

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**PrKISQALI™**  
(ribociclib tablets)

200 mg ribociclib (as ribociclib succinate)

Protein kinase inhibitor, L01XE42

Anti-neoplastic agent

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Pr **KISQALI**<sup>TM</sup>  
(ribociclib tablets)

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Non-medical Ingredients</b>
Oral	tablet 200 mg ribociclib (as ribociclib succinate)	No clinically relevant non-medical ingredients. <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING</i>

**INDICATIONS AND CLINICAL USE**

KISQALI<sup>TM</sup> (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.

**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 DOSAGE AND ADMINISTRATION).

**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.

## CONTRAINDICATIONS

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

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

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

## 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 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  $>500$  msec 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  $\geq$  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 Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION sections).

KISQALI should be avoided 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 DOSAGE AND ADMINISTRATION, DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections). Use caution when KISQALI is in combination with agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine 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 6: Dose Modification and Management-QT

prolongation (see DOSAGE AND ADMINISTRATION, ADVERSE DRUG REACTIONS and CLINICAL PHARMACOLOGY sections).

When drugs that prolong the QTc interval are prescribed, healthcare 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 healthcare provider 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 ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). In E2301 (MONALEESA-7), the observed mean QTcF 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 subgroup, suggesting that tamoxifen had a QTcF prolongation effect which contributed to the QTcF prolongation observed in the ribociclib plus tamoxifen group (see ACTION AND 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%) patients receiving ribociclib plus tamoxifen and in 18/245 (7.3%) of the patients receiving ribociclib plus an NSAI.

Tamoxifen exposure (C<sub>max</sub> and AUC<sub>0-24h</sub>) was increased approximately 2-fold following co-administration of ribociclib and tamoxifen (see DRUG INTERACTIONS).

## **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 11 (see 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 DOSAGE AND ADMINISTRATION).

### **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.

## **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  $\geq 3$  (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 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 4: Dose Modification and Management for Neutropenia (see 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 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 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION sections).

## **Hepatic/Biliary**

## 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 adverse events reported in the patients treated with KISQALI plus any combination (11.4% vs. 5.4%, respectively). Dose interruptions and/or adjustments due to hepatobiliary toxicity events were reported in 10.4% of KISQALI -treated patients, primarily due to ALT increased (6.9%) and/or AST increased (6.1%). Discontinuation of treatment with KISQALI plus letrozole due to abnormal liver function tests and hepatotoxicity were 2.3% and 0.4% 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 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  $\leq 2$ ) 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  $\geq 2$  LFT abnormality, more frequent monitoring is required (see Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION sections).

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation as described in Table 5: Dose modification and management – Hepatobiliary toxicity (see DOSAGE AND ADMINISTRATION section). Recommendations for patients who have elevated AST/ALT Grade  $\geq 3$  at baseline have not been established.

### **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

### **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 DRUG INTERACTION section).

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 DRUG INTERACTION section).

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 DRUG INTERACTION section).

### **Sexual Function/Reproduction**

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 TOXICOLOGY section).

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 TOXICOLOGY section).

### **Special Populations**

**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 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.

**Nursing Women:** 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 TOXICOLOGY section).

**Pediatrics ( $\leq 18$  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 ( $\geq 65$  years of age):** Of 334 patients who received KISQALI plus letrozole in the phase III study A2301, 150 patients (44.9%) were  $\geq 65$  years of age. Of 484 patients who received KISQALI plus fulvestrant in the phase III study F2301, 226 patients (46.7%) were  $\geq 65$  years of age and 65 patients (13.4%) were  $\geq 75$  years of age. No major differences in safety of KISQALI were observed between these patients and patients  $< 65$  years of age (see DOSAGE AND ADMINISTRATION section).

**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  $\geq 5$  x ULN or total serum bilirubin  $\geq$  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 CLINICAL PHARMACOLOGY and DOSE AND ADMINISTRATION sections).

**Renal Impairment:** KISQALI has not been studied in breast cancer patients with severe renal impairment

No dose adjustment is necessary for patients with mild or moderately impaired renal function and patients should be closely monitored (see CLINICAL PHARMACOLOGY and DOSE AND ADMINISTRATION sections).

Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment, a starting dose of 200 mg is recommended 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 CLINICAL PHARMACOLOGY)

### **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.

## ADVERSE REACTIONS

### Adverse Drug 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 arm, MONALEESA-3) in HR-positive, HER2-negative advanced or metastatic breast cancer.

The median duration of exposure to KISQALI treatment across the pooled phase 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  $\geq 20\%$  and for which the rate for KISQALI exceeds 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  $\geq 2\%$  and for which the frequency for KISQALI exceeds 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 both KISQALI and 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 cases (2.0%) of patients treated with KISQALI plus any combination versus 16 cases (2.0%) of patients treated with placebo plus any combination treatment. Excluding the most frequent cause 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 the setting of Grade 3 hypokalaemia and Grade 2 QT prolongation) 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.

## **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 DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS sections).

## **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating*

rates.

ADRs from the phase III clinical studies (Table 1, 2 and 3 ) 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 1 Adverse drug reactions observed in the phase III clinical study A2301**

<b>System Organ Class Adverse drug reactions</b>	<b>KISQALI plus Letrozole N=334 n (%) All grades</b>	<b>KISQALI plus Letrozole N=334 n (%) Grades 3/4</b>	<b>Placebo plus Letrozole N=330 n (%) All grades</b>	<b>Placebo plus Letrozole N=330 n (%) Grades 3/4</b>
<b>Blood and lymphatic system disorders</b>				
Neutropenia	248 (74.3)	198 (59.3)	17 (5.2)	3 (0.9)
Leukopenia	110 (32.9)	70 (21.0)	13 (3.9)	2 (0.6)
Anaemia	63 (18.9)	4 (1.2)	15 (4.5)	4 (1.2)
Lymphopenia	35 (10.5)	23 (6.9)	7 (2.1)	3 (0.9)
Thrombocytopenia	30 (9.0)	2 (0.6)	2 (0.6)	0
Febrile neutropenia	5 (1.5)	4 (1.2)	0	0
<b>Eye disorders</b>				
Lacrimation increased	23 (6.9)	0	6 (1.8)	0
Dry eye	19 (5.7)	0	7 (2.1)	0
<b>Cardiac disorders</b>				
Syncope	9 (2.7)	6 (1.8)	3 (0.9)	2 (0.6)
<b>Gastrointestinal disorders</b>				
Nausea	172 (51.5)	8 (2.4)	94 (28.5)	2 (0.6)
Diarrhea	117 (35.0)	4 (1.2)	73 (22.1)	3 (0.9)
Vomiting	98 (29.3)	12 (3.6)	51 (15.5)	3 (0.9)
Constipation	83 (24.9)	4 (1.2)	63 (19.1)	0
Stomatitis	41 (12.3)	1 (0.3)	22 (6.7)	0
Abdominal pain	35 (10.5)	4 (1.2)	25 (7.6)	0
Dysgeusia	31 (9.3)	1 (0.3)	19 (5.8)	0
Dyspepsia	22 (6.6)	0	14 (4.2)	0

<b>System Organ Class Adverse drug reactions</b>	<b>KISQALI plus Letrozole N=334 n (%) All grades</b>	<b>KISQALI plus Letrozole N=334 n (%) Grades 3/4</b>	<b>Placebo plus Letrozole N=330 n (%) All grades</b>	<b>Placebo plus Letrozole N=330 n (%) Grades 3/4</b>
<b>General disorders and administration site conditions</b>				
Fatigue	122 (36.5)	8 (2.4)	99 (30.0)	3 (0.9)
Peripheral edema	51 (15.3)	0	34 (10.3)	0
Asthenia	43 (12.9)	3 (0.9)	38 (11.5)	2 (0.6)
Pyrexia	42 (12.6)	1 (0.3)	18 (5.5)	0
<b>Hepatic</b>				
Hepatotoxicity <sup>1</sup>	5 (1.5)	5 (1.5)	1 (0.3)	0
<b>Infections</b>				
Urinary tract infection	44 (13.2)	2 (0.6)	28 (8.5)	0 (0.0)
<b>Investigations</b>				
Abnormal liver function tests <sup>3</sup>	60 (18.0)	32 (9.6)	18 (5.5)	8 (2.4)
Blood creatinine increased	23 (6.9)	2 (0.6)	3 (0.9)	0
Weight decreased	20 (6.0)	1 (0.3)	11 (3.3)	0
Electrocardiogram QT prolonged	15 (4.5)	1 (0.3)	4 (1.2)	0
<b>Metabolism and nutrition disorders</b>				
Decreased appetite	62 (18.6)	5 (1.5)	50 (15.2)	1 (0.3)
Hypocalcemia	18 (5.4)	5 (1.5)	6 (1.8)	0
Hypokalemia	15 (4.5)	4 (1.2)	10 (3.0)	3 (0.9)
Hypophosphatemia	14 (4.2)	12 (3.6)	3 (0.9)	2 (0.6)
<b>Musculoskeletal and connective tissue disorders</b>				
Back pain	66 (19.8)	7 (2.1)	58 (17.6)	1 (0.3)
<b>Nervous system disorders</b>				
Headache	74 (22.2)	1 (0.3)	63 (19.1)	1 (0.3)
Insomnia	39 (11.7)	1 (0.3)	31 (9.4)	0
<b>Respiratory, thoracic and mediastinal disorders</b>				
Dyspnoea	39 (11.7)	4 (1.2)	29 (8.8)	2 (0.6)

<b>System Organ Class Adverse drug reactions</b>	<b>KISQALI plus Letrozole N=334 n (%) All grades</b>	<b>KISQALI plus Letrozole N=334 n (%) Grades 3/4</b>	<b>Placebo plus Letrozole N=330 n (%) All grades</b>	<b>Placebo plus Letrozole N=330 n (%) Grades 3/4</b>
Epistaxis	15 (4.5)	0	6 (1.8)	0
Pulmonary embolism	4 (1.2)	3 (0.9)	1 (0.3)	1 (0.3)
<b>Skin and subcutaneous tissue disorders</b>				
Alopecia	111 (33.2)	0	51 (15.5)	0
Rash <sup>2</sup>	67 (20.1)	3 (0.9)	27 (8.2)	0
Pruritus	49 (14.7)	2 (0.6)	20 (6.1)	0
Erythema	17 (5.1)	0	4 (1.2)	0

<sup>1</sup>Hepatotoxicity: hepatocellular injury, drug-induced liver injury, hepatotoxicity, hepatic failure (single non- fatal case), autoimmune hepatitis (single case).

<sup>2</sup>Rash: rash, rash maculopapular.

<sup>3</sup>Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

**Table 2 Adverse Drug Reactions Observed in  $\geq 10\%$  and  $\geq 2\%$  higher than Placebo Arm in the phase III clinical Study E2301 (NSAI)**

<b>System Organ Class Adverse drug reactions</b>	<b>KISQALI plus NSAI plus goserelin N=248</b>			<b>Placebo plus NSAI plus goserelin N=247</b>		
	<b>All Grades %</b>	<b>Grade 3 %</b>	<b>Grade 4 %</b>	<b>All Grades %</b>	<b>Grade 3 %</b>	<b>Grade 4 %</b>
<b>Blood and lymphatic system disorders</b>						
Neutropenia	78	55	10	7	2	< 1
Leukopenia	29	13	< 1	3	< 1	0
Anemia	19	3	0	8	1	0
<b>Gastrointestinal disorders</b>						
Nausea	31	0	0	20	0	0
Constipation	16	0	0	12	0	0
Stomatitis	10	0	0	8	< 1	0
<b>General disorders and administration site conditions</b>						
Pyrexia	17	< 1	0	6	0	0
Pain in extremity	10	0	0	8	1	0

**Infections and Infestations**

Infections <sup>1</sup>	35	2	0	24	< 1	0
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**Investigations**

Alanine aminotransferase increased	13	5	0	9	1	0
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Aspartate aminotransferase increased	13	4	0	10	1	0
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**Musculoskeletal and connective tissue disorders**

Arthralgia	33	< 1	0	29	1	0
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**Respiratory, thoracic and mediastinal disorders**

Cough	15	0	0	10	0	0
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**Skin and subcutaneous tissue disorders**

Alopecia	21	0	0	13	0	0
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Rash	17	< 1	0	9	0	0
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Pruritus	10	0	0	4	0	0
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Grading according to CTCAE 4.03 (Common Terminology Criteria for Adverse Events)

<sup>1</sup> Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (<1%).

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Additional adverse reactions in Study E2301 for patients receiving KISQALI plus NSAID included dry skin (8%) and vitiligo (3%)

**Table 3 Adverse Drug Reactions Observed in  $\geq 10\%$  and  $\geq 2\%$  higher than Placebo Arm in phase III clinical Study F2301**

System Organ Class	KISQALI + fulvestrant			Placebo + fulvestrant		
	All Grades	N = 483 Grade 3	Grade 4	All Grades	N = 241 Grade 3	Grade 4
Adverse drug reactions	%	%	%	%	%	%
<b>Blood and lymphatic system disorders</b>						
Neutropenia	69	46	7	2	0	0
Leukopenia	27	12	< 1	< 1	0	0
Anemia	17	3	0	5	2	0
<b>Gastrointestinal disorders</b>						
Nausea	45	1	0	28	< 1	0
Diarrhea	29	< 1	0	20	< 1	0
Vomiting	27	1	0	13	0	0
Constipation	25	< 1	0	12	0	0

Abdominal pain	17	1	0	13	< 1	0
<b>General disorders and administration site conditions</b>						
Edema peripheral	15	0	0	7	0	0
Pyrexia	11	< 1	0	7	0	0
<b>Infections and Infestations</b>						
Infections <sup>1</sup>	42	5	0	30	2	0
<b>Investigations</b>						
Alanine aminotransferase increased	15	7	2	5	< 1	0
Aspartate aminotransferase increased	13	5	1	5	< 1	0
<b>Metabolism and nutrition disorders</b>						
Decreased appetite	16	< 1	0	13	0	0
<b>Nervous system disorders</b>						
Dizziness	13	< 1	0	8	0	0
<b>Respiratory, thoracic and mediastinal disorders</b>						
Cough	22	0	0	15	0	0
Dyspnea	15	1	< 1	12	2	0
<b>Skin and subcutaneous tissue disorders</b>						
Alopecia	19	0	0	5	0	0
Pruritus	20	< 1	0	7	0	0
Rash	23	< 1	0	7	0	0

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

<sup>1</sup>Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (< 1%).

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Additional adverse reactions in Study F2301 for patients receiving KISQALI plus fulvestrant included vertigo (5%), erythema (4%),

### QT 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 prolonged, syncope). Dose interruptions and/or adjustments were reported in 2.3% of KISQALI-treated patients due to electrocardiogram QT prolonged and syncope.

A central analysis of ECG data (average of triplicate) showed 52 patients (4.9%) and 11 patients (1.4%) with at least one post-baseline QTcF >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 msec, the median time to onset was 15 days regardless of combination and these changes were reversible with dose interruption and/or dose reduction (see DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY sections)

### **Abnormal Hematologic and Clinical Chemistry Findings**

Clinically relevant abnormalities of routine hematological or biochemical laboratory values from the phase III studies, are presented in Tables 4, 5 and 6.

**Table 4 Laboratory abnormalities observed in the phase III clinical study A2301**

<b>Laboratory abnormalities</b>	<b>KISQALI plus Letrozole N=334 n (%) All grades</b>	<b>KISQALI plus Letrozole N= 334 n (%) Grades 3/4</b>	<b>Placebo plus Letrozole N=330 n (%) All grades</b>	<b>Placebo plus Letrozole N=330 n (%) Grades 3/4</b>
Leukocyte count decreased	311 (93.1)	115 (34.4)	97 (29.4)	5 (1.5)
Neutrophil count decreased	311 (93.1)	199 (59.6)	79 (23.9)	4 (1.2)
Hemoglobin decreased	189 (56.6)	6 (1.8)	87 (26.4)	4 (1.2)
Lymphocyte count decreased	169 (50.6)	45 (13.5)	74 (22.4)	13 (3.9)
Platelet count decreased	97 (29.0)	3 (0.9)	21 (6.4)	1 (0.3)
Alanine aminotransferase increased (ALT)	155 (46.4)	34 (10.2)	119 (36.1)	4 (1.2)
Aspartate aminotransferase increased (AST)	147 (44.0)	23 (6.9)	106 (32.1)	5 (1.5)
Creatinine increased	65 (19.5)	2 (0.6)	18 (5.5)	0
Phosphorous decreased	44 (13.2)	17 (5.1)	14 (4.2)	2 (0.6)
Potassium decreased	38 (11.4)	4 (1.2)	24 (7.3)	4 (1.2)
Bilirubin increased	17 (5.1)	4 (1.2)	9 (2.7)	1 (0.3)

**Table 5 Laboratory Abnormalities Observed in  $\geq 10\%$  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 %
<b>HEMATOLOGY</b>						
Leukocyte count decreased	93	34	2	30	< 1	< 1
Neutrophil count decreased	92	54	9	27	2	0
Hemoglobin decreased	84	2	0	51	< 1	0
Lymphocyte count decreased	55	12	2	18	2	< 1
Platelet count decreased	26	< 1	0	9	0	< 1
<b>CHEMISTRY</b>						
Alanine aminotransferase increased	33	6	0	31	1	< 1
Aspartate aminotransferase increased	37	5	0	35	1	< 1
Creatinine increased	21	2	< 1	20	< 1	< 1
Phosphorous decreased	14	2	0	11	< 1	< 1
Potassium decreased	11	< 1	< 1	14	< 1	< 1
Gamma-glutamyl transferase increased	42	5	2	42	8	1
Glucose serum decreased	10	< 1	0	10	< 1	0

**Table 6 Laboratory Abnormalities Observed in  $\geq 10\%$  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 %
<b>HEMATOLOGY</b>						
Leukocyte count decreased	95	25	< 1	26	< 1	0
Neutrophil count decreased	92	46	7	21	< 1	0
Hemoglobin decreased	60	4	0	35	3	0
Lymphocyte count decreased	69	14	1	35	4	< 1
Platelet count decreased	33	< 1	1	11	0	0
<b>CHEMISTRY</b>						
Creatinine increased	65	< 1	< 1	33	< 1	0
Gamma-glutamyl transferase increased	52	6	1	49	8	2

	KISQALI + fulvestrant N = 483			Placebo + fulvestrant N = 241		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
<b>Laboratory abnormalities</b>						
Aspartate aminotransferase increased	49	5	2	43	3	0
Alanine aminotransferase increased	44	8	3	37	2	0
Glucose serum decreased	23	0	0	18	0	0
Phosphorous decreased	18	5	0	8	< 1	0
Albumin decreased	12	0	0	8	0	0

### Post marketing 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)
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## 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.

### Drug-Drug Interactions

#### 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 low potential to inhibit CYP3A should be considered and patients should be monitored for ADRs (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS sections).

If co-administration of KISQALI with a strong CYP3A inhibitor cannot be avoided, KISQALI dose should be reduced to 200 mg. However, there are no clinical data with this dose adjustment (see DOSAGE AND ADMINISTRATION). If the strong inhibitor is discontinued, the KISQALI dose should be resumed (after at least 5 half-lives of the CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Due to inter-patient variability (see 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 is resolved (see 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 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 IC 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)<sub>3</sub> 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 WARNINGS AND PRECAUTIONS; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). Data from a clinical trial in patients with breast cancer indicated that tamoxifen exposure (C<sub>max</sub> and AUC<sub>0-24h</sub>) 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, digitalis glycosides, non-dihydropyridine calcium channel blockers, cholinesterase inhibitors, alpha2-adrenoceptor agonists, I<sub>f</sub> 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.

### **Drug-Food Interactions**

KISQALI can be administered with or without food (see 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 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.

### **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.

### **Drug-Laboratory Interactions**

Interactions between KISQALI and laboratory tests have not been studied.

### **Drug-Lifestyle Interactions**

Interactions between KISQALI and lifestyle have not been studied. However, fatigue and syncope have been reported with the use of KISQALI. Patients should exercise caution when driving or operating machinery while taking KISQALI.

## **DOSAGE AND ADMINISTRATION**

## **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 CLINICAL PHARMACOLOGY and Drug-Food Interactions sections).

When co-administered with KISQALI, the recommended dose of letrozole is 2.5 mg taken once daily throughout the 28-day cycle. Refer to the Product Monograph for letrozole for detailed conditions of use.

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.

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

### **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 7.

**Table 7 Recommended Dose Modification Guidelines for Adverse Drug Reactions**

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

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

Tables 8,9, 10 and 11 and 12 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 WARNINGS AND PRECAUTIONS and ADVERSE DRUG REACTIONS sections).

**Table 8 Dose Modification and Management for Neutropenia**

<b>Neutropenia</b>	<b>Grade 1 or 2</b> (ANC <sup>1</sup> 1,000/mm <sup>3</sup> – <LLN <sup>2</sup> )	<b>Grade 3</b> (ANC <sup>1</sup> 500 - <1,000/mm <sup>3</sup> )	<b>Grade 3 febrile* neutropenia</b>	<b>Grade 4</b> (ANC <sup>1</sup> <500/mm <sup>3</sup> )
	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) above 38°C for more than one hour and/or concurrent infection Grading according to CTCAE Version 4.03 CTCAE=Common Terminology Criteria for Adverse Events.  1: absolute neutrophil count 2: lower limit of normal				

**Table 9 Dose Modification and Management for Hepatobiliary Toxicity**

<b>AST and/or ALT elevations from baseline*, without increase in total bilirubin above 2 x ULN</b>	<b>Grade 1</b> (>ULN – 3 x ULN)	<b>Grade 2</b> (>3 to 5 x ULN)	<b>Grade 3</b> (>5 to 20 x ULN)	<b>Grade 4</b> (>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
<b>Combined elevations in AST and/or ALT together with total bilirubin increase, in the absence of cholestasis</b>	If patients develop ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN irrespective of baseline grade, discontinue KISQALI.			
Perform Liver Function Tests (LFTs) before initiating treatment with KISQALI.				

After initiating treatment with KISQALI, monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and monitor periodically as clinically indicated.
If Grade $\geq 2$ abnormalities are observed, more frequent monitoring, for example, twice weekly, is recommended.
<i>*Baseline = prior to treatment initiation.</i>
<i>Grading according to CTCAE Version 4.03 CTCAE=Common Terminology Criteria for Adverse Events.</i>

**Table 10 Dose Modification and Management for QT Prolongation**

<b>ECGs with QTcF &gt;480 msec</b>	<ol style="list-style-type: none"> <li>1. Interrupt the KISQALI dose</li> <li>2. If QTcF prolongation resolves to &lt;481 msec, resume KISQALI at the next lower dose level</li> <li>3. If QTcF <math>\geq 481</math> msec recurs, interrupt the KISQALI dose until QTcF resolves to &lt;481 msec; and then resume KISQALI at next lower dose level</li> </ol>
<b>ECGs with QTcF &gt;500 msec</b>	If QTcF is greater than 500 msec, interrupt KISQALI until QTcF reaches <481 msec then resume KISQALI at next lower dose level
<b>Torsade de Pointes, polymorphic ventricular tachycardia, unexplained syncope, or signs/symptoms of serious arrhythmia</b>	Permanently discontinue KISQALI
<p>Assess ECG prior to initiation of treatment.</p> <p>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.</p>	

**Table 11 Dose modification and management for ILD/Pneumonitis**

<b>ILD/pneumonitis</b>	<b>Grade 1 (asymptomatic)</b>	<b>Grade 2 (symptomatic)</b>	<b>Grade 3 or 4 (severe)</b>
	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Interrupt Kisqali until recovery to Grade $\leq 1$ , 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 12 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 $\leq 1$ , then resume KISQALI at the same dose level.  If Grade 3 recurs, resume KISQALI at the next lower dose level.	Discontinue KISQALI.
<p><i>*excluding neutropenia, hepatobiliary toxicity, and QT interval prolongation.</i></p> <p><i>Grading according to CTCAE Version 4.03. CTCAE=Common Terminology Criteria for Adverse Events.</i></p>			

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 half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor (see WARNINGS AND PRECAUTIONS, 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 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, no adjustment of the starting dose is necessary in patients with mild or moderate renal impairment.

Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment, a starting dose of 200 mg is recommended. Caution should be used in patients with severe renal impairment with close monitoring for signs of toxicity. (see 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.

### **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.

### **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.

## **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 overdose.

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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## **ACTION AND CLINICAL PHARMACOLOGY**

### **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 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.

## **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 21 consecutive 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 NSAID. 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 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 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<sub>max</sub> at steady-state compared to 34.7 msec (90% CI: 31.64, 37.78) in combination with tamoxifen (see WARNING AND PRECAUTIONS).

### **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 ranging of 400 or 600 mg or repeated daily oral doses (8 days) of 400 mg.

**Table 14 Summary of Ribociclib Pharmacokinetic Parameters**

	<b>C<sub>max</sub></b> (ng/mL)	<b>T<sub>max</sub></b> (h)	<b>AUC<sub>0-24h</sub></b> (hr•ng/mL)	<b>T<sub>1/2,acc</sub></b> (h)	<b>CL/F</b> (L/h)
<b>Multiple doses (C1, D18/21) 600 mg (study X2101) Pooled<sup>1</sup></b>	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)

<b>Multiple doses (C1 D21) 600 mg (study X2107)</b>	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)
<p>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<sub>max</sub> which is presented as median (range)  <sup>1</sup> 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)</p>					

**Absorption:** Following oral administration of ribociclib to patients with advanced solid tumors or lymphomas peak plasma levels (C<sub>max</sub>) of ribociclib were achieved between 1 and 4 hours (time to reach maximum concentration, T<sub>max</sub>). Ribociclib exhibited slightly over-proportional increases in exposure (C<sub>max</sub> 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<sub>max</sub> GMR: 1.00; 90% CI: 0.898, 1.11; AUC<sub>inf</sub> GMR: 1.06; 90% CI: 1.01, 1.12) (see 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 (V<sub>ss</sub>/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 ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of [<sup>14</sup>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%

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 ( $\leq 2.78\%$  of the administered dose).

**Excretion:** The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63% CV) and the geometric mean apparent oral clearance (CL/F) was 25.5 L/hr (66% CV) at steady-state at 600 mg in patients with advanced cancer. The 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 [ $^{14}\text{C}$ ] 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 ( $\geq 65$ years of age):**

Of 334 patients who received KISQALI plus letrozole in the phase III study A2301 (MONALEESA 2), 150 patients (44.9%) were  $\geq 65$  years of age. Of 484 patients who received KISQALI plus fulvestrant in the phase III study F2301 (MONALEESA 3), 226 patients (46.7%) were  $\geq 65$  years of age and 65 patients (13.4%) were  $\geq 75$  years of age. No major differences in safety of KISQALI were observed between these patients and younger patients (see 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  $\text{AUC}_{\text{inf}}$ ) and severe (GMR: 1.32 for  $C_{\max}$ ; 1.29 for  $\text{AUC}_{\text{inf}}$ ) 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  $\leq$  ULN and  $\text{AST} >$  ULN, or total bilirubin  $> 1$  to  $\leq 1.5 \times$  ULN and  $\text{AST}$  any value), mild hepatic impairment had no effect on the exposure of ribociclib.

**Renal Impairment:** Based on a population pharmacokinetic analysis that included 77 patients with normal renal function [estimated glomerular filtration rate (eGFR)  $\geq 90$  mL/min/1.73 m<sup>2</sup>], 76

patients with mild renal impairment (eGFR 60 to <90 mL/min/1.73 m<sup>2</sup>) and 35 patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m<sup>2</sup>), mild and moderate renal impairment had no effect on the exposure of ribociclib.

The effect of renal impairment on the pharmacokinetics of ribociclib was also assessed in a renal impairment study that included 7 subjects with normal renal function (eGFR  $\geq$ 90 mL/min/1.73 m<sup>2</sup>), 7 subjects with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m<sup>2</sup>), and 3 subjects with end stage renal disease (ESRD) (eGFR <15 mL/min/1.73 m<sup>2</sup>) at single ribociclib dose of 400 mg/day. The geometric mean AUC<sub>inf</sub> (geometric %CV, n) of 5570 ng\*hr/mL (22.8%, 7), 10900 ng\*hr/mL (38.1%, 7), 13600 ng\*hr/mL (20.9%, 3) and C<sub>max</sub> (geometric %CV, n) of 356 ng/mL (15%, 7), 538 ng/mL (43.3%, 7), 593 ng/mL (11.3%, 3) was observed in subjects with normal renal function, severe renal impairment and ESRD, respectively. In subjects with severe renal impairment AUC<sub>inf</sub> increased by 1.96 fold, and C<sub>max</sub> increased by 1.51 fold compared to subjects with normal renal function. Based on this study, a starting dose of 200 mg is recommended for patients with severe renal impairment (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY)

## **STORAGE AND STABILITY**

KISQALI should not be stored above 30°C.

Store in original package to protect from moisture.

## **SPECIAL HANDLING INSTRUCTIONS**

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

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

DOSAGE FORM: tablet.

### **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.

Medicinal ingredient: ribociclib succinate

Strength: Each tablet contains 200 mg ribociclib (as ribociclib succinate)

### **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.

**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

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper/Common 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)

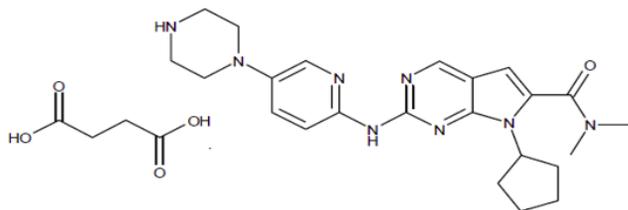
Molecular formula:

Free base: C<sub>23</sub>H<sub>30</sub>N<sub>8</sub>O

Succinate salt: C<sub>23</sub>H<sub>30</sub>N<sub>8</sub>O·C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>

Molecular weight: 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).

## CLINICAL TRIALS

### Study CLEE011A2301 (MONALEESA-2)

#### Study demographics and trial design

**Table 15 - Summary of patient demographics for MONALEESA-2**

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age (Range)	Gender
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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	<p>Route of Administration : Oral</p> <p>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)</p> <p>Placebo (daily, on Days 1-21 of a 28-day cycle) plus letrozole (2.5 mg once daily in a 28-day cycle)</p> <p>Duration: Until disease progression, unacceptable toxicity, death, or study treatment discontinuation for any other reason.</p> <p>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</p>	<p>A total of 668 patients with advanced breast cancer</p> <p>Ribociclib plus Letrozole: 334 female patients</p> <p>Placebo plus Letrozole: 330 female patients</p> <p>4 patients in Placebo plus Letrozole never treated</p>	<p>Ribociclib plus letrozole Mean= 61.4 (23-91)years of age</p> <p>Placebo plus letrozole All patients 61.9 (29-88) years of age</p>	Post-menopausal women
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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%), Asians (7.6%), and Black (2.5%). All patients had an ECOG performance status of 0 or 1. A total of 43.6% of patients had received chemotherapy in the neoadjuvant or adjuvant setting and 51.8% had received antihormonal therapy in the neo/adjuvant setting prior to study entry. 34.1% of patients had *de novo* metastatic disease. 20.7% of patients had bone only disease and 59.0% of patients had visceral disease. Patients with CNS metastases documented at baseline were not permitted in this study.

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

The efficacy results (29 January 2016 cut-off) demonstrated a statistically significant improvement in PFS in patients receiving KISQALI plus letrozole compared to patients receiving placebo plus letrozole in the full analysis set [hazard ratio (HR) = 0.556 with 95% CI: 0.429, 0.720, one sided stratified log-rank test p-value 0.00000329], with an estimated 44% reduction in risk of progression for patients treated with the combination of reduction in KISQALI plus letrozole. The median PFS was not reached in the KISQALI plus letrozole arm [95% CI: 19.3 – not reached (NR)] at the time of primary analysis. The median PFS was 14.7 months (95% CI, 13.0, and 16.5) for 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, bone only metastasis disease (Figure 2).

Updated progression free survival is summarized in Table 16 and the Kaplan-Meier curve for PFS is provided in Figure 1.

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

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

As shown in Table 16, an update of efficacy data (02 January 2017 cutoff) 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 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.

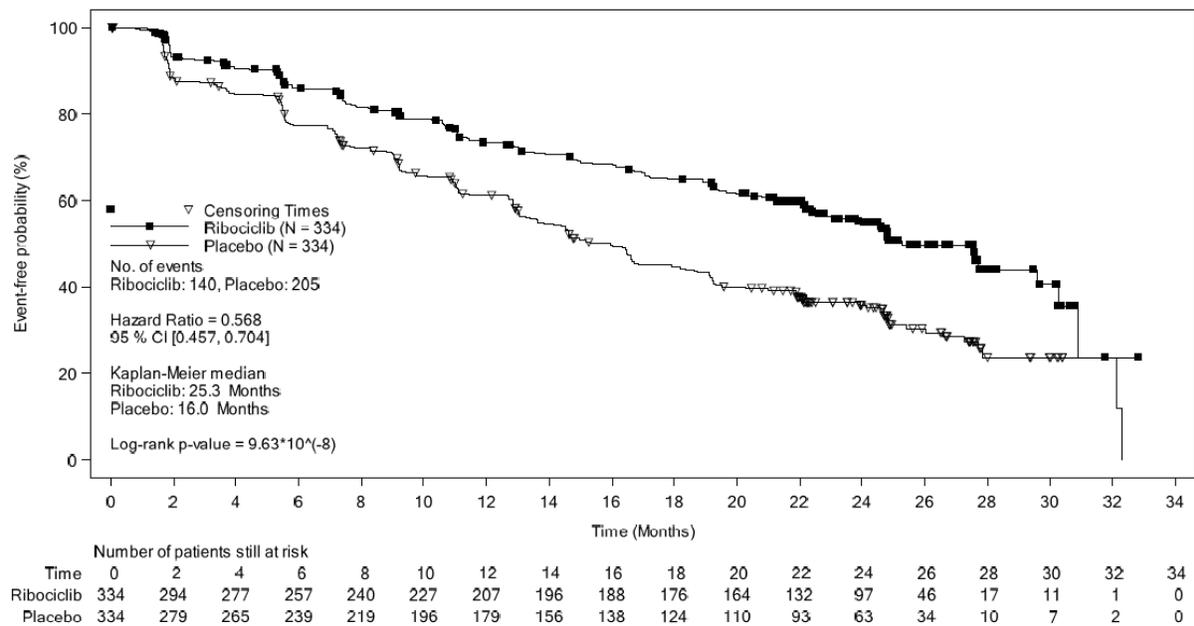
**Table 16 Efficacy Results Based on Investigator Assessment for MONALEESA-2**

	<b>KISQALI plus letrozole N=334</b>	<b>Placebo plus letrozole  N=334</b>
<b>Progression free survival</b>		
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 <sup>a</sup>	9.63×10 <sup>-8</sup>	

CI=confidence interval; N=number of patients;

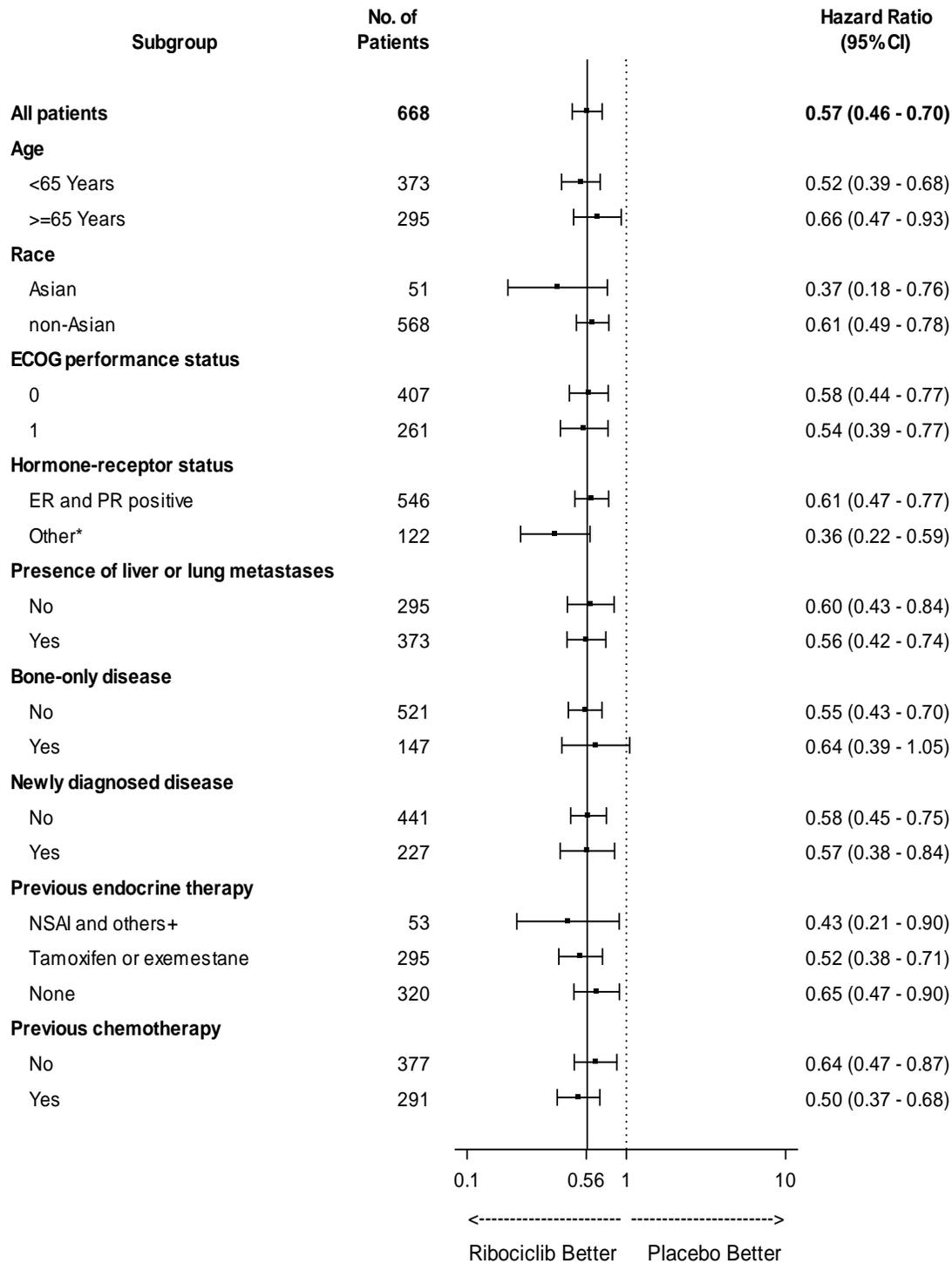
<sup>a</sup>p-value is obtained from the one-sided stratified log-rank test.

**Figure 1 Kaplan-Meier plot of PFS based on Investigator assessment – MONALEESA-2 (Full analysis set )**



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)**



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 (02 January 2017 cut-off) 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 of 0.561 [95% CI: 0.424, 0.743]), median progression-free survival [mPFS] 24.8 months versus 13.4 months respectively for ribociclib and placebo arm, or without liver and/or lung disease (HR of 0.597 [95% CI: 0.426, 0.837], mPFS 27.6 months versus 18.2 months).

### **Study CLEE011E2301 (MONALEESA-7)**

#### **Study demographics and trial design**

#### **Table 17- Summary of patient demographics for MONALEESA-7**

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-negative advanced breast cancer who received no prior hormonal therapy for advanced breast cancer.	<p>Route of Administration : Oral</p> <p>Dosage</p> <p>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).</p> <p>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).</p> <p>Duration of treatment: until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.</p> <p>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.</p>	Total of 672 Randomized 1:1 335 patients in ribociclib arm and 337 patients in placebo arm. All randomized patients received study treatment.	<p>Median age of patients in the study was 44 years (min to max: 25 to 58) and 72.3% were <math>\geq</math> 40 years of age.</p> <p>Ribociclib arm: median age was 43 years (min to max: 25 - 58) and 70.7% were <math>\geq</math> 40 years of age.</p> <p>Placebo arm: median age was 45 years (min to max: 29 - 58) and 73.9% were <math>\geq</math> 40 years of age.</p>	Pre- or Peri menopausal women with HR-positive, HER2-negative advanced breast cancer who received no prior hormonal therapy for their advanced disease
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Study CLEE011E2301 was a randomized, double-blind, placebo-controlled multicenter phase III clinical study of KISQALI plus either a non-steroidal aromatase inhibitor (NSAI) or tamoxifen and goserelin versus placebo plus either a NSAI or tamoxifen and goserelin 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 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.

## Results

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

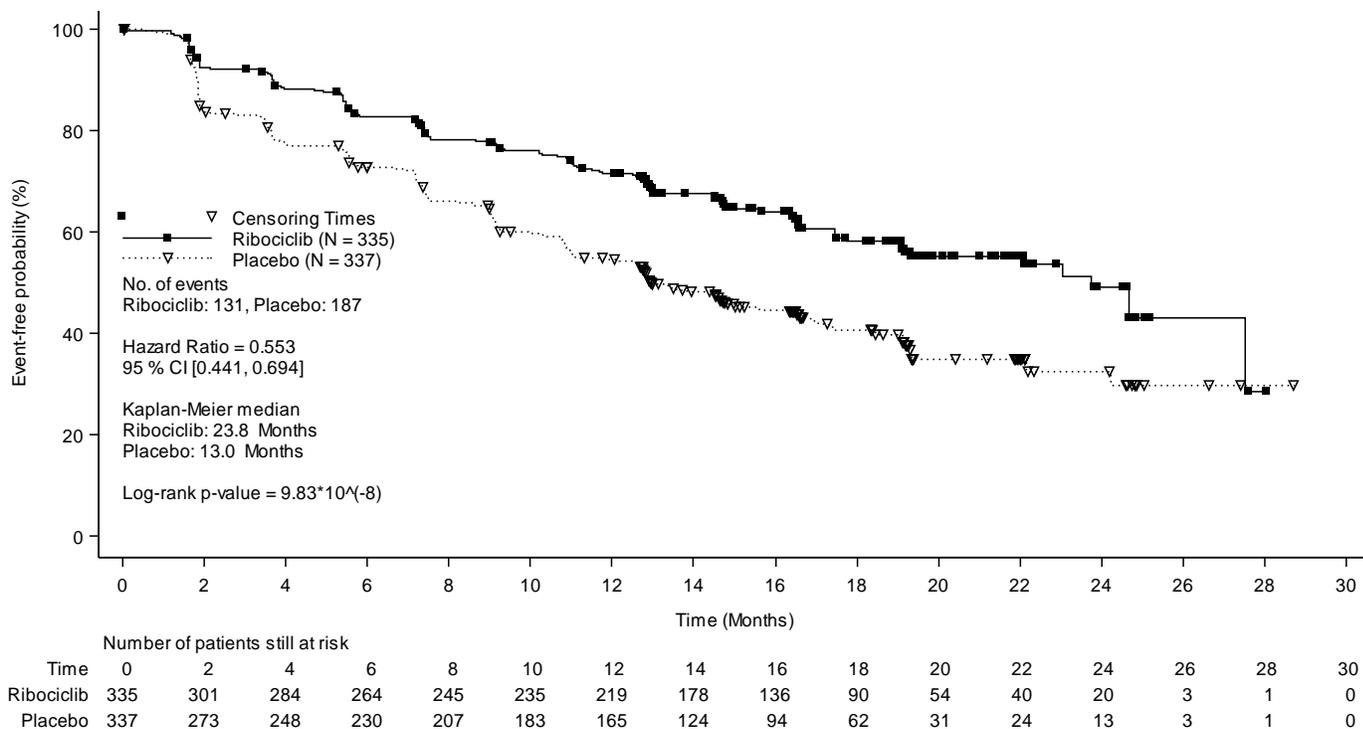
The median follow-up duration at the time of primary PFS analysis was 19.2 months.

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, NE) in the KISQALI plus NSAI subgroup and 13.8 months (12.6, 17.4) in the placebo plus NSAI subgroup [HR: 0.569 (95% CI: 0.436, 0.743)], which was consistent with the overall study population regardless of combination partner. Efficacy results are summarized in Table 18 and the Kaplan-Meier curve for PFS in Figures 3 and 4. Results in the KISQALI plus NSAI subgroup 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).

At the time of primary PFS analysis, overall survival data were not mature with 89 (35 %) events.

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**

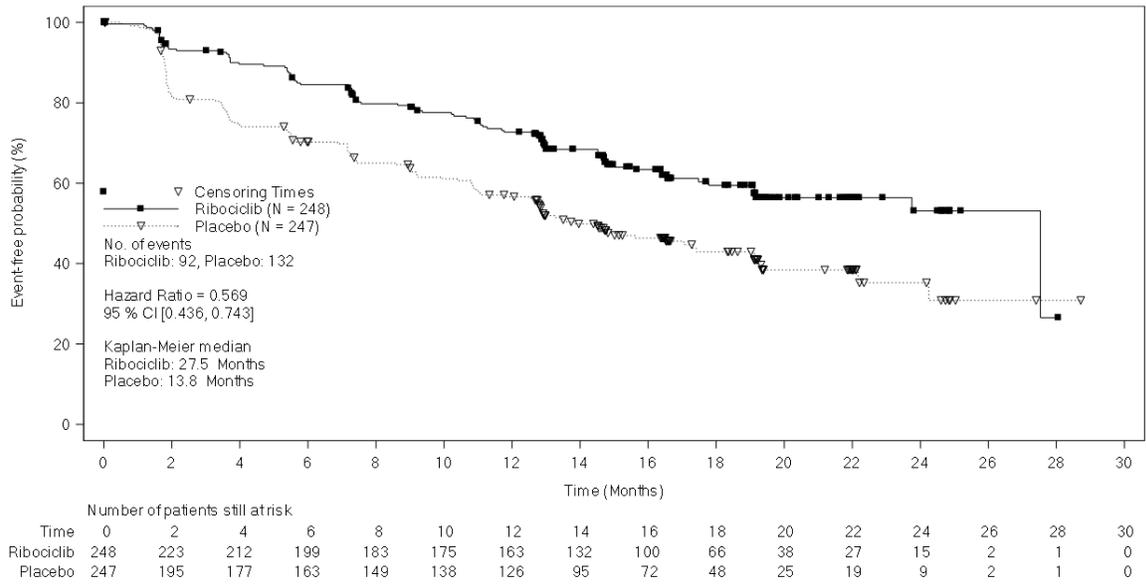


**Table 18 CLEE011E2301 efficacy results based on investigator assessment from MONALEESA-7 (in patients who received NSAI)**

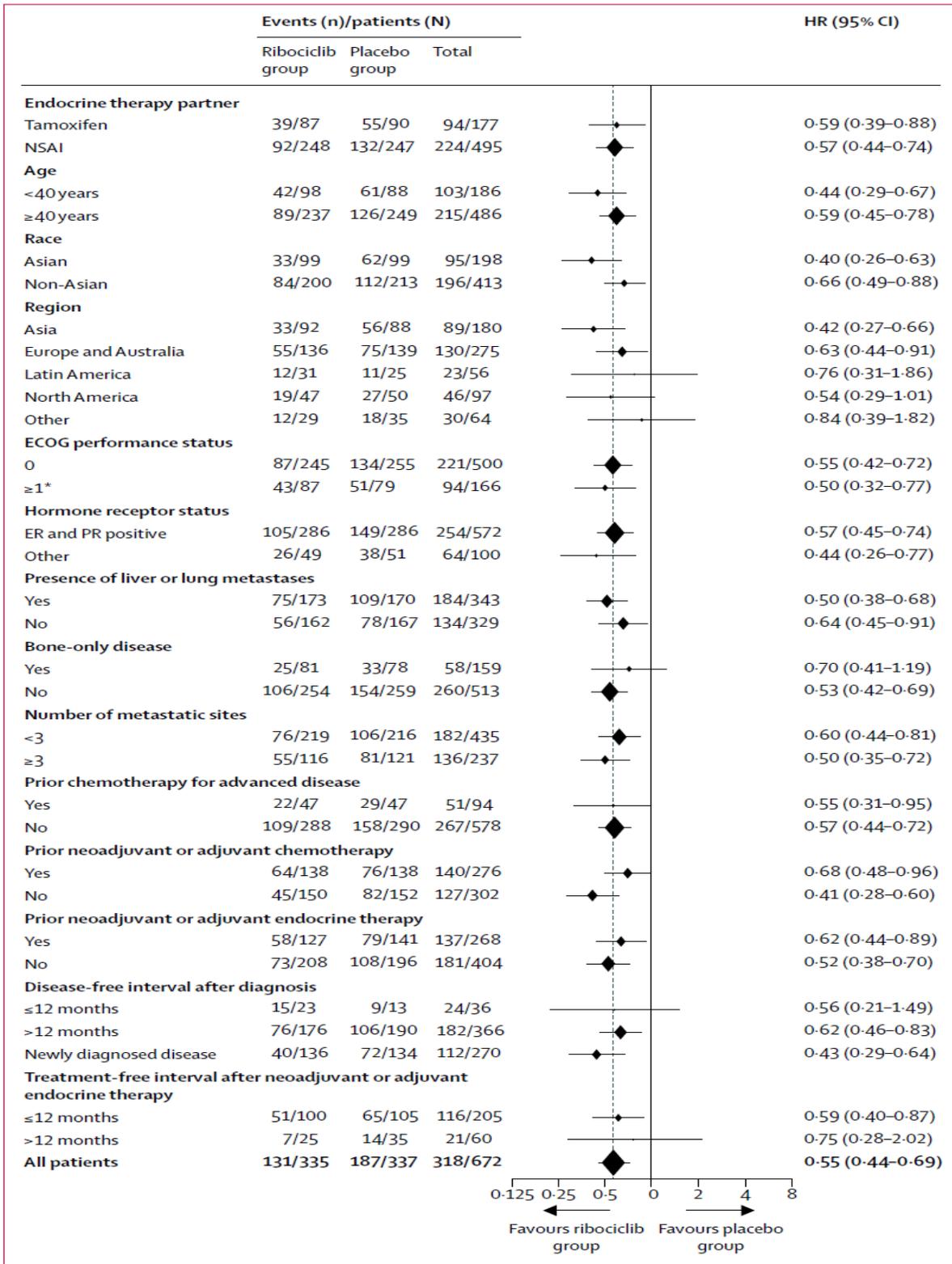
Analysis	KISQALI plus NSAI plus goserelin (%, 95% CI)	Placebo plus NSAI plus goserelin (%, 95% CI)
<b>Progression- free survival<sup>c</sup></b>	<b>N=248</b>	<b>N=247</b>
Median [months] (95% CI)	27.5 (19.1, NE)	13.8 (12.6, 17.4)
Hazard ratio (95% CI)	0.569 (0.436, 0.743)	
<b>Patients with measurable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

<sup>a</sup>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 – MONALEESA-7 (patients who received NSAI)**



**Figure 5 Forest plot of PFS based on Investigator assessment in patients who received NSAI<sup>1</sup>**



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.

<sup>1</sup> KISQALI is not indicated for use in combination with tamoxifen and combined treatment is not recommended.

## Study CLEE011F2301 (MONALEESA-3)

### Study demographics and trial design

**Table 19 – Summary of patient demographics for MONALEESA-3**

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.	<p>Route of Administration : Oral</p> <p>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).</p> <p>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).</p> <p>Duration until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.</p>	<p>726 patients were randomized 2:1 with 484 patients in the ribociclib plus fulvestrant arm and 242 patients in the placebo plus fulvestrant arm.</p> <p>2 patients never received study treatment.</p>	<p>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.</p> <p>Ribociclib arm: Median age was 63 years (min to max: 31 to 89).</p> <p>Placebo arm: Median age was 63 years (min to max: 34 to 86).</p>	Post menopausal women
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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 (see Figure 6 footnote). 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 of age 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 which 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 neo-adjuvant setting prior to study entry. Approximately 21% of patients had bone only disease and 60.5% of patients had visceral disease.

## Results

The primary efficacy endpoint for the study was assessed after observing 361 progression-free survival (PFS) events using 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.

The median (95% CI) PFS was 20.5 months (18.5, 23.5) in the KISQALI plus fulvestrant arm and 12.8 months (10.9, 16.3) in the placebo plus fulvestrant arm (see Table 20 and the Kaplan-Meier curve for PFS in Figure 6).

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

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

At the time of primary PFS analysis, with a median follow-up of 20.4 months, overall survival was not mature with 34% of events.

### **Table 20 Efficacy Results based on Investigator assessment – MONALEESA-3**

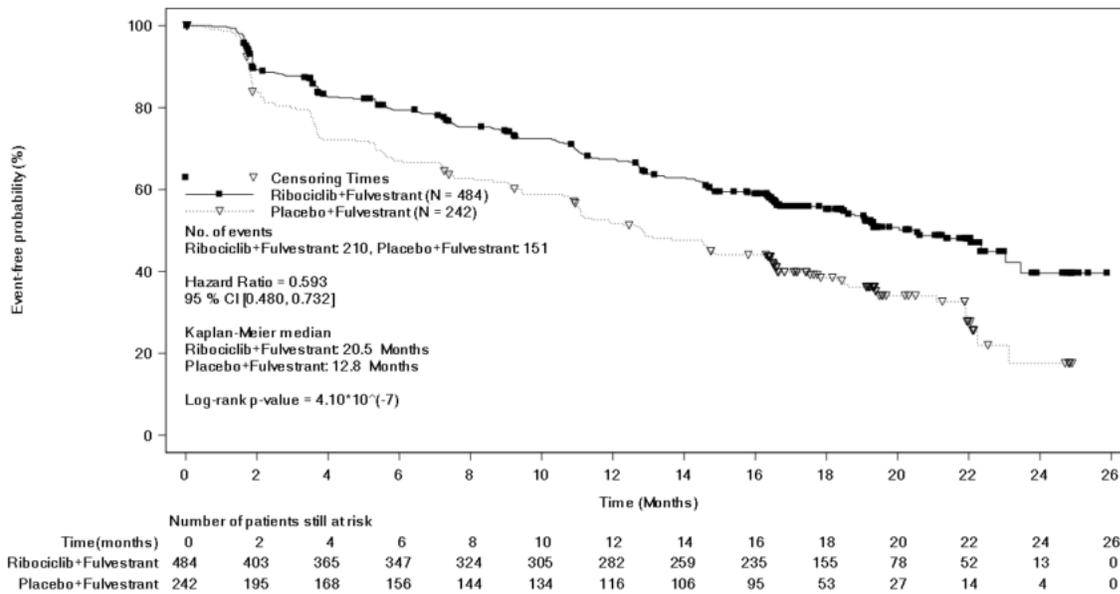
Analysis	KISQALI plus fulvestrant (%, 95% CI)	Placebo plus fulvestrant (%, 95% CI)	p-value <sup>e</sup>
<b>Progression free survival</b>	N=484	N=242	
Median [months] (95% CI)	20.5 (18.5 – 23.5)	12.8 (10.9 – 16.3)	0.00000041 <sup>c</sup>
Hazard ratio (95% CI)	0.593 (0.480 - 0.732)		
	<b>N=484</b>	<b>N=242</b>	
<b>Patients with measurable disease</b>	<b>N=379</b>	<b>N=181</b>	
Overall Response Rate <sup>a</sup>	40.9 (35.9 , 45.8)	28.7 (22.1, 35.3)	0.003

<sup>a</sup>ORR: proportion of patients with complete response + partial response

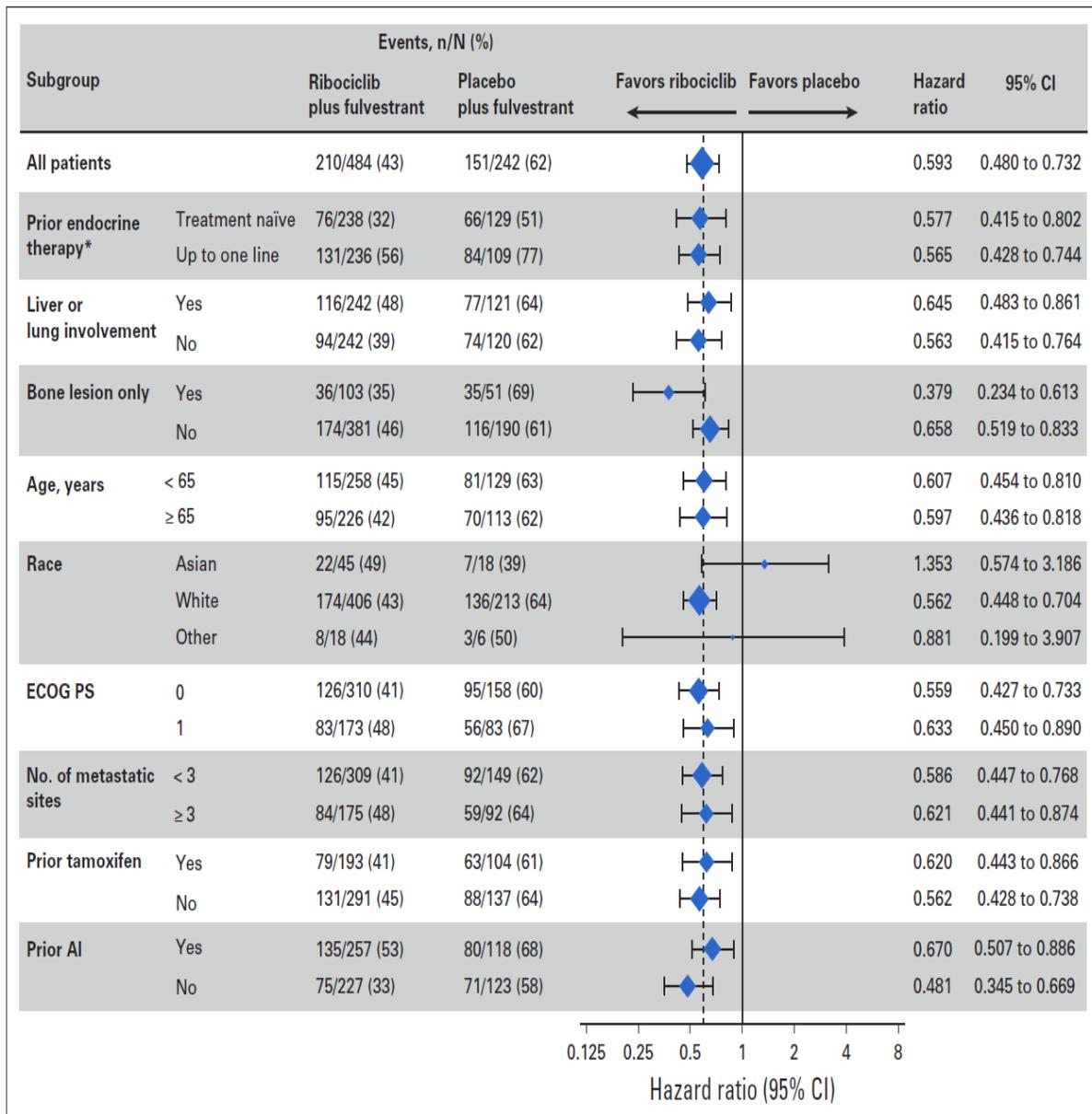
CI=confidence interval; N=number of patients; NE = Not estimable.

<sup>c</sup> p-value is obtained from the one-sided stratified log-rank test.

**Figure 6 Kaplan-Meier plot of PFS based on Investigator assessment –MONALEESA-3**



**Figure 7 Forest plot of PFS based on Investigator assessment – 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.

## 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**

<b>Ribociclib (3 x 200 mg) From measured data  Geometric Mean</b>
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<b>Parameter</b>	<b>Test</b>	<b>Reference</b>	<b>Ratio of Geometric Means</b>	<b>90% Confidence Interval (Lower, Upper)</b>
AUC <sub>T</sub> (hr*ng/mL)	10600 n=31	10600 n=31	1	(0.881, 1.14)
AUC <sub>I</sub> (hr*ng/mL)	10800 n=31	11500 n=30	0.937	(0.885, 0.991)
C <sub>MAX</sub> (ng/mL)	601 n=31	596 n=31	1.01	(0.869, 1.17)
T <sub>MAX</sub> (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<sub>T</sub> = AUC<sub>last</sub>

- 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 Tmax, 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

## **DETAILED PHARMACOLOGY**

### Pharmacodynamics

In biochemical assays, ribociclib inhibits CDK4/Cyclin D1 and CDK6/Cyclin D3 enzyme complexes with IC<sub>50</sub> 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 (IC<sub>50</sub> >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 IC<sub>50</sub>

values of 2.0  $\mu\text{M}$ , 9.0  $\mu\text{M}$ , and 7.7  $\mu\text{M}$ , 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  $\text{IC}_{50}$  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  $\mu\text{M}$  and the  $\text{IC}_{50}$  values for inhibition of phosphorylation of pRb and G1 arrest were 0.180 and 0.100  $\mu\text{M}$ , respectively. The  $\text{IC}_{50}$  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 the 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  $\text{IC}_{50}$  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  $\text{IC}_{50}\text{s} < 1 \mu\text{M}$ , while majority (21 out of 29) of the ER-negative cell lines have  $\text{IC}_{50}\text{s} > 1 \mu\text{M}$ .

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 ( $\text{IC}_{50}$ = 0.59  $\mu\text{M}$ , n=2), rat vesicular monoamine transporter VMAT2 ( $\text{IC}_{50}$  = 6.3  $\mu\text{M}$ , n=2), orexin-2 receptor (70% inhibition at 10  $\mu\text{M}$ ) and apelin receptor (54% inhibition at 10  $\mu\text{M}$ ).  $\text{IC}_{50}$  values were not determined for the last two mentioned targets.

For LEQ803, activities were found on phosphodiesterase PDE4d ( $\text{IC}_{50}$  = 0.6  $\mu\text{M}$ ), serotonin 5HT3 channel ( $\text{IC}_{50}$  = 2.63  $\mu\text{M}$ ), neuronal nicotinic alpha 2 channel ( $\text{IC}_{50}$  = 5.7  $\mu\text{M}$ ), cannabinoid CB1 receptor ( $\text{IC}_{50}$  = 28  $\mu\text{M}$ ), peripheral rat imidazoline I2 receptor (71% inhibition at 10  $\mu\text{M}$ ), rabbit

monoamine transporter VMAT2 (84% inhibition at 10  $\mu$ M) and rat brain sodium channel site II (70% inhibition at 10  $\mu$ M). IC50 values were not determined for the last three mentioned targets.

The clinical free Cmax at the recommended dose of 600 mg ribociclib was 1.2  $\mu$ M, and the free Cmax of LEQ803 was 0.03  $\mu$ M.

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  $\mu$ M.

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

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

*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 Cmax).

## **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  $\geq$ 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 ( $\leq$ 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  $\geq 75$  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  $\geq 75$  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  $\geq 75$  mg/kg/day in the 4 week study, at 150 mg/kg/day in the 15 week study, and at  $\geq 75$  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<sup>th</sup> 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.

### **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.

### **Carcinogenesis**

No carcinogenesis studies have been conducted with ribociclib.

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## PART III: PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

#### PATIENT MEDICATION INFORMATION

##### **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; croscopovidone (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); xanthan gum.

### **What KISQALI looks like and contents of the pack**

KISQALI is supplied in aluminum blister packs.

The tablet is light greyish violet, unscored, round, curved with beveled edges, debossed with “RIC” on one side and “NVR” on the other side

### **KISQALI comes in the following dosage forms:**

Tablets; 200 mg ribociclib (as ribociclib succinate)

### **Do not use KISQALI if you:**

- are allergic (hypersensitive) to ribociclib succinate or to any of the other ingredients of KISQALI.
- 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.**

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

**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, digitalis glycosides, non-dihydropyridine calcium channel blockers, cholinesterase inhibitors, alpha2-adrenoceptor agonists, I<sub>f</sub> 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.

You should also tell your healthcare professional if you are already taking KISQALI and you are

prescribed a new medicine that you have not taken before.

Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

### **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 starting dose:**

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.

### **Overdose:**

If you think you have taken too much KISQALI, or if someone else accidentally takes your medicine, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. Show the KISQALI packet. Medical treatment may be necessary.

### **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.

**If you stop taking KISQALI:**

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 doctor or pharmacist.

**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.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>VERY COMMON</b>			
<b>Liver problems:</b> 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.			√
<b>Anemia (low levels of red blood cells):</b> fatigue, loss of energy, weakness, shortness of breath		√	
<b>Pneumonia (infection in the lungs):</b> 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			√
<b>Gastroenteritis (Infections of the stomach and intestines):</b> Abdominal pain, diarrhea, nausea and vomiting			√
<b>Urinary tract infection:</b> pain and/or burning when urinating, blood in the urine, increased urge to urinate		√	
<b>COMMON</b>			
<b>Low levels of platelets:</b> spontaneous bleeding or bruising			√

<b>Febrile neutropenia:</b> 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			√
<b>Low levels of potassium in the blood:</b> irregular heartbeat, muscle weakness			√
<b>Low levels of calcium in the blood:</b> muscle cramps and spasms, numbness and tingling in the hands, feet and face			√
<b>Fainting</b> (syncope)			√
<b>Heart problems:</b> chest pain or discomfort, heart palpitations, fast or slow heartbeat, dizziness, lightheadedness, fainting, sudden death			√
<b>UNCOMMON</b>			
<b>Pneumonitis/ Interstitial lung disease (inflammation of the lung tissue):</b> Trouble breathing, cough and shortness of breath, fever, feeling tired			√
<b>Pulmonary embolism (blood clot in the lung):</b> sudden, severe chest pain and trouble breathing, coughing up blood, rapid breathing and heartbeat			√
<b>Sepsis and septic shock (Infection of the blood):</b> fever or dizziness, chills, high or very low body temperature, little or no urine, low blood pressure, palpitations, rapid breathing, rapid heartbeat.			√
<b>UNKNOWN FREQUENCY</b>			
<b>Severe skin reaction that might include a combination of:</b> 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/adverse-reaction-reporting.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 healthcare 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](http://www.canada.ca/en/health-canada.html) (<http://www.canada.ca/en/health-canada.html>); the manufacturer's website (<http://www.novartis.ca>) or by calling 1-800-363-8883.

KISQALI is a trademark.

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