ribociclib arm and 337 patients in placebo arm. All randomized patients received study treatment.	Median age of patients in the study was 44 years (min to max: 25 to 58) and 72.3% were ≥ 40 years of age. Ribociclib arm: median age was 43 years (min to max: 25 - 58) and 70.7% were ≥ 40 years of age. Placebo arm: median age was 45 years (min to max: 29 - 58) and 73.9% were ≥ 40 years of age.	Pre- or Peri menopausal women with HR-positive, HER2-negative advanced breast cancer who received no prior hormonal therapy for their advanced disease

	negative advanced breast cancer who received no prior hormonal therapy for advanced breast cancer.	disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason. The median duration of follow-up (defined as the time from randomization to the data cut-off date) was 19.2 months (min-max: 12.6 - 32.1). The study is currently ongoing.			

Study CLEE011E2301 was a randomized, double-blind, placebo-controlled multicenter phase III clinical study comparing KISQALI plus either a non-steroidal aromatase inhibitor (NSAI) or tamoxifen and goserelin versus placebo plus either a NSAI or tamoxifen and goserelin for the treatment of pre- and perimenopausal women with (HR)-positive, HER2-negative, advanced breast cancer.

A total of 672 patients were randomized 1:1 to receive KISQALI 600 mg 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 (NSAI and goserelin versus tamoxifen and goserelin). Demographics and baseline disease characteristics were balanced and comparable between study arms.

Tamoxifen 20 mg or NSAI (letrozole 2.5 mg or anastrozole 1 mg) were given orally once daily on a continuous schedule; goserelin 3.6 mg was administered as sub-cutaneous injection on day 1 of each 28 day cycle, with either KISQALI 600 mg or placebo given orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. Patients were not allowed to cross over from placebo to KISQALI during the study or after disease progression. Patients were not allowed to switch between endocrine combination partners.

Patients enrolled in the study had a median age of 44 years (range 25 to 58) and 27.7% of patients were younger than 40 years of age. The majority were Caucasian (57.7%), Asian (29.5%), or Black (2.8%) and nearly all patients (99.0%) had an ECOG performance status of 0 or 1. Of these 672 patients, 14.0% had received prior chemotherapy for metastatic disease. Of the 672 patients, 32.6% of patients had received chemotherapy in the adjuvant vs 18.0% in the neo-adjuvant setting and 39.6% had received endocrine therapy in the adjuvant vs 0.7% in the neo-adjuvant setting prior to study entry. Approximately 40.2% of patients had *de novo* metastatic disease, 23.7% had bone only disease, and 56.7% had visceral disease.

Study CLEE011F2301 (MONALEESA-3)

Table 17 – Summary of patient demographics for MONALEESA-3

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age (Range)	Gender

LEE011 F2301	A randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2 negative, advanced breast cancer who have received no or only one line of prior endocrine treatment.	Route of Administration: Oral Dosage: Ribociclib (600 mg orally once daily on Days 1-21 of a 28-day cycle) plus fulvestrant (500 mg intramuscular [im] injection on Cycle 1 Days 1 and 15 and on Day 1 of subsequent cycles). Placebo (orally once daily on Days 1-21 of a 28-day cycle) plus fulvestrant (500 mg im injection on Cycle 1 Days 1 and 15 and on Day 1 of subsequent cycles). Duration until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.	726 patients were randomized 2:1 with 484 patients in the ribociclib plus fulvestrant arm and 242 patients in the placebo plus fulvestrant arm. 2 patients never received study treatment.	Median age of patients in the study was 63 years (min to max: 31 to 89); 46.7% were ≥ 65 years of age and 13.8 were ≥ 75 years of age. Ribociclib arm: Median age was 63 years (min to max: 31 to 89). Placebo arm: Median age was 63 years (min to max: 34 to 86).	Men and Post menopausal women

MONALEESA-3 was a randomized double-blind, placebo controlled study of KISQALI in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor (HR)-positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment.

A total of 726 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. First-line patients with advanced breast cancer (A) include de novo advanced breast cancer with no prior endocrine therapy, and patients who relapsed after 12 months of (neo) adjuvant endocrine therapy completion.

Second-line patients' subgroup (B) includes those patients whose disease relapsed during adjuvant therapy or less than 12 months after endocrine adjuvant therapy completion, and those who progressed to first line endocrine therapy. Demographics and baseline disease characteristics were balanced and comparable between study arms. KISQALI 600 mg or placebo was given orally daily for 21 consecutive days followed by 7 days off treatment in combination with fulvestrant 500 mg administered intramuscularly on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1 and every 28 days thereafter.

Patients enrolled in this study had a median age of 63 years (range 31 to 89); 46.7% of patients were 65 years and older, including 13.8% of patients 75 years of age and older. The patients included were Caucasian (85.3%), Asian (8.7%), or 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 whom 19.1 % of patients had *de novo* metastatic disease). Approximately 43% of patients had received chemotherapy in the adjuvant vs 13.1% in the neo-adjuvant setting and 58.5% had received endocrine therapy in the adjuvant vs 1.4% in the neo-adjuvant setting prior to study entry, Approximately 21% of patients had bone-only disease and 60.5% of patients had visceral disease.

14.2 Study Results

Study CLEE011A2301 (MONALEESA-2)

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 the 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 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 (FAS) (HR = 0.556; 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 KISQALI plus letrozole. The median PFS was not reached in the KISQALI plus letrozole arm [95% CI: 19.3 – not reached (NR)] at the time of the primary analysis. The median PFS was 14.7 months (95% CI, 13.0, and 16.5) for the placebo plus letrozole arm.

Results were consistent across the subgroups of age, race, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone only metastatic disease (Figure 2).

Updated progression free survival is summarized in Table 18 and the Kaplan-Meier curve for PFS is provided in Figure 1.

The global health status/Quality of Life (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 the primary PFS analysis, overall survival was not mature with 11% of events.

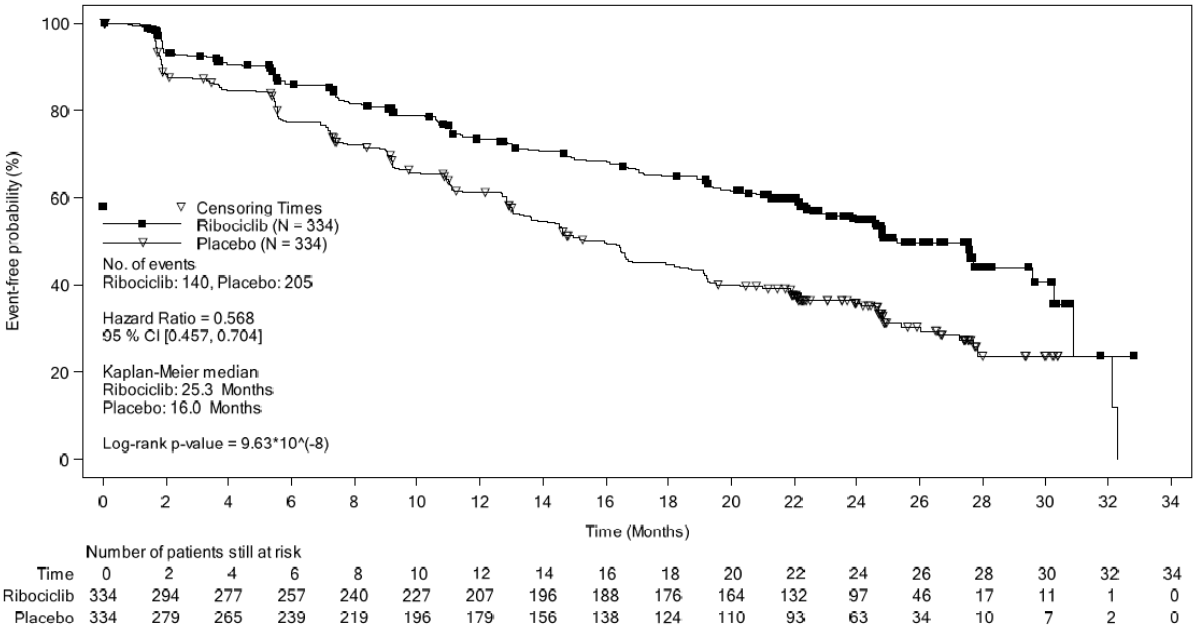
As shown in Table 18, an update of efficacy data resulted in a median PFS of 25.3 months (95% CI: 23.0, 30.3) for ribociclib plus letrozole treated patients and 16.0 months (95% CI: 13.4, 18.2) for patients receiving placebo plus letrozole; 54.7% of patients receiving ribociclib plus letrozole were estimated to be disease 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 18 Efficacy Results Based on Investigator Assessment for MONALEESA-2 (02-Jan-17 cut-off)

	Ribociclib plus letrozole N=334	**Placebo plus letrozole N=334**
Progression free survival		
Median [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 – MONALEESA-2 (Full analysis set -02-Jan-17 cut-off)**

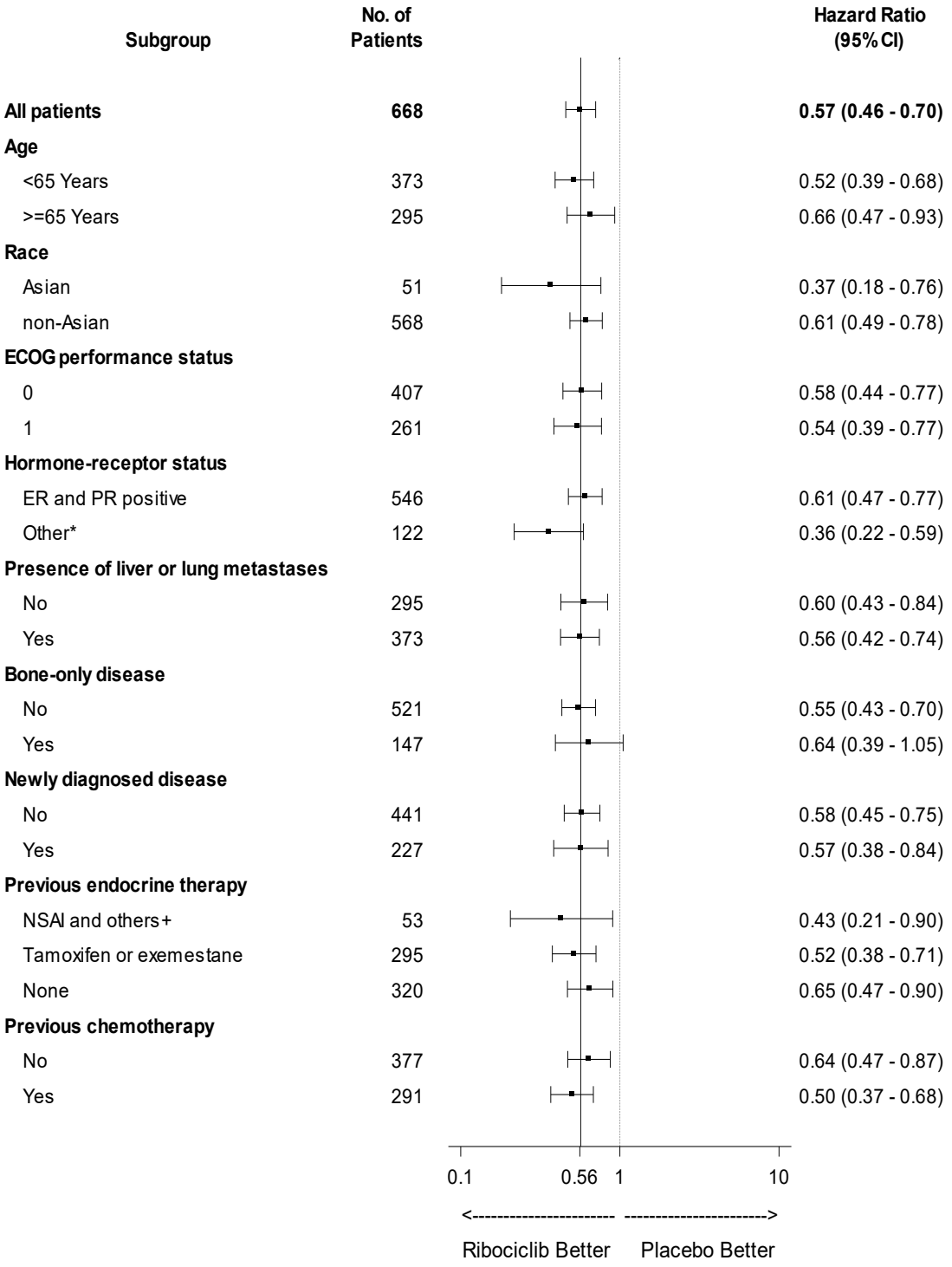


Number of patients still at risk

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

In patients with measurable disease, the overall response rate according to local radiologist assessment was 52.7% of patients (95% CI: 46.6%, 58.9%) in the KISQALI plus letrozole arm and 37.1% (95% CI: 31.1%, 43.2%) in the placebo plus letrozole arm.

Figure 2 **Forest plot of Subgroup analysis of PFS based on Investigator assessment – MONALEESA-2 (Full analysis set 02-Jan-17 cut-off)**



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

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 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; 0.561 [95% CI: 0.424, 0.743]), median progression-free survival [mPFS] 24.8 months vs 13.4 months respectively for the ribociclib and placebo arms respectively; the same benefit was observed for those patients, without liver and/or lung disease (HR; 0.597 [95% CI: 0.426, 0.837], mPFS 27.6 months versus 18.2 months).

Study CLEE011E2301 (MONALEESA-7)

Primary analysis

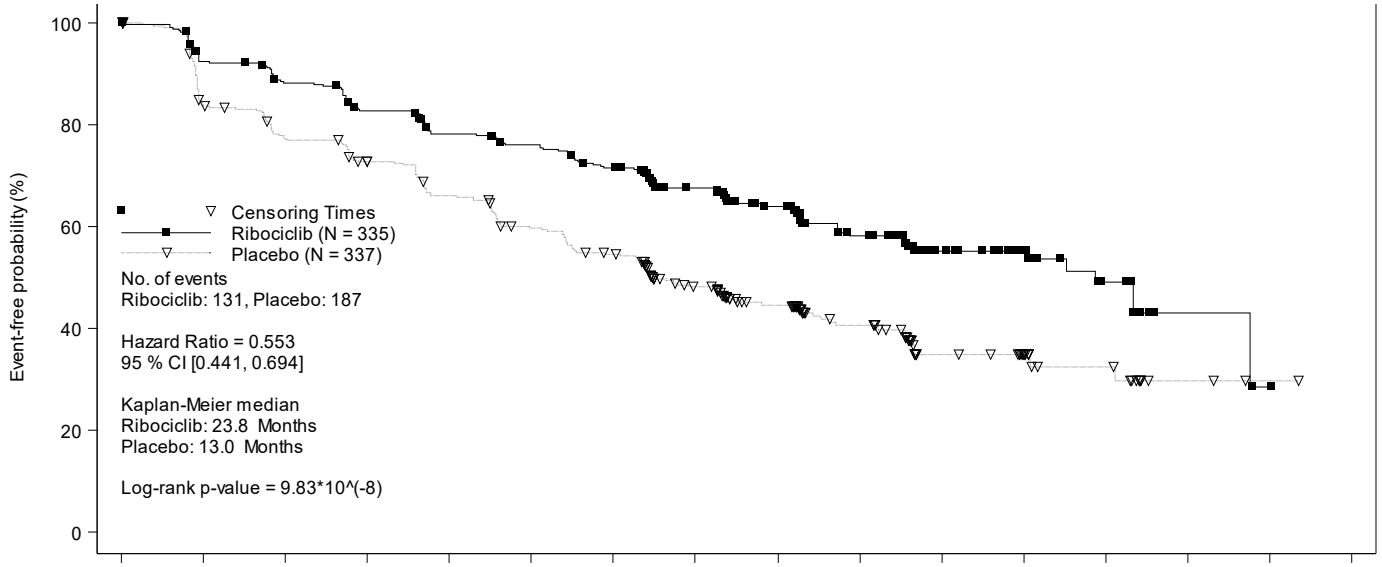
The primary efficacy endpoint for the study was met after observing 318 progression-free survival (PFS) events using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, based on the investigator assessment in the full analysis set, and supported by a blinded independent central radiological assessment.

The median follow-up duration at the time of the primary PFS analysis was 19.2 months.

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 (19.1, not estimable (NE)) in the KISQALI plus NSAI subgroup and 13.8 months (12.6, 17.4) in the placebo plus NSAI population [HR: 0.569 (95% CI: 0.436, 0.743)], which was consistent with the overall study population regardless of combination partner. Efficacy results are presented in Table 19 and the Kaplan-Meier curve for PFS in Figures 3 and 4. Results in the KISQALI plus NSAI population were consistent across subgroups of age, race, prior adjuvant/ neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone only metastatic disease (Figure 5).

The global health status./QoL showed no relevant difference between KISQALI compared with placebo.

Figure 3 Kaplan-Meier plot of PFS based on investigator assessment -MONALEESA-7 (Full analysis set 20-Aug-17 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
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

Table 19 **CLEE011E2301 efficacy results based on investigator assessment in patients who received NSAI - MONALEESA-7 (20-Aug-17 cut-off)**

Analysis	**Ribociclib plus NSAI plus goserelin (%, 95% CI)**	**Placebo plus NSAI plus goserelin (%, 95% CI)**
Progression-free survival[c]	**N=248**	**N=247**
Median [months] (95% CI)	27.5 (19.1, NE)	13.8 (12.6, 17.4)
Hazard ratio (95% CI)	0.569 (0.436, 0.743)	
Patients with measurable disease	**N=192**	**N=199**
Overall Response Rate[a]	50.5 (43.4 , 57.6)	36.2 (29.5 , 42.9)

[a]ORR: proportion of patients with complete response + partial response
CI=confidence interval; N=number of patients; NE = Not estimable.

Figure 4 **Kaplan-Meier plot of PFS based on investigator assessment in patients who received NSAI – MONALEESA-7 (20-Aug-17 cut-off)**

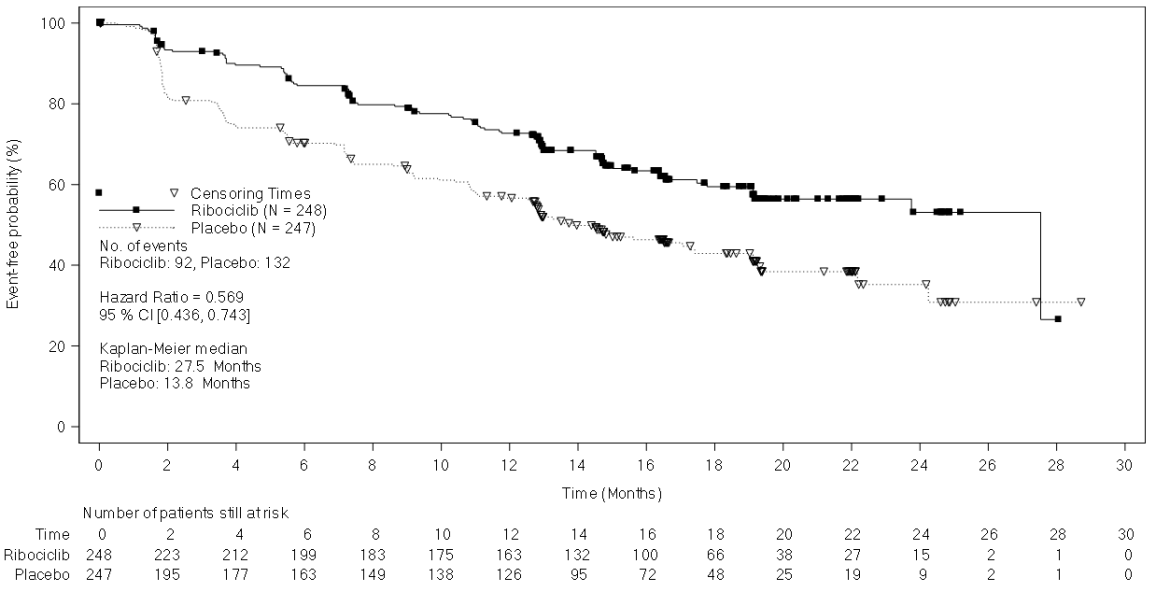
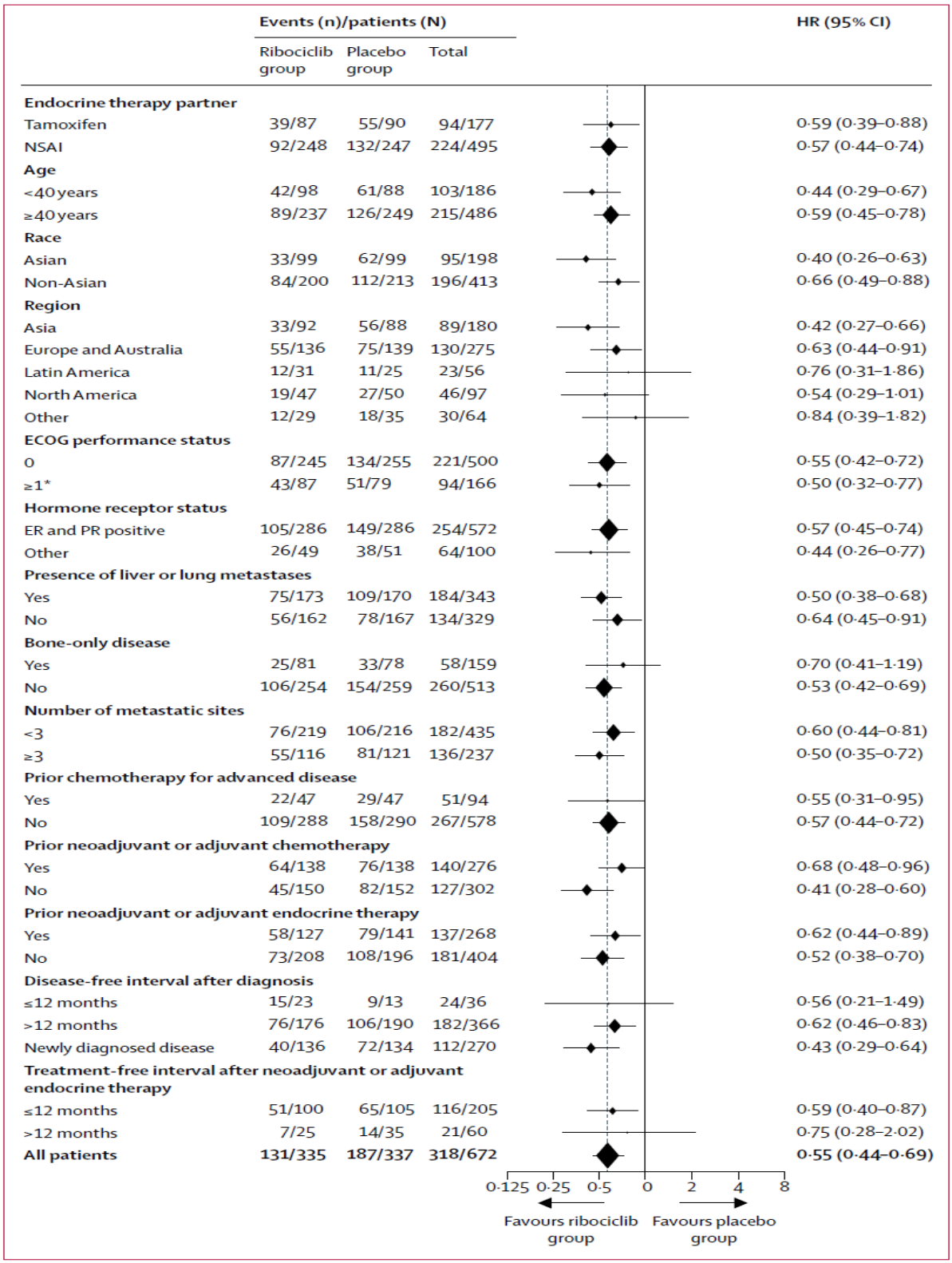


Figure 5 **Forest plot of PFS based on investigator assessment in patients who received NSAI [1] (20-Aug-17 cut-off)**


Events (n)/patients (N)
Ribociclib group
Placebo group
Total
HR (95% CI)
Endocrine therapy partner
Tamoxifen 39/87 55/90 94/177 0·59 (0·39–0·88)
NSAI 92/248 132/247 224/495 0·57 (0·44–0·74)
Age
<40 years 42/98 61/88 103/186 0·44 (0·29–0·67)
≥40 years 89/237 126/249 215/486 0·59 (0·45–0·78)
Race
Asian 33/99 62/99 95/198 0·40 (0·26–0·63)
Non-Asian 84/200 112/213 196/413 0·66 (0·49–0·88)
Region
Asia 33/92 56/88 89/180 0·42 (0·27–0·66)
Europe and Australia 55/136 75/139 130/275 0·63 (0·44–0·91)
Latin America 12/31 11/25 23/56 0·76 (0·31–1·86)
North America 19/47 27/50 46/97 0·54 (0·29–1·01)
Other 12/29 18/35 30/64 0·84 (0·39–1·82)
ECOG performance status
0 87/245 134/255 221/500 0·55 (0·42–0·72)
≥1* 43/87 51/79 94/166 0·50 (0·32–0·77)
Hormone receptor status
ER and PR positive 105/286 149/286 254/572 0·57 (0·45–0·74)
Other 26/49 38/51 64/100 0·44 (0·26–0·77)
Presence of liver or lung metastases
Yes 75/173 109/170 184/343 0·50 (0·38–0·68)
No 56/162 78/167 134/329 0·64 (0·45–0·91)
Bone-only disease
Yes 25/81 33/78 58/159 0·70 (0·41–1·19)
No 106/254 154/259 260/513 0·53 (0·42–0·69)
Number of metastatic sites
<3 76/219 106/216 182/435 0·60 (0·44–0·81)
≥3 55/116 81/121 136/237 0·50 (0·35–0·72)
Prior chemotherapy for advanced disease
Yes 22/47 29/47 51/94 0·55 (0·31–0·95)
No 109/288 158/290 267/578 0·57 (0·44–0·72)
Prior neoadjuvant or adjuvant chemotherapy
Yes 64/138 76/138 140/276 0·68 (0·48–0·96)
No 45/150 82/152 127/302 0·41 (0·28–0·60)
Prior neoadjuvant or adjuvant endocrine therapy
Yes 58/127 79/141 137/268 0·62 (0·44–0·89)
No 73/208 108/196 181/404 0·52 (0·38–0·70)
Disease-free interval after diagnosis
≤12 months 15/23 9/13 24/36 0·56 (0·21–1·49)
>12 months 76/176 106/190 182/366 0·62 (0·46–0·83)
Newly diagnosed disease 40/136 72/134 112/270 0·43 (0·29–0·64)
Treatment-free interval after neoadjuvant or adjuvant endocrine therapy
≤12 months 51/100 65/105 116/205 0·59 (0·40–0·87)
>12 months 7/25 14/35 21/60 0·75 (0·28–2·02)
All patients 131/335 187/337 318/672 0·55 (0·44–0·69)
0·125 0·25 0·5 0 2 4 8
Favours ribociclib group
Favours placebo group

All subgroup analyses presented were prespecified in the protocol. The size of the data points is proportional to the number of patients included in the subgroup analysis. ECOG=Eastern Cooperative Oncology Group. ER=oestrogen receptor. HR=hazard ratio. NSAI=non-steroidal aromatase inhibitor. PR=progesterone receptor. *One patient had an ECOG performance status of 2.

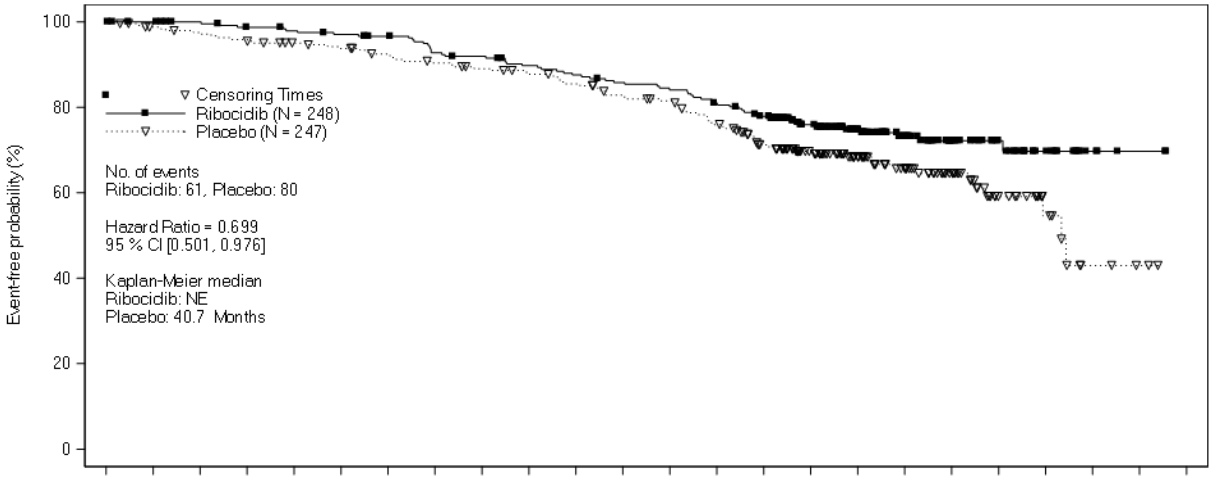
[1] KISQALI is not indicated for use in combination with tamoxifen and combined treatment is not recommended.

Final Overall Survival Analysis

At the time of the second (final) prespecified OS analysis (30-Nov-2018 cut-off), the study met its key secondary endpoint of OS, demonstrating a statistically significant improvement in OS (HR: 0.712; 95% CI: 0.535, 0.948; one-sided stratified log-rank test p-value: 0.00973), and was consistent for the NSAI population (Figure 6) and across exploratory subgroups. Median OS was not reached in the KISQALI arm and was 40.9 months (95% CI: 37.8, NE) in the placebo arm. The median duration of follow-up was 34.6 months.

These data suggest an estimated relative risk reduction of death of approximately 29% in the KISQALI arm compared to the placebo arm.

Figure 6 MONALEESA-7 (E2301) Kaplan-Meier plot of OS in patients who received NSAI (30-Nov-18 cut-off)



Hazard ratio is based on unstratified Cox model.

The median time to progression on next-line therapy or death (PFS2) in the NSAI population was 32.3 months (26.9, 38.3) in the placebo arm and was not reached (39.4, NE) in the KISQALI arm [HR:0.660 (CI: 0.503, 0.868)].

Study CLEE011F2301 (MONALEESA-3)

The primary efficacy endpoint for the study was assessed after observing 361 progression-free survival (PFS) events using the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), based on the investigator assessment in the full analysis set. The median follow-up duration at the time of primary PFS analysis was 20.4 months.

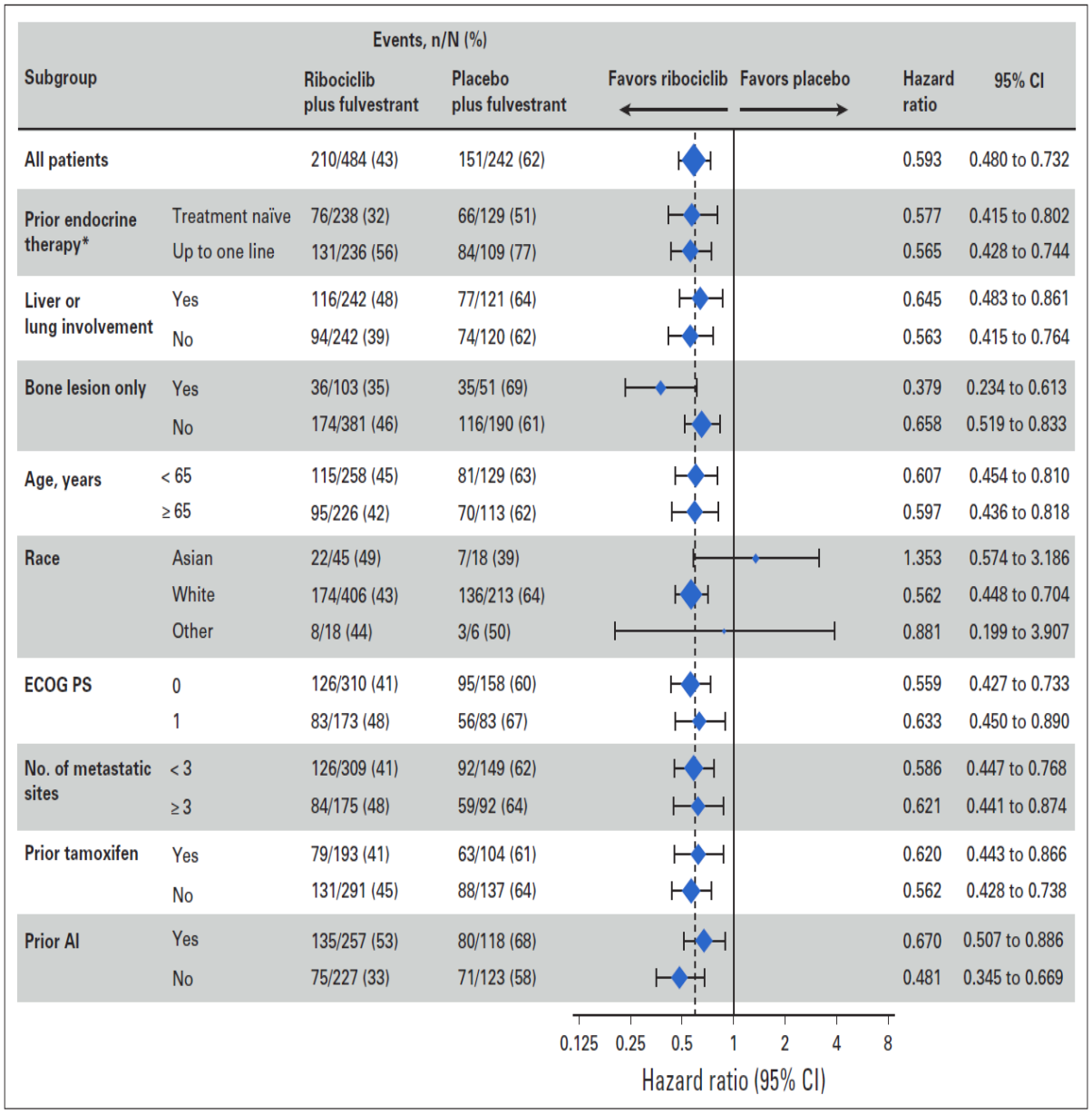
The primary efficacy results demonstrated a statistically significant improvement in PFS in patients receiving KISQALI plus fulvestrant compared to patients receiving placebo plus fulvestrant with an estimated 41% reduction in relative risk of progression or death in favor of the KISQALI plus fulvestrant arm (HR = 0.593, 95% CI: 0.480, 0.732, one-sided stratified log rank test p-value = 0.00000041). The descriptive updated PFS results support the primary PFS analyses.

PFS analyses based on the blinded independent central radiological assessment (hazard ratio 0.492) were supportive of the primary efficacy results.

In patients with measurable disease, the overall response rate according to local radiologist assessment was 40.9% of patients (95% CI: 35.9%, 45.8%) in the KISQALI plus fulvestrant arm and 28.7% (95% CI: 22.1%, 35.3%) in the placebo plus fulvestrant arm with a reported p-value of 0.003.

Results were consistent across pre-specified sub-groups of age, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, bone-only metastatic disease. The subgroup analysis is presented in a Forest Plot in Figure 7.

Figure 7 Forest plot of primary PFS results based on investigator assessment (FAS) (03 Nov 17 cut-off) – Study CLEE011F2301



Progression-free survival outcomes in patient subgroups. Hazard ratios were estimated on the basis of stratified Cox proportional hazards model, except in subgroups related to stratification factors (presence or absence of lung or liver metastases and prior endocrine therapy), where an unstratified analysis was used. AI, aromatase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status. (*) Prior endocrine therapy for advanced disease; 14 patients were not included in the prior endocrine therapy subgroup analysis because of missing data or criteria not being met.

Since the median PFS for first-line patients had not been reached at the time of the primary analysis, a descriptive update of primary efficacy results (PFS) was performed at the time of the second OS interim analysis, and the updated PFS results are summarized in Table 20 and the Kaplan-Meier curve is provided in Figure 8.

Table 20 MONALEESA-3 (F2301) descriptive updated PFS results (03-Jun-19 cut-off)

Overall population	**Ribociclib plus fulvestrant N=484**	**Placebo plus fulvestrant N=242**
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	**Ribociclib 600 mg N=237**	**Placebo N=128**
Number of events – n [%]	112 (47.3)	95 (74.2)
Median PFS [months] (95% CI)	33.6 (27.1, 41.3)	19.2 (14.9, 23.6)
Hazard ratio (95% CI)	0.546 (0.415, 0.718)	
Second-line setting or with an early relapse	**Ribociclib 600 mg N=237**	**Placebo N=109**
Number of events – n [%]	167 (70.5)	95 (87.2)
Median PFS [months] (95% CI)	14.6 (12.5, 18.6)	9.1 (5.8, 11.0)
Hazard ratio (95% CI)	0.571 (0.443, 0.737)	

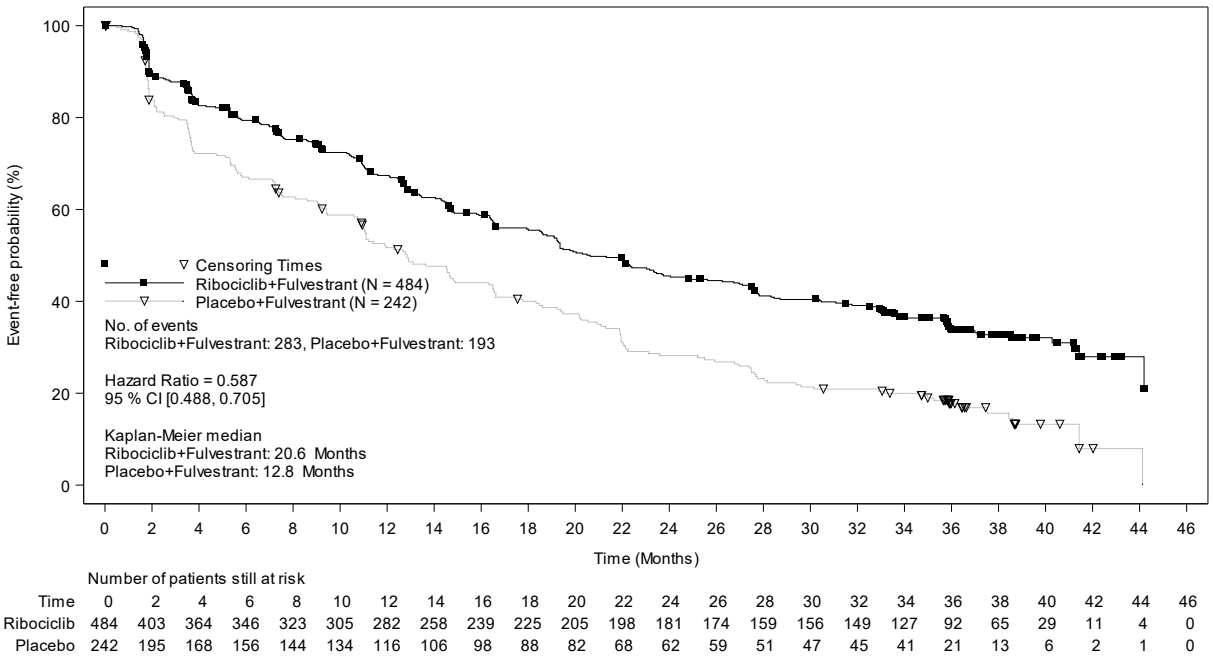
CI=confidence interval

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

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

The global health status/QoL showed no relevant difference between KISQALI plus fulvestrant arm and the placebo plus fulvestrant arm.

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



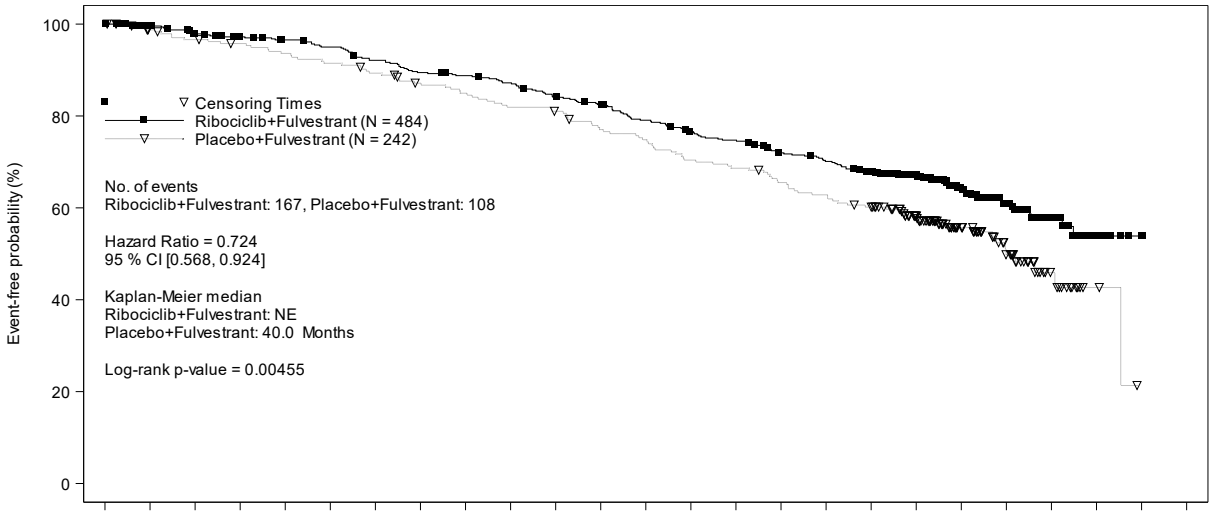
Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Ribociclib	484	403	364	346	323	305	282	258	239	225	205	198	181	174	159	156	149	127	92	65	29	11	4	0
Placebo	242	195	168	156	144	134	116	106	98	88	82	68	62	59	51	47	45	41	21	13	6	2	1	0

Final OS Analysis

At the time of the second interim OS analysis the study met its key secondary endpoint demonstrating a statistically significant improvement in OS for the overall population (Figure 9) and was consistent for the prior endocrine therapy subgroups (Figures 10, 11).and across all other subgroups.

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



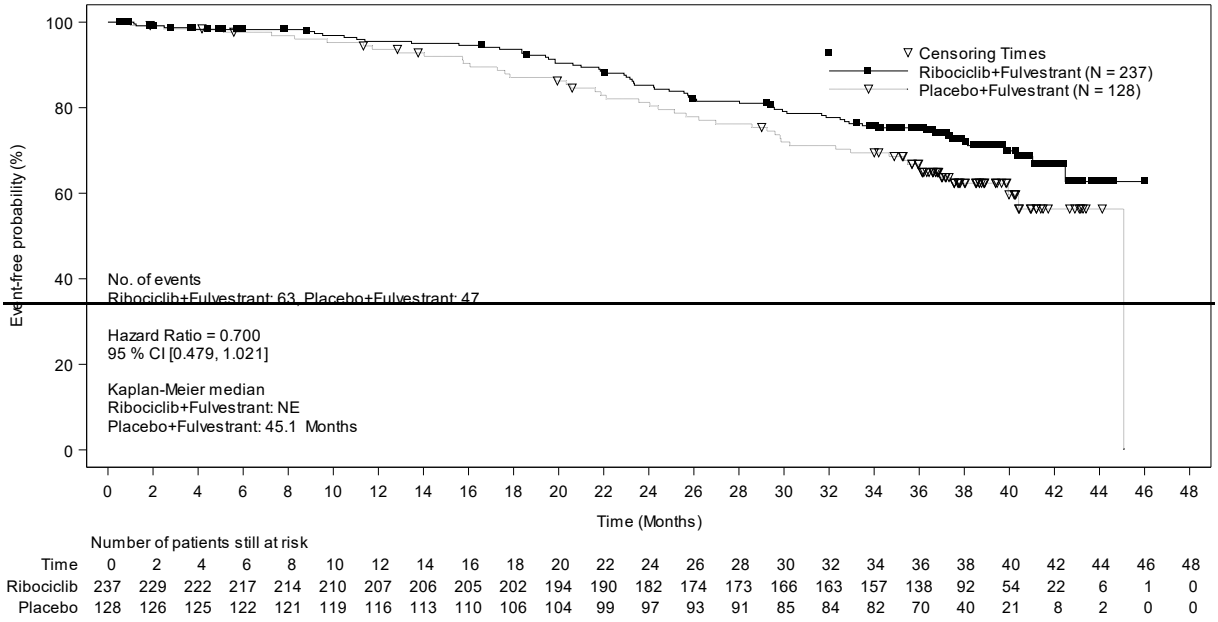
Number of patients still at risk

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

Log-rank test and Cox model are stratified by lung and/or liver metastasis, prior chemotherapy for advanced

disease, and endocrine combination partner per IRT
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.

Figure 10 MONALEESA-3 (F2301) Kaplan Meier plot of OS for patients in first-line[1] setting (FAS) (03-Jun-19 cut-off)



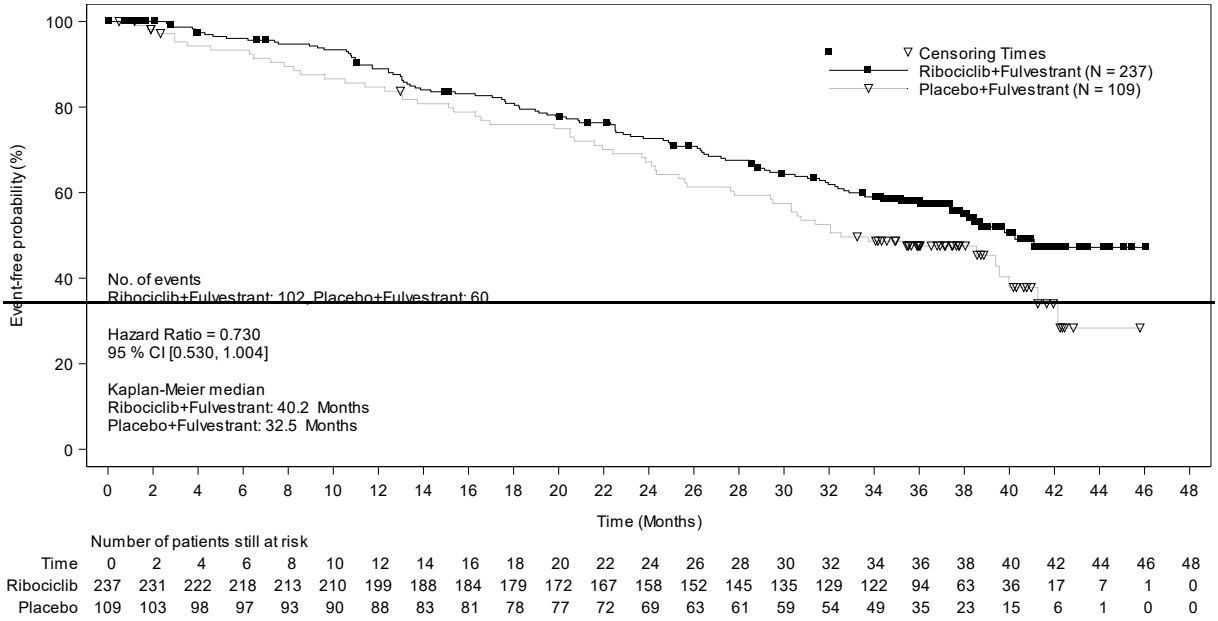
Number of patients still at risk

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

Hazard ratio is based on unstratified Cox model

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

Figure 11 MONALEESA-3 (F2301) Kaplan Meier plot of OS for patients in second-line setting or with an early relapse[1] (FAS) (03-Jun-19 cut-off)



Hazard ratio is based on unstratified Cox model

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

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

14.3 Comparative Bioavailability Studies

Study A2103 was a randomized, open-label, single-center, crossover study to evaluate the BE of a new tablet formulation of ribociclib in comparison to a capsule formulation of ribociclib and the effect of food following a single oral dose of 600 mg in healthy subjects.

Table 21 Study A2103

Ribociclib (3 x _200_ mg) From measured data Geometric Mean				
Parameter	**Test**	**Reference**	**Ratio of Geometric Means**	**90% Confidence Interval (Lower, Upper)**

AUC_T (hr*ng/mL)	10600 n=31	10600 n=31	1	(0.881, 1.14)
AUC_I (hr*ng/mL)	10800 n=31	11500 n=30	0.937	(0.885, 0.991)
C_{MAX} (ng/mL)	601 n=31	596 n=31	1.01	(0.869, 1.17)
T_{MAX} (h)	3 n=31	3 n=31	0	(-4, 3)

Reference: 600mg LEE011 capsule, Test: 600mg LEE011 tablet.
- Model is a linear effects model of the log-transformed PK parameters. Included in the model were treatment, period and sequence as fixed effects and subjects nested within sequences as a random effect.
- n = number of subjects with non-missing values.
-AUC_T = AUC_{last}
- The analysis is conducted on log transformed PK parameters. Then the results are back transformed to get adjusted geo-mean, Geo-mean ratio, and 90% CI.
- For T_{max}, median is presented under 'Test' and 'Reference', median difference under 'Ratio of Geometric Means', and minimum and maximum differences under 90% CI.
- Source: Table 14.2-1.1a

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

DETAILED PHARMACOLOGY

Pharmacodynamics

In biochemical assays, ribociclib inhibits CDK4/Cyclin D1 and CDK6/Cyclin-D3 enzyme complexes with IC50 values of 0.01 µM (4.3 ng/mL) and 0.039 µM (16.9 ng/mL), respectively. In a panel of serine/threonine and tyrosine kinases, inhibition of CDK4/D1 or CDK6/D3 was selective, ribociclib was inactive (IC50 >10 µM) against 34 other serine/threonine and tyrosine kinases and showing weak inhibition (> 2.0 µM) against Aurora A, HER1, and LCK with the IC50 values of 2.0 µM, 9.0 µM, and 7.7 µM, respectively, further demonstrating its relative inactivity against kinases other than CDK4/6.

Ribociclib was a potent inhibitor of cell proliferation in a wide variety of cancer cell lines. A functional pRb protein was a requirement for the inhibition of cell proliferation. Cancer cell lines with genetic aberrations in the CDK4/6 signalling pathways were particularly susceptible to the anti-proliferative effects of ribociclib. The IC_{50} value for cell proliferation inhibition by ribociclib in the mantle cell lymphoma cell line Jeko-2 with a translocation in the CCND1 gene (coding for cyclin D1) was 0.080 µM and the IC_{50} values for inhibition of phosphorylation of pRb and G1 arrest were 0.180 and 0.100 µM, respectively. The IC_{50} values for target phosphorylation of pRb, cell cycle assays and proliferation are similar and consistent with pRb phosphorylation tightly linked to G1 to S transition, with the inhibition of pRb phosphorylation leading to G1 arrest in cells. The main mode inhibition of cell proliferation was

growth arrest and there were no significant cell death. In Jeko-1 cells, the metabolites M4 (LEQ803) and M13 (CCI28) were less potent inhibitors than ribociclib, with G1 arrest occurring at IC50 values of >13 times that of ribociclib.

Ribociclib was tested in a panel of 47 breast cancer cell lines annotated with ER status. Luminal ER+ breast cancer cell lines were most sensitive to ribociclib, with 16 of the 18 cell lines with IC50s < 1 µM, while majority (21 out of 29) of the ER-negative cell lines have IC50s> 1 µM.

In immunocompromised mice with established MCF7 ER+ human breast cancer xenograft model, ribociclib monotherapy at 75 mg/kg p.o., once per day resulted in exposure approximately similar to 400 mg to 600 mg once daily in human. Ribociclib treatment resulted in tumor regression with minimal effect on body weight. In immunocompromised mice with a patient-derived ER+ breast cancer xenograft model (PDX191), ribociclib at 75 mg/kg/day exhibited tumor growth inhibition which correlated with inhibition of pRb phosphorylation.

The anti-tumor efficacy of ribociclib and letrozole was assessed in immunocompromised mice using a primary ER+ breast cancer xenograft model derived from a patient tumor with a known sensitivity to letrozole. Ribociclib at 75 mg/kg combined with letrozole at 2.5 mg/kg, both dosed orally every day for 55 days, induced greater tumor growth inhibition than each agent alone. The combination of ribociclib and letrozole demonstrated statistically significant antitumor activity with complete tumor growth inhibition, 2 out of 10 partial and 2 out of 10 complete tumor regressions. Tumor growth delay after stopping dosing was also observed.

Secondary Pharmacodynamics

Ribociclib and LEQ803 were assessed for their off-target activity on respectively 147 and 144 G protein-coupled receptors (GPCRs), transporters, ion channels, nuclear receptors and enzymes.

For ribociclib, activities were found on phosphodiesterase PDE4d (IC50= 0.59 µM, n=2), rat vesicular monoamine transporter VMAT2 (IC50 = 6.3 µM, n=2), orexin-2 receptor (70% inhibition at 10 µM) and apelin receptor (54% inhibition at 10 µM). IC_{50} values were not determined for the last two mentioned targets.

For LEQ803, activities were found on phosphodiesterase PDE4d (IC50 = 0.6 µM), serotonin 5HT3 channel (IC50 = 2.63 µM), neuronal nicotinic alpha 2 channel (IC50 = 5.7 µM), cannabinoid CB1 receptor (IC50 = 28 µM), peripheral rat imidazoline I2 receptor (71% inhibition at 10 µM), rabbit monoamine transporter VMAT2 (84% inhibition at 10 µM) and rat brain sodium channel site II (70% inhibition at 10 µM). IC50 values were not determined for the last three mentioned targets.

The clinical free C_{max} at the recommended dose of 600 mg ribociclib was 1.2 µM, and the free C_{max} of LEQ803 was 0.03 µM.

Given the absence of brain penetration by ribociclib following oral administration and intracarotid injection in rats, centrally-mediated effects resulting from interactions with targets expressed in the central nervous system (VMAT-2, PDE4d, serotonin 5-HT3, rat brain sodium channel site II, neuronal nicotinic alpha 2 channel receptors, orexin receptor OX2 and cannabinoid CB1 receptors) are unlikely to develop in humans.

Safety pharmacology

Ribociclib caused a concentration-dependent decrease in hERG potassium channel currents in stably transfected HEK293 cells with an estimated IC50 of up to 53.0 µM.

Ribociclib caused a concentration-dependent inhibition of the Nav1.5 sodium channel currents in stably transfected HEK293 cells with an IC50 of 24 µM.

LEQ803, a major metabolite of ribociclib, caused a concentration-dependent suppression of hERG channel currents in stably transfected HEK293 cells with an IC50 of 4.5µM.

In vivo cardiac safety studies in dogs demonstrated dose and concentration related QTc interval prolongation at exposures that would be expected to be achieved in patients following the recommended dose of 600 mg. Increased premature ventricular contractions (PVCs) were reported in a dog receiving a single oral dose of 100 mg/kg (resulting an exposure approximately 5-fold the clinical C_{max}).

TOXICOLOGY

Repeated dose toxicity

The repeat dose toxicity was characterized in dogs and rats at doses up to and including maximum tolerated dose. In the dog, body weight loss, vomiting and severe liver/gall bladder toxicity occurred at 25 and 20 mg/kg/day in 2 and 4 week study. In the rat there were 2 potentially ribociclib related deaths in male rats after ≥17 weeks of dosing at 150 mg/kg/day. Both animals had irregular respiration and microscopically there were increased alveolar macrophage infiltrates.

Mild to moderate decreases in circulating red and white blood cells correlated with bone marrow hypocellularity and lymphoid tissue findings (atrophy/lymphoid depletion) in dogs and rats in studies ranging from 2 to 27 weeks in rats and 2 to 39 weeks in dogs. These changes as well as findings in intestinal mucosa (atrophy), skin (atrophy) and bone (decreased bone formation) in dog in the 2 and 4 week studies and are considered related to the pharmacological mechanism of action. They were reversible or partially reversible after 4 weeks without treatment.

Testicular changes with seminiferous tubule degeneration and secondary effects in the epididymis with reduced luminal sperm with luminal cellular debris and epithelial vacuolation were noted in rats and dogs. In the 15- and 27-week rat studies, the NOAEL was 25 mg/kg/day, while in the 15- and 39-week studies in the dog, a NOAEL was not identified (≤1 mg/kg/day). After a 4 week withdrawal period, the changes were consistent with partial recovery. The withdrawal period, given the length of the spermatogenic cycle, was not long enough for complete recovery.

Kidney changes, consisting of degeneration/regeneration of tubular epithelial cells, were noted in male rats only at ≥75 mg/kg/day in the 15 and 27 week studies. Vacuolation of bile duct epithelium was noted in males at 150 mg/kg/day after 4 and 15 weeks, in males at ≥75 mg/kg/day and in females at 300 mg/kg/day after 27 weeks of dosing. Increased incidence and severity of alveolar macrophage infiltrates in the lung of males at ≥75 mg/kg/day in the 4 week study, at 150 mg/kg/day in the 15 week study, and at ≥75 mg/kg/day in the 27 week study, as well as at 300 mg/kg/day in females in the 27 week study. The changes in kidney, bile duct and lung were reversible after a 4 week withdrawal period.

The pathogenesis of the bile duct toxicity, lymph node histiocytosis and lung macrophage infiltrates in the rat was suggested to be due to phospholipidosis. Liver/bile ducts/gallbladder was also identified as a target organ of toxicity for ribociclib in the dog. Findings in the dog included proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile and the proliferative changes within the intra- and extra-hepatic biliary tree may be indicative of irritation as a consequence of excretion of ribociclib and/or its metabolites via the biliary system. Mass balance data in rats and dogs show that the majority of ribociclib-related radioactivity is eliminated by metabolism via hepatic metabolism and biliary excretion.

The ribociclib exposures at the maximal feasible dose in repeat dose studies in rats and dogs were generally less than or similar to exposure in patients at MRHD. Thus, even for findings where NOAELs were identified, ribociclib exposure was less than clinical exposure at MRHD.

Reproductive toxicity/Fertility

A fertility study in male rats has not been performed, however ribociclib general toxicology studies clearly identified the testes as a target tissue in rats and dogs (see Repeated Dose Toxicity) and reduced fertility or infertility is to be expected in males.

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

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

In rats, 1,000 mg/kg/day was lethal in the maternal animals with embryofetal mortality. At 300 mg/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 300 mg/kg/day. The no-observed-adverse-effect level (NOAEL) for maternal toxicity was considered to be 300 mg/kg/day. The no-observed-effect-level (NOEL) for embryo-fetal development was considered to be 50 mg/kg/day.

In rabbits at doses of 30 and 60 mg/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 60 mg/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 30 mg/kg/day and the NOEL for the embryo-fetal development was 10 mg/kg/day.

At 300 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal systemic exposures (AUC) were lower than or at 1.5 times that achieved in patients at the highest recommended dose of 600 mg/day. Animal/human exposure margins at the no-effect doses for embryofetal toxicity in both species were well below therapeutic levels.

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

Carcinogenicity:

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

Oral administration of ribociclib for 2 years resulted in an increased incidence of endometrial epithelial adenocarcinoma 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 tumors 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-times 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-times 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. Mean exposure at steady state (AUC_0-24h) was below and 1.4-times that achieved in patients at the recommended dose of 600 mg/day, respectively. Mean exposure at steady state (AUC_0-24h) was below and 2.5-times that achieved in patients at a dose of 400 mg/day, respectively.

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

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

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

Considering important differences between rodents and humans with regard to synthesis and role of prolactin, the consequence of CDK4 inhibition in this context in humans is unclear.

Genotoxicity:

Ribociclib was not genotoxic *in vitro* in bacterial and mammalian cell assays with and without metabolic activation and in an *in vivo* study in rats.

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 low.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr**KISQALI®**

ribociclib tablets

Read this carefully before you start taking **KISQALI®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **KISQALI**.

Your breast cancer may be treated with **KISQALI** in combination with another drug (aromatase inhibitors or fulvestrant). Read the Patient Medication Information for the other drug as well as this one.

Serious Warnings and Precautions

KISQALI should only be administered by a healthcare professional experienced in the use of anti-cancer drugs.

The following serious side effects have been seen in people taking KISQALI:

- **Heart problems:** chest pain or discomfort, heart palpitations, fast or slow heartbeat, dizziness, lightheadedness, fainting, sudden death
- **Liver problems:** itching, yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite
- **Low levels of white blood cells:** fever, sore throat, mouth ulcers or other signs of infections

What is KISQALI used for?

KISQALI is used to treat breast cancer in adult women, when it has spread to other parts of the body. The breast cancer must be hormone receptor positive and human epidermal growth factor receptor 2-negative. It is taken with:

- aromatase inhibitors. This is an initial hormone therapy. Women who have not gone through menopause need to take a drug to stop their ovaries from making estrogen.
- fulvestrant. This is used as an initial hormone therapy or when other hormone therapies do not work. Women must have gone through menopause to take KISQALI this way.

How does KISQALI work?

KISQALI belongs to a family of medications called kinase inhibitors. These medications work by stopping cancer cells from dividing and growing. KISQALI has to be used together with an aromatase inhibitor or with fulvestrant. When given together with one of these drugs, KISQALI may slow down the growth and spread of breast cancer cells.

What are the ingredients in KISQALI?

Medicinal ingredient: ribociclib succinate
Non-medicinal ingredients: Colloidal silicon dioxide, crospovidone (Type A), iron oxide black (E172), iron

oxide red (E172), lecithin (soy) (E322), low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol (partially hydrolysed), talc, titanium dioxide (E171) and xanthan gum.

KISQALI comes in the following dosage forms:
Tablets; 200 mg ribociclib (as ribociclib succinate)

Do not use KISQALI if:

- you are allergic to ribociclib succinate or to any of the other ingredients of KISQALI.
- you have serious heart problems including a condition known as "congenital long QT syndrome".

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KISQALI. Talk about any health conditions or problems you may have, including if you:

- have fever, sore throat or mouth ulcers due to infections (signs of low level of white blood cells).
- have or have ever had any problems with your liver or kidneys.
- have or have ever had heart problems, such as an irregular heartbeat, rate or rhythm, or low levels of potassium, magnesium, calcium or phosphorous in your blood.
- have a family history of sudden cardiac death.
- are dehydrated, suffer from persistent vomiting or an eating disorder.
- have diabetes.
- have a condition called "autonomic neuropathy" that causes problems with blood pressure, heart rate, sweating, bowel and bladder control and digestion.
- are taking any medicines or supplements.

Other warnings you should know about:

Pregnancy, breast-feeding and fertility

- If you are pregnant, still able to get pregnant, or think you are pregnant, there are specific risks you must discuss with your healthcare professional.
- Avoid becoming pregnant while taking KISQALI. It may harm your unborn baby.
- If you are able to become pregnant, your healthcare professional will make sure that you are not pregnant before starting KISQALI.
- Use effective birth control if you can get pregnant while taking KISQALI and for at least 21 days after your last dose. Ask your healthcare professional about ways to avoid becoming pregnant.
- You should not breastfeed while you are taking KISQALI or for 21 days after your last dose.

Driving and Using Machines: KISQALI can cause fatigue and fainting. You should use caution when driving or operating potentially dangerous machinery while you are taking KISQALI.

During your treatment with KISQALI, tell your healthcare professional straight away:

- If you have fever, chills, weakness and frequent infections with signs such as, sore throat or mouth ulcers. This could be due to a low level of white blood cells.
- If you have tiredness, itchiness, yellow skin, nausea, vomiting, yellowing of the whites of your eyes, loss of appetite, pain in the abdomen, dark or brown urine, or more than normal bleeding or bruising. These could be signs of problems with your liver.

- If you have chest pain or discomfort, changes in heart beat (faster or slower), palpitations, if your lips turn blue, if you feel lightheaded, dizzy or faint, if you have trouble breathing, or if your skin or your legs swell. These could be signs of problems with your heart.
- If you have trouble breathing, cough and shortness of breath. Tell your healthcare professional right away if you experience new or worsening symptoms. These could be signs of serious lung problems during treatment that can lead to death.
- If you have a combination of any of the following symptoms: rash, red skin, blistering of the lips, eyes or mouth, skin peeling, high fever, flu-like symptoms and enlarged lymph nodes (signs of serious skin reaction). **Tell your doctor immediately if you experience new or worsening symptoms**

Children and adolescents (under 18 years old)

KISQALI is not to be used in children and adolescents under 18 years of age.

Fertility in male patients

KISQALI may reduce fertility in male patients.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with KISQALI:

- Some medicines used to treat infections. These include medicines which treat fungal infections, such as ketoconazole, itraconazole, fluconazole, voriconazole, amphotericin B and posaconazole, or medicines which treat certain types of bacterial infections, such as telithromycin, clarithromycin, erythromycin, azithromycin, moxifloxacin, levofloxacin, ciprofloxacin and pentamidine
- Some medicines used to treat malaria such as quinine and chloroquine
- Some medicines used to treat HIV/AIDS such as ritonavir, saquinavir, indinavir, lopinavir, nelfinavir, telaprevir and efavirenz
- Some medicines used to treat seizures or fits (anti-epileptics) such as carbamazepine, phenytoin, rifampin and midazolam
- St. John's Wort, an herbal product used to treat depression and other conditions (also known as hypericum perforatum)
- Some medicines used to treat heart rhythm problems such as amiodarone, disopyramide, procainamide, quinidine, sotalol, ibutilide, dronedarone, flecainide and propafenone
- Some medicines used to treat heart problems such as ivabradine, beta-blockers, digitialis glycosides, non-dihydropyridine calcium channel blockers, cholinesterase inhibitors, alpha2-adrenoceptor agonists, If inhibitors and sphingosine-1 phosphate receptor modulators
- Some medicines used to treat high blood pressure such as verapamil and loop, thiazide and other diuretics ("water pills")
- Some medicines used to treat mental health problems such as olanzapine, chlorpromazine, pimozide, haloperidol, droperidol and ziprasidone
- Some medicines used to treat depression such as fluoxetine, citalopram, venlafaxine, amitriptyline, imipramine and maprotiline
- Some medicines used to treat migraines such as dihydroergotamine and ergotamine

- Some anesthetics used during surgery and pain medicines such as alfentanil, fentanyl and methadone
- Some medicines used to suppress the immune system in people who have had organ transplants such as cyclosporine, everolimus, sirolimus and tacrolimus
- Some medicines used to treat cancer such as ondansetron, sunitinib, nilotinib, ceritinib, vandetanib, arsenic trioxide and vorinostat
- Some medicines used to treat breathing problems, like asthma, such as salmeterol and formoterol
- Domperidone used to increase milk supply in breastfeeding mothers
- Anagrelide, used to treat high levels of blood platelets
- Corticosteroids, used to treat swelling and to suppress the immune system
- Proton Pump Inhibitors (PPIs), used to treat heartburn
- Laxatives and enemas
- Do not eat grapefruits or drink grapefruit juice while you are taking KISQALI.

Know the medicines you take. Keep a list of them to show your healthcare professional.

Ask your healthcare professional if you are not sure whether your medicine is one of the medicines listed above.

You should also tell your healthcare professional if you are prescribed a new medicine while taking KISQALI .

How to take KISQALI:

Take KISQALI exactly as prescribed for you by your healthcare professional. They will tell you exactly how many tablets to take along with the other drugs and which days to take them on. Check with your healthcare professional if you are not sure. Do not change the KISQALI dose or schedule without talking to your healthcare professional.

Do not take more pills than the number prescribed by your healthcare professional.

You should not eat grapefruit or drink grapefruit juice while you are taking KISQALI. They may increase the amount of KISQALI in your blood and affect how KISQALI works.

- You should take KISQALI once daily, for 21 consecutive days. This is followed by 7 days off-treatment.
- Taking KISQALI at the **same time of day** will help you to remember when to take it. It is better to take KISQALI in the morning.
- KISQALI tablets should be **swallowed whole** (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be taken if it is broken, cracked, or otherwise not intact.
- KISQALI tablets can be taken with or without food.

It is very important to follow your healthcare professional's advice. If you have certain side effects, your healthcare professional may ask you to take less medicine, to skip a dose or to stop treatment.

Usual dose:

The usual starting dose is 600 mg orally (3 tablets of 200 mg) taken once daily for 21 consecutive days followed by 7 days off-treatment.

Continue taking KISQALI for as long as your healthcare professional tells you to. This is a long-term treatment, possibly lasting for months or years. Your healthcare professional will regularly monitor your condition to check that the treatment is working.

Stopping your treatment with KISQALI may cause your condition to become worse. Do not stop taking KISQALI unless your healthcare professional tells you to stop.

If you have any further questions on the use of KISQALI, ask your healthcare professional.

Overdose:

If you think you, or a person you are caring for, have taken too much KISQALI, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose or vomit after taking your dose, skip the missed dose that day. Take the next dose at your regular time.

Do not take a double dose to make up for a forgotten or a missed dose. Instead, wait until it is time for your next dose and then take your usual prescribed dose.

What are possible side effects from using KISQALI?

These are not all the possible side effects you may feel when taking KISQALI. If you experience any side effects not listed here, contact your healthcare professional.

Some side effects are very common

- Reduced appetite
- Shortness of breath, labored breathing
- Back pain
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Mouth sores or ulcers with gum inflammation
- Abdominal pain
- Hair loss or hair thinning
- Rash
- Itching
- Tiredness
- Dizziness or light headedness
- Weakness
- Fever
- Headache
- Swollen hands, ankles or feet

- Cough

Some side effects are common

- Watering or tearing of eyes
- Dry eyes
- Strange taste in the mouth
- Dry mouth
- Sore throat
- Upset stomach, indigestion
- Skin reddening
- Dry skin
- A sensation of losing balance
- Loss of skin color in patches (vitiligo)

KISQALI can cause abnormal blood test results and changes in the electrical signal of the heart. Your healthcare professional will do some tests before and during your treatment. They will tell you if your test results are abnormal and if you need treatment.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Anemia (low levels of red blood cells)**:** fatigue, loss of energy, weakness, shortness of breath		**√**	
Gastroenteritis (infections of the stomach and intestines)**:** Abdominal pain, diarrhea, nausea and vomiting			**√**
Liver problems: itchiness, yellow skin, nausea, vomiting, yellowing of the whites of your eyes, loss of appetite, pain in the abdomen, dark or brown urine, or more than normal bleeding or bruising.			**√**
Pneumonia (infection in the lungs): chest pain when you breath or cough, confusion, cough which may produce phlegm, fatigue, fever, sweating and shaking chills, nausea, vomiting or			**√**

diarrhea, shortness of breath			
Urinary tract infection: pain and/or burning when urinating, blood in the urine, increased urge to urinate		√	
COMMON			
Fainting (syncope)			√
Febrile neutropenia: sore throat or mouth ulcers with a single episode of fever >38.3°C (or) above 38°C for more than one hour and/or with infection			√
Heart problems: chest pain or discomfort, heart palpitations, fast or slow heartbeat, dizziness, lightheadedness, fainting, sudden death			√
Low levels of calcium in the blood: muscle cramps and spasms, numbness and tingling in the hands, feet and face			√
Low levels of platelets: spontaneous bleeding or bruising			√
Low levels of potassium in the blood: irregular heartbeat, muscle weakness			√
UNCOMMON			
Pneumonitis/ Interstitial lung disease (inflammation of the lung tissue)**:** Trouble breathing, cough and shortness of breath, fever, feeling tired			√
Pulmonary embolism (blood clot in the lung)**:** sudden, severe chest pain and trouble breathing, coughing up blood, rapid breathing and heartbeat			√
Sepsis and septic shock (infection of the blood)**:** fever or dizziness, chills, high or very low body temperature, little or no urine, low blood pressure, palpitations, rapid breathing, rapid heartbeat.			√
UNKNOWN			

Severe skin reaction that might include a combination of: rash, red skin, blistering of the lips, eyes or mouth, skin peeling, high fever, flu-like symptoms and enlarged lymph nodes (toxic epidermal necrolysis (TEN)).			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep this medicine out of the sight and reach of children.
- Do not take this medicine after the expiry date, which is stated on the box.
- Do not store above 30°C. Store in the original packaging to protect from moisture.
- Do not take this medicine if you notice any damage to the packaging or if there are any signs of tampering.

Ask your pharmacist how to dispose of medicines you no longer use.

If you want more information about KISQALI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.novartis.ca) or by calling 1-800-363-8883.

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KISQALI is a registered trademark.