## 1. NAME OF THE MEDICINAL PRODUCT

Kisqali 200 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect

Each film-coated tablet contains 0.344 mg soya lecithin.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Early breast cancer

Kisqali in combination with an aromatase inhibitor is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence (see section 5.1 for selection criteria).

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

Advanced or metastatic breast cancer

Kisqali is indicated for the treatment of women with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

In pre- or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist.

### 4.2 Posology and method of administration

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

HR-positive, HER2-negative testing

Patient selection for treatment with Kisqali based on the tumour expression of HR and HER2 should be assessed by a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used.

Posology

*Early breast cancer*
The recommended dose is 400 mg (two 200 mg film-coated tablets) of ribociclib once daily for 21 consecutive days followed by 7 days off treatment, resulting in a complete cycle of 28 days. In patients with early breast cancer, Kisqali should be taken until completion of 3 years of treatment or until disease recurrence or unacceptable toxicity occur.

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

In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a LHRH agonist.

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

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

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

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

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

**Table 1 Recommended dose modification guidelines**

| | Kisqali | |
|---|---|---|
| | Dose | Number of 200 mg tablets |
| **Early breast cancer** | | |
| Starting dose | 400 mg/day | 2 |
| Dose reduction | 200 mg*/day | 1 |
| **Advanced or metastatic breast cancer** | | |
| Starting dose | 600 mg/day | 3 |
| First dose reduction | 400 mg/day | 2 |
| Second dose reduction | 200 mg*/day | 1 |
| * If further dose reduction below 200 mg/day is required, the treatment should be permanently discontinued. | | |

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

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

**Table 2 Dose modification and management – Neutropenia**

| | **Grade 1 or 2*** (ANC 1 000/mm$^3$ - ≤LLN) | **Grade 3*** (ANC 500 - <1 000/mm$^3$) | **Grade 3* febrile neutropenia**** | **Grade 4*** (ANC <500/mm$^3$) |
|---|---|---|---|---|
| **Neutropenia** | No dose adjustment is required | Dose interruption until recovery to grade ≤2. Resume Kisqali at the same dose level. If toxicity recurs at grade 3: dose interruption until recovery to grade ≤2, then resume Kisqali and reduce by 1 dose level. | Dose interruption until recovery to grade ≤2. Resume Kisqali and reduce by 1 dose level | Dose interruption until recovery to grade ≤2. Resume Kisqali and reduce by 1 dose level. |
| * Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)<br>** Grade 3 neutropenia with a single fever >38.3°C (or 38°C and above for more than one hour and/or concurrent infection)<br>ANC = absolute neutrophil count; LLN = lower limit of normal | | | | |

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

**Table 3 Dose modification and management – Hepatobiliary toxicity**

| | **Grade 1*** **(> ULN – 3 x ULN)** | **Grade 2*** **(>3 to 5 x ULN)** | **Grade 3*** **(>5 to 20 x ULN)** | **Grade 4*** **(>20 x ULN)** |
|---|---|---|---|---|
| **AST and/or ALT elevations from baseline**, without increase in total bilirubin above 2 x ULN** | No dose adjustment is required. | Baseline grade <2: Dose interruption until recovery to ≤ baseline grade, then resume Kisqali at same dose level. If grade 2 recurs, resume Kisqali at next lower dose level.<br>Baseline grade = 2: No dose interruption. | Dose interruption of Kisqali until recovery to ≤ baseline grade, then resume at next lower dose level. If grade 3 recurs, discontinue Kisqali. | Discontinue Kisqali. |
| **Combined elevations in AST and/or ALT together with total bilirubin increase, in the absence of cholestasis** | If patients develop ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN irrespective of baseline grade, discontinue Kisqali. | | | |
| * Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)<br>** Baseline = prior to treatment initiation<br>ULN = upper limit of normal | | | | |

ECG should be assessed before initiating treatment with Kisqali in all patients.

**Treatment with Kisqali should be initiated only in patients with QTcF values less than 450 msec.** After initiating treatment, ECG should be repeated at approximately day 14 of the first cycle, then as clinically indicated.

In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended in patients with early breast cancer and advanced or metastatic breast cancer.

**Table 4 Dose modification and management – QT prolongation**

| **QTcF* prolongation** | **Early breast cancer** | **Advanced or metastatic breast cancer** |
|---|---|---|
| **>480 msec and ≤500 msec** | Dose interruption of Kisqali until QTcF resolves to <481 msec. | |
| | Resume at the same dose level. | Reduce to the next lower dose level. |
| | If QTcF ≥481 msec recurs, interrupt Kisqali treatment until QTcF resolves to <481 msec, then resume at next lower dose level. | |
| **>500 msec** | Dose interruption of Kisqali until QTcF resolves to <481 msec, then resume at next lower dose level.<br>If QTcF >500 msec recurs, discontinue Kisqali. | |
| If QTcF interval is greater than 500 msec or shows a greater than 60 msec change from baseline in combination with torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue Kisqali. | | |
| Note: If further dose reductions are required at the 200 mg dose, Kisqali should be discontinued.<br>*QTcF = QT interval corrected by Fridericia's formula. | | |

**Table 5 Dose modification and management – ILD/pneumonitis**

| | **Grade 1*** (asymptomatic) | **Grade 2*** (symptomatic) | **Grade 3 or 4*** (severe) |
|---|---|---|---|
| **ILD/pneumonitis** | No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated. | Dose interruption until recovery to grade ≤1, then resume Kisqali at the next lower dose level**. | Discontinue Kisqali. |
| *Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)<br>**An individualised benefit-risk assessment should be performed when considering resuming Kisqali.<br>ILD = interstitial lung disease | | | |

**Table 6 Dose modification and management – Other toxicities***

| **Other toxicities** | **Grade 1 or 2**** | **Grade 3**** | **Grade 4**** |
|---|---|---|---|
| | No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated. | Dose interruption until recovery to grade ≤1, then resume Kisqali at the same dose level. If grade 3 recurs, resume Kisqali at the next lower dose level. | Discontinue Kisqali. |
| * Excluding neutropenia, hepatotoxicity, QT interval prolongation and ILD/pneumonitis.<br>** Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events) | | | |

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

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

In patients taking 600 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, the dose should be reduced to 400 mg.

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

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

Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients, therefore close monitoring of signs of toxicity is recommended. If the strong inhibitor is discontinued, the Kisqali dose should be changed to the dose used prior to the initiation of the strong CYP3A4 inhibitor after at least 5 half-lives of the strong CYP3A4 inhibitor (see sections 4.4, 4.5 and 5.2).

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

*Hepatic impairment*
No dose adjustment is necessary in patients with early breast cancer with hepatic impairment (see section 5.2). In patients with advanced or metastatic breast cancer, no dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A); patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) can have increased (less than 2-fold) exposure to ribociclib and the starting dose of 400 mg Kisqali once daily is recommended (see section 5.2).

*Paediatric population*
The safety and efficacy of Kisqali in children and adolescents aged below 18 years have not been established. Currently available data on Kisqali in combination with topotecan and temozolomide (TOTEM) in paediatric patients are described in sections 5.1 and 5.2, but no recommendation on a posology can be made.

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

Method of administration

Kisqali should be taken orally once daily with or without food (see section 4.5). Patients should be encouraged to take their dose at approximately the same time each day, preferably in the morning. If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. The tablets should be swallowed whole and should not be chewed, crushed or split prior to swallowing. No tablet should be ingested if it is broken, cracked or otherwise not intact.

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

Critical visceral disease

A longer time to response (TTR) has been observed in patients treated with ribociclib plus a non-steroidal aromatase inhibitor (NSAI) compared to those treated with combination chemotherapy in a clinical study (see section 5.1). This should be considered by the treating physician managing patients with critical visceral disease who may be considered for ribociclib plus NSAI therapy.

Neutropenia

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

Hepatobiliary toxicity

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

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

QT interval prolongation

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

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

The use of Kisqali with medicinal products known to prolong QTc interval and/or strong CYP3A4 inhibitors should be avoided as this may lead to clinically meaningful prolongation of the QTcF interval (see sections 4.2, 4.5 and 5.1). If co-administration of Kisqali with a strong CYP3A4 inhibitor cannot be avoided, the Kisqali dose should be changed as described in section 4.2.

Based on the findings from study E2301 (MONALEESA-7), Kisqali is not recommended for use in combination with tamoxifen (see sections 4.8 and 5.1).

*Early breast cancer*
In study O12301C (NATALEE), a QTcF interval increase >60 msec from baseline was observed in 19 (0.8%) patients receiving Kisqali plus AI.

ECG should be assessed before initiating treatment. Treatment with Kisqali should be initiated only in patients with QTcF values less than 450 msec. ECG should be repeated at approximately day 14 of the first cycle, then as clinically indicated (see sections 4.2 and 4.8).

In patients with early breast cancer, appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed before initiating treatment, at the beginning of the first 6 cycles and then as clinically indicated. Any abnormality should be corrected before initiating treatment with Kisqali and during treatment with Kisqali.

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

*Advanced or metastatic breast cancer*
In study E2301 (MONALEESA-7), a QTcF interval increase >60 msec from baseline was observed in 14/87 (16.1%) patients receiving Kisqali plus tamoxifen and in 18/245 (7.3%) patients receiving Kisqali plus a non-steroidal aromatase inhibitor (NSAI).

ECG should be assessed before initiating treatment. Treatment with Kisqali should be initiated only in patients with QTcF values less than 450 msec. ECG should be repeated at approximately day 14 of the first cycle, then as clinically indicated (see sections 4.2 and 4.8).

In patients with advanced or metastatic breast cancer, appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed before initiating treatment, at the beginning of the first 6 cycles and then as clinically indicated. Any abnormality should be corrected before initiating treatment with Kisqali and during treatment with Kisqali.

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

Severe cutaneous reactions

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

Interstitial lung disease/pneumonitis

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

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

Blood creatinine increase

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

CYP3A4 substrates

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

Renal impairment

The recommended starting dose of 200 mg for patients with severe renal impairment is estimated to result in approximately 45% lower exposure compared with the standard starting dose of 600 mg in advanced or metastatic breast cancer patients with normal renal function. The efficacy at this starting dose has not been studied. Caution should be used in patients with severe renal impairment with close monitoring for signs of toxicity (see sections 4.2 and 5.2).

Women of childbearing potential

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

Soya lecithin

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

## 4.5 Interaction with other medicinal products and other forms of interaction

Substances that may increase ribociclib plasma concentrations

Ribociclib is primarily metabolised by CYP3A4. Therefore, medicinal products that can influence CYP3A4 enzyme activity may alter the pharmacokinetics of ribociclib. Co-administration of the strong CYP3A4 inhibitor ritonavir (100 mg twice daily for 14 days) with a single 400 mg dose of ribociclib increased ribociclib exposure ($AUC_{inf}$) and the peak concentration ($C_{max}$) in healthy subjects 3.2- and 1.7-fold, respectively, relative to a single 400 mg ribociclib dose given alone. $C_{max}$ and $AUC_{last}$ for LEQ803 (a prominent metabolite of ribociclib accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively. Physiologically-based pharmacokinetic (PBPK) simulations with co-administered ritonavir (100 mg twice daily) estimated that the steady-state $C_{max}$ and $AUC_{0\text{-}24h}$ of ribociclib (400 mg once daily) increased by 1.5- and 1.8-fold, respectively.

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

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

PBPK simulations suggested that at a 600 mg dose of ribociclib, a moderate CYP3A4 inhibitor (erythromycin) may increase ribociclib steady-state $C_{max}$ and AUC 1.1- and 1.1-fold, respectively. PBPK simulations suggested that a moderate CYP3A4 inhibitor may increase $C_{max}$ and AUC of ribociclib 400 mg steady state by 1.1- and 1.2-fold, respectively. The effect at the 200 mg once-daily dose was predicted to be a 1.3- and 1.5-fold increase in steady-state $C_{max}$ and AUC, respectively. No dose adjustments of ribociclib are required at initiation of treatment with mild or moderate CYP3A4 inhibitors. However, monitoring of ribociclib-related ARs is recommended.

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

<u>Substances that may decrease ribociclib plasma concentrations</u>

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

The effect of a moderate CYP3A4 inducer on ribociclib exposure has not been studied. PBPK simulations suggested that a moderate CYP3A4 inducer (efavirenz) may decrease steady-state ribociclib $C_{max}$ and AUC by 55% and 74%, respectively, at a ribociclib dose of 400 mg, and by 52% and 71%, respectively, at a ribociclib dose of 600 mg. The concomitant use of moderate CYP3A4 inducers may therefore lead to decreased exposure and consequently a risk for impaired efficacy, in particular in patients treated with ribociclib at 400 mg or 200 mg once daily.

<u>Substances that may have plasma concentrations altered by Kisqali</u>

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

Co-administration of midazolam (CYP3A4 substrate) with multiple doses of Kisqali (400 mg) increased the midazolam exposure by 280% (3.80-fold) in healthy subjects, compared with administration of midazolam alone. PBPK simulations suggested that Kisqali given at the dose of 600 mg is expected to increase the midazolam AUC by 5.2-fold. Therefore, in general, when ribociclib is co-administered with other medicinal products, the SmPC of the other medicinal product must be

consulted for the recommendations regarding co-administration with CYP3A4 inhibitors. Caution is recommended in case of concomitant use with sensitive CYP3A4 substrates with a narrow therapeutic index (see section 4.4). The dose of a sensitive CYP3A4 substrate with a narrow therapeutic index, including but not limited to alfentanil, ciclosporin, everolimus, fentanyl, sirolimus and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

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

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

Substances that are substrates of transporters

*In vitro* evaluations indicated that ribociclib has a potential to inhibit the activities of drug transporters P-gp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1 and BSEP. Caution and monitoring for toxicity are advised during concomitant treatment with sensitive substrates of these transporters which exhibit a narrow therapeutic index, including but not limited to digoxin, pitavastatin, pravastatin, rosuvastatin and metformin.

Drug-food interactions

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

Medicinal products that elevate gastric pH

Ribociclib exhibits high solubility at or below pH 4.5 and in bio-relevant media (at pH 5.0 and 6.5). Co-administration of ribociclib with medicinal products that elevate the gastric pH was not evaluated in a clinical study; however, altered ribociclib absorption was not observed in population pharmacokinetic and non–compartmental pharmacokinetic analyses.

Drug-drug interaction between ribociclib and letrozole

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

Drug-drug interaction between ribociclib and anastrozole

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

Drug-drug interaction between ribociclib and fulvestrant

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

Drug-drug interaction between ribociclib and tamoxifen

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

Drug-drug interactions between ribociclib and oral contraceptives

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

Anticipated interactions

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

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

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

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

Pregnancy

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

Breast-feeding

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

Fertility

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

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Summary of the safety profile

*Early breast cancer*
The most common adverse drug reactions (ADRs) (reported at a frequency ≥20%) in the dataset for which the frequency for Kisqali plus aromatase inhibitor (AI) exceeds the frequency for AI alone were neutropenia, infections, nausea, headache, fatigue, leukopenia and abnormal liver function tests.

The most common grade 3/4 ADRs (reported at a frequency of ≥2%) in the dataset for which the frequency for Kisqali plus AI exceeds the frequency for AI alone were neutropenia, abnormal liver function tests and leukopenia.

Dose reduction due to adverse events, regardless of causality, occurred in 22.8% of patients receiving Kisqali plus AI in the phase III clinical study. Permanent discontinuation was reported in 19.7% of patients receiving Kisqali plus AI in the phase III clinical study.

*Advanced or metastatic breast cancer*
The most common adverse drug reactions (ADRs) (reported at a frequency ≥20%) in the pooled dataset for which the frequency for Kisqali plus any combination exceeds the frequency for placebo plus any combination were neutropenia, infections, nausea, fatigue, diarrhoea, leukopenia, vomiting, headache, constipation, alopecia, cough, rash, back pain, anaemia and abnormal liver function tests.

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

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

Tabulated list of adverse reactions

*Early breast cancer*
The overall safety evaluation of Kisqali is based on the dataset from 2 525 patients who received Kisqali in combination with AI and who were included in the randomised, open-label phase III clinical study NATALEE.

The median duration of exposure to ribociclib across the study was 33.0 months, with 69.4% patients exposed for >24 months, and 42.8% patients completing the 36-month ribociclib regimen.

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

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

ADRs from the phase III clinical studies and post-marketing experience (Table 7) in patients with early breast cancer and advanced or metastatic breast cancer are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is

based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); and not known (cannot be estimated from the available data).

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

| Frequency | Patients with early breast cancer with starting dose 400 mg ribociclib | Patients with advanced or metastatic breast cancer with starting dose 600 mg ribociclib |
|---|---|---|
| **Infections and infestations** | | |
| Very common | Infections[1] | Infections[1] |
| **Blood and lymphatic system disorders** | | |
| Very common | Neutropenia, leukopenia | Neutropenia, leukopenia, anaemia, lymphopenia |
| Common | Anaemia, thrombocytopenia, lymphopenia | Thrombocytopenia, febrile neutropenia |
| Uncommon | Febrile neutropenia | - |
| **Metabolism and nutrition disorders** | | |
| Very common | - | Appetite decreased |
| Common | Hypocalcaemia, hypokalaemia, appetite decreased | Hypocalcaemia, hypokalaemia, hypophosphataemia |
| **Nervous system disorders** | | |
| Very common | Headache | Headache, dizziness |
| Common | Dizziness | Vertigo |
| **Eye disorders** | | |
| Common | - | Lacrimation increased, dry eye |
| **Cardiac disorders** | | |
| Common | - | Syncope |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Very common | Cough | Dyspnoea, cough |
| Common | Dyspnoea, interstitial lung disease (ILD) / pneumonitis | Interstitial lung disease (ILD) / pneumonitis |
| **Gastrointestinal disorders** | | |
| Very common | Nausea, diarrhoea, constipation, abdominal pain[2] | Nausea, diarrhoea, vomiting, constipation, abdominal pain[2], stomatitis, dyspepsia |
| Common | Vomiting, stomatitis[3] | Dysgeusia |
| **Hepatobiliary disorders** | | |
| Common | Hepatotoxicity[4] | Hepatotoxicity[4] |
| **Skin and subcutaneous tissue disorders** | | |
| Very common | Alopecia | Alopecia, rash[5], pruritus |
| Common | Rash[5], pruritus | Dry skin, erythema, vitiligo |
| Rare | - | Erythema multiforme |
| Not known | - | Toxic epidermal necrolysis (TEN) |
| **Musculoskeletal and connective tissue disorders** | | |
| Very common | - | Back pain |
| **General disorders and administration site conditions** | | |
| Very common | Fatigue, asthenia, pyrexia | Fatigue, peripheral oedema, pyrexia, asthenia |
| Common | Peripheral oedema, oropharyngeal pain | Oropharyngeal pain, dry mouth |

| **Investigations** | | |
|---|---|---|
| Very common | Abnormal liver function tests[6] | Abnormal liver function tests[6] |
| Common | Blood creatinine increased, electrocardiogram QT prolonged | Blood creatinine increased, electrocardiogram QT prolonged |

[1] Infections: urinary tract infections, respiratory tract infections, gastroenteritis (only in patients with advanced or metastatic breast cancer), sepsis (<1% only in patients with advanced or metastatic breast cancer).
[2] Abdominal pain: abdominal pain, abdominal pain upper.
[3] Stomatitis for early breast cancer includes: stomatitis, mucositis.
[4] Hepatotoxicity: hepatic cytolysis, hepatocellular injury (only in patients with advanced or metastatic breast cancer), drug-induced liver injury (<1% in patients with early breast cancer and in patients with advanced or metastatic breast cancer), hepatotoxicity, hepatic failure (only in patients with advanced or metastatic breast cancer), autoimmune hepatitis.
[5] Rash: rash, rash maculopapular, rash pruritic.
[6] Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

Description of selected adverse reactions

*Neutropenia*
In the phase III study in patients with early breast cancer, neutropenia was the most frequently reported adverse reaction (62.5%) and a grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 45.1% of patients receiving Kisqali plus aromatase inhibitor (AI).

Among the patients with early breast cancer who had grade 2, 3 or 4 neutropenia, the median time to onset was 0.6 months, for those patients who had an event. The median time to resolution of grade ≥3 (to normalisation or grade <3) was 0.3 months in the Kisqali plus AI arm following treatment interruption and/or reduction and/or discontinuation. Febrile neutropenia was reported in 0.3% of patients exposed to Kisqali plus AI. Treatment discontinuation due to neutropenia was low (1.1%) in patients receiving Kisqali plus AI (see sections 4.2 and 4.4).

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

Among the patients with advanced or metastatic breast cancer who had grade 2, 3 or 4 neutropenia, the median time to onset was 17 days, for those patients who had an event. The median time to resolution of grade ≥3 (to normalisation or grade <3) was 12 days in the Kisqali plus any combination arms following treatment interruption and/or reduction and/or discontinuation. Febrile neutropenia was reported in about 1.7% of patients exposed to Kisqali in the phase III studies. Treatment discontinuation due to neutropenia was low (0.8%) (see sections 4.2 and 4.4).

All patients should be instructed to report any fever promptly.

*Hepatobiliary toxicity*
In the phase III clinical studies in patients with early breast cancer and advanced or metastatic breast cancer, increases in transaminases were observed.

In the phase III study in patients with early breast cancer, hepatobiliary toxicity events occurred in a higher proportion of patients in the Kisqali plus AI arm versus the AI alone arm (26.4% versus 11.2%, respectively), with more grade 3/4 adverse events reported in patients treated with Kisqali plus AI (8.6% versus 1.7%, respectively). Concurrent elevations of ALT or AST greater than three times the upper limit of normal and total bilirubin greater than two times the upper limit of normal, with normal alkaline phosphatase levels, occurred in 8 patients treated with Kisqali plus AI (in 6 patients ALT or AST levels recovered to normal within 65 to 303 days after discontinuation of Kisqali).

Dose interruptions due to hepatobiliary toxicity events were reported in 12.4% of patients with early breast cancer treated with Kisqali plus AI, primarily due to ALT increased (10.1%) and/or AST increased (6.8%). Dose adjustment due to hepatobiliary toxicity events was reported in 2.6% of patients treated with Kisqali plus AI, primarily due to ALT increased (1.9%) and/or AST increased (0.6%). Discontinuation of treatment with Kisqali due to abnormal liver function tests or hepatotoxicity occurred in 8.9% and 0.1% of patients, respectively (see sections 4.2 and 4.4).

In the phase III clinical study in patients with early breast cancer, 80.9% (165/204) of grade 3 or 4 ALT or AST elevation events occurred within the first 6 months of treatment. Among the patients who had grade 3 or 4 ALT/AST elevation, the median time to onset was 2.8 months for the Kisqali plus AI arm. The median time to resolution (to normalisation or grade ≤2) was 0.7 months in the Kisqali plus AI arm.

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

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

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

*QT prolongation*

In the phase III study in patients with early breast cancer, 5.3% of patients in the Kisqali plus AI arm and 1.4% of patients in the AI alone arm reported events of QT interval prolongation. In the Kisqali plus AI arm QT interval prolongation events were presented primarily by ECG QT prolonged (4.3%) which was the only confirmed adverse reaction with Kisqali. Dose interruptions due to ECG QT prolonged and syncope were reported in 1.1% of patients treated with Kisqali. Dose adjustments due to ECG QT prolonged were reported in 0.1% of patients treated with Kisqali.

A central analysis of ECG data showed 10 patients (0.4%) and 4 patients (0.2%) with at least one post-baseline QTcF interval >480 msec for the Kisqali plus AI arm and the AI alone arm, respectively. Among the patients who had QTcF interval prolongation of >480 msec in the Kisqali plus AI arm, the median time to onset was 15 days and these changes were reversible with dose interruption and/or dose adjustment. QTcF interval >60 msec change from baseline was observed in 19 patients (0.8%) in the Kisqali plus AI arm and post-baseline QTcF interval >500 msec was observed in 3 patients (0.1%) in the Kisqali plus AI arm.

In study E2301 (MONALEESA-7) in patients with advanced or metastatic breast cancer, the observed mean QTcF increase from baseline was approximately 10 msec higher in the tamoxifen plus placebo subgroup compared with the NSAI plus placebo subgroup, suggesting that tamoxifen alone had a

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

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

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

*Patients with renal impairment*
In the phase III clinical study in patients with early breast cancer, 983 patients with mild renal impairment and 71 patients with moderate renal impairment were treated with ribociclib. No patient with severe renal impairment was enrolled (see section 5.1).

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

## 4.9 Overdose

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EF02

Mechanism of action

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

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

*In vivo* studies using patient-derived oestrogen receptor-positive breast cancer xenograft model combinations of ribociclib and antioestrogens (i.e. letrozole) resulted in superior tumour growth inhibition with sustained tumour regression and delayed tumour regrowth after stopping dosing compared to each substance alone. When administered to patients ribociclib can also be immunomodulatory, decreasing regulatory T-cells and relative levels of CD3+ T-cells. Additionally, *in vivo* antitumour activity of ribociclib in combination with fulvestrant was assessed in immune-deficient mice bearing the ZR751 ER+ human breast cancer xenografts and the combination with fulvestrant resulted in complete tumour growth inhibition.

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

*Cardiac electrophysiology*
Serial, triplicate ECGs were collected following a single dose and at steady state to evaluate the effect of ribociclib on the QTc interval in patients with advanced cancer. A pharmacokinetic-pharmacodynamic analysis included a total of 997 patients treated with ribociclib at doses ranging from 50 to 1 200 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval.

In patients with advanced or metastatic breast cancer the estimated QTcF mean change from baseline for 600 mg Kisqali in combination with NSAI or fulvestrant was 22.0 msec (90% CI: 20.56, 23.44) and 23.7 msec (90% CI: 22.31, 25.08), respectively at the geometric mean $C_{max}$ at steady-state compared to 34.7 msec (90% CI: 31.64, 37.78) in combination with tamoxifen (see section 4.4).

In patients with early breast cancer a similar concentration-dependent increase in the QTc interval exists. The estimated QTcF mean change from baseline is estimated to be lower in patients with early breast cancer treated with 400 mg Kisqali compared to patients with advanced or metastatic breast cancer treated with 600 mg Kisqali.

Clinical efficacy and safety

*Early breast cancer*
*Study CLEE011O12301C (NATALEE)*
Kisqali was evaluated in a randomised, open-label, multicentre phase III clinical study in the treatment of pre-/postmenopausal women, and of men, with HR-positive, HER2-negative, early breast cancer

with anatomic stage II or III irrespective of nodal status at high risk of recurrence in combination with an aromatase inhibitor (AI, letrozole or anastrozole) versus AI alone that was:

- Anatomic stage group IIB-III, or
- Anatomic stage group IIA that is either:
  - Node positive or
  - Node negative, with:
    - Histologic grade 3, or
    - Histologic grade 2, with any of the following criteria:
      - Ki67 ≥20%
      - High risk by gene signature testing

Premenopausal women, and men, also received goserelin. Applying TNM criteria, NATALEE included patients with any lymph node involvement, or if no nodal involvement either tumour size >5 cm, or tumour size 2-5 cm with either grade 2 (and high genomic risk or Ki67 ≥20%) or grade 3.

A total of 5 101 patients, including 20 male patients, were randomised in a 1:1 ratio to receive either Kisqali 400 mg and AI (n=2 549) or AI alone (n=2 552). Randomisation to the treatment was stratified by anatomic stage (group II [n=2 154 (42.2%)] versus group III [n=2 947 (57.8%)]), prior treatment (neoadjuvant/adjuvant chemotherapy Yes [n=4 432 (86.9%)] versus No [n=669 (13.1%)]), menopausal status (premenopausal women and men [n=2 253 (44.2%)] versus postmenopausal women [n=2 848 (55.8%)]) and region (North America/Western Europe/Oceania [n=3 128 (61.3%)] versus rest of the world [n=1 973 (38.7%)]). Kisqali was given orally at a dose of 400 mg once daily for 21 consecutive days followed by 7 days off treatment in combination with letrozole 2.5 mg or anastrozole 1 mg orally once daily for 28 days. Goserelin was given at a dose of 3.6 mg as injectable subcutaneous implant administered on day 1 of each 28-day cycle. Therapy with Kisqali continued until completion of 3-year treatment from the randomisation date (approximately 39 cycles).

Patients enrolled in this study had a median age of 52 years (range 24 to 90). 15.2% patients were aged 65 years and older, including 123 patients (2.4%) aged 75 years and older. The patients included were Caucasian (73.4%), Asian (13.2%) and Black or African American (1.7%). All patients had an ECOG performance status of 0 or 1. A total of 88.2% of patients had received chemotherapy in the neoadjuvant or adjuvant setting and 71.6% had received endocrine therapy in the neoadjuvant or adjuvant setting within 12 months prior to study entry.

The primary endpoint for the study was invasive disease-free survival (iDFS) defined as the time from randomisation to the first occurrence of: local invasive breast recurrence, regional invasive recurrence, distant recurrence, death (any cause), contralateral invasive breast cancer, or second primary non-breast invasive cancer (excluding basal and squamous cell carcinomas of the skin).

The primary endpoint of the study was met at the primary analysis (11 January 2023 cut-off). A statistically significant improvement in iDFS (HR: 0.748, 95% CI: 0.618, 0.906; one-sided stratified log-rank test p-value 0.0014) was demonstrated in patients receiving Kisqali plus AI over AI alone. Consistent results were observed across sub-groups of anatomic stage, menopausal status, region, nodal status, age, race, and prior adjuvant/neo-adjuvant chemotherapy or hormonal therapies.

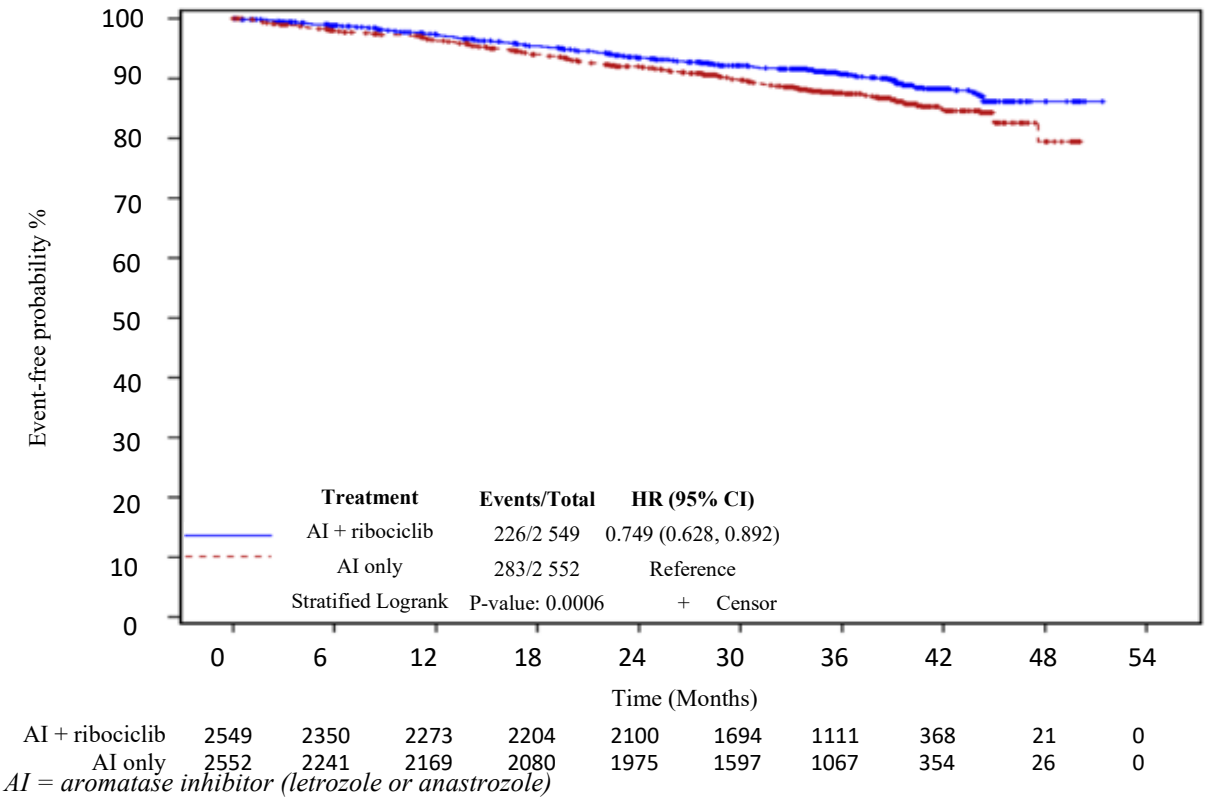
Data from a further analysis (21 July 2023 cut-off) is summarised in Table 8, the Kaplan-Meier curve for iDFS is provided in Figure 1. The median treatment duration at the time of the final iDFS analysis was approximately 30 months with the median follow-up time for iDFS 33.3 months across the two study arms. The overall survival (OS) remains immature. A total of 172 patients (3.5%) had died (83/2 525 in the ribociclib arm versus 89/2 442 in the AI alone arm, HR 0.892, 95% CI: 0.661, 1.203).

**Table 8 NATALEE - Efficacy results (iDFS) based on investigator assessment (FAS) (21 July 2023 cut-off)**

| | Kisqali plus AI* N=2 549 | AI N=2 552 |
|---|---|---|
| **Invasive disease-free survival (iDFS[a])** | | |
| Number of patients with an event (n, %) | 226 (8.9%) | 283 (11.1%) |
| Hazard ratio (95% CI) | 0.749 (0.628, 0.892) | |
| p-value[b] | 0.0006 | |
| iDFS at 36 months (%, 95% CI) | 90.7 (89.3, 91.8) | 87.6 (86.1, 88.9) |

CI=confidence interval; N=number of patients.
[a] iDFS defined as the time from randomisation to the first occurrence of: local invasive breast recurrence, regional invasive recurrence, distant recurrence, death (any cause), contralateral invasive breast cancer, or second primary non-breast invasive cancer (excluding basal and squamous cell carcinomas of the skin)
[b] nominal p-value is obtained from the one-sided stratified log-rank test.
* Letrozole or anastrozole

**Figure 1 NATALEE - Kaplan-Meier plot of iDFS based on investigator assessment (21 July 2023 cut-off)**




*AI = aromatase inhibitor (letrozole or anastrozole)*
*P-value from stratified log-rank test is one-sided.*

There were 204 (8.0%) distant disease-free survival (DDFS) events in the Kisqali plus AI arm compared to 256 (10%) events in the AI alone arm (HR: 0.749, 95% CI: 0.623, 0.900).

*Advanced breast cancer*
*Study CLEE011A2301 (MONALEESA-2)*
Kisqali was evaluated in a randomised, double-blind, placebo-controlled, multicentre phase III clinical study in the treatment of postmenopausal women with hormone receptor-positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease in combination with letrozole versus letrozole alone.

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

Patients enrolled in this study had a median age of 62 years (range 23 to 91). 44.2% patients were aged 65 years and older, including 69 patients older than 75 years. The patients included were Caucasian (82.2%), Asian (7.6%), and Black (2.5%). All patients had an ECOG performance status of 0 or 1. In the Kisqali arm 46.6% of patients had received chemotherapy in the neoadjuvant or adjuvant setting and 51.3% had received antihormonal therapy in the neoadjuvant or adjuvant setting prior to study entry. 34.1% of patients were *de novo*. 22.0% of patients had bone-only disease and 58.8% of patients had visceral disease. Patients with prior (neo)adjuvant therapy with anastrozole or letrozole must have completed this therapy at least 12 months before study randomisation.

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

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

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

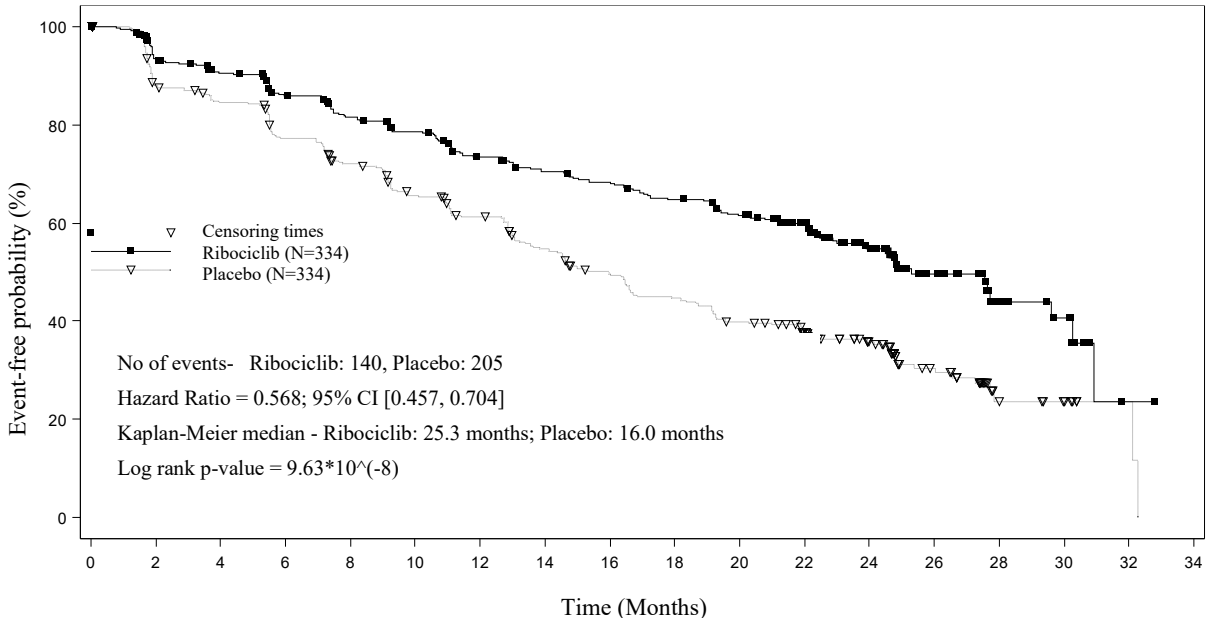
A more mature update of efficacy data (02 January 2017 cut-off) is provided in Tables 9 and 10.

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

**Table 9 MONALEESA-2- Efficacy results (PFS) based on investigator radiological assessment (02 January 2017 cut-off)**

| | **Updated analysis** | |
|---|---|---|
| | **Kisqali plus letrozole N=334** | **Placebo plus letrozole N=334** |
| **Progression-free survival** | | |
| Median PFS [months] (95% CI) | 25.3 (23.0, 30.3) | 16.0 (13.4, 18.2) |
| Hazard ratio (95% CI) | 0.568 (0.457, 0.704) | |
| p-value[a] | $9.63\times10^{-8}$ | |
| CI=confidence interval; N=number of patients<br>[a] p-value is obtained from the one-sided stratified log-rank test. | | |

**Figure 2 MONALEESA-2 - Kaplan-Meier plot of PFS based on investigator assessment (02 January 2017 cut-off)**




Number of patients still at risk

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

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

Updated results for overall response and clinical benefit rates are displayed in Table 10.

**Table 10 MONALEESA-2 - Efficacy results (ORR, CBR) based on investigator assessment (02 January 2017 cut-off)**

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

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

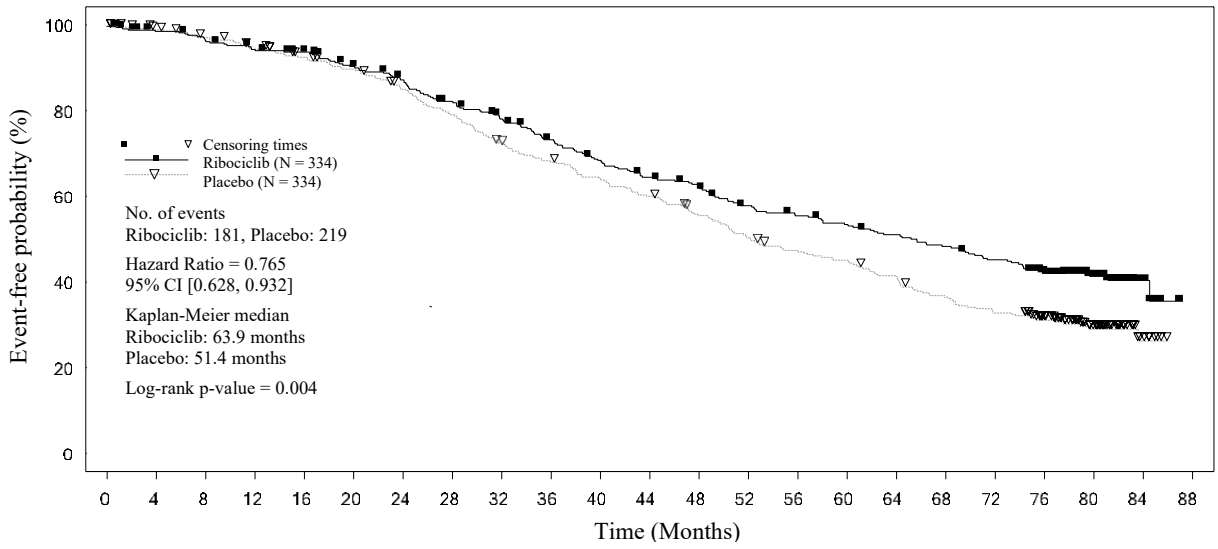
*Final OS analysis*
The results from this final OS analysis on the overall study population are provided in Table 11 and Figure 3.

**Table 11 MONALEESA-2- Efficacy results (OS) (10 June 2021 cut-off)**

| **Overall survival, overall study population** | **Kisqali plus letrozole N=334** | **Placebo plus letrozole N=334** |
|---|---|---|
| **Number of events – n [%]** | 181 (54.2) | 219 (65.6) |
| Median OS [months] (95% CI) | 63.9 (52.4, 71.0) | 51.4 (47.2, 59.7) |
| Hazard ratio[a] (95% CI) | 0.765 (0.628, 0.932) | |
| p-value[b] | 0.004 | |
| OS event-free rate, (%) (95% CI) | | |
| 24 months | 86.6 (82.3, 89.9) | 85.0 (80.5, 88.4) |
| 60 months | 52.3 (46.5, 57.7) | 43.9 (38.3, 49.4) |
| 72 months | 44.2 (38.5, 49.8) | 32.0 (26.8, 37.3) |

CI=confidence interval
[a] Hazard ratio is obtained from stratified Cox PH model
[b] p value is obtained from the one-sided log rank test (p<0.0219 to claim superior efficacy). Stratification performed by lung and/or liver metastases status as per IRT

**Figure 3 MONALEESA-2 - Kaplan-Meier plot of OS in overall population (10 June 2021 cut-off)**




Number of patients still at risk

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

*Log-rank test and Cox PH model are stratified by liver and/or lung metastasis as per IRT.*
*One sided P-value is obtained from stratified log rank test.*

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

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

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

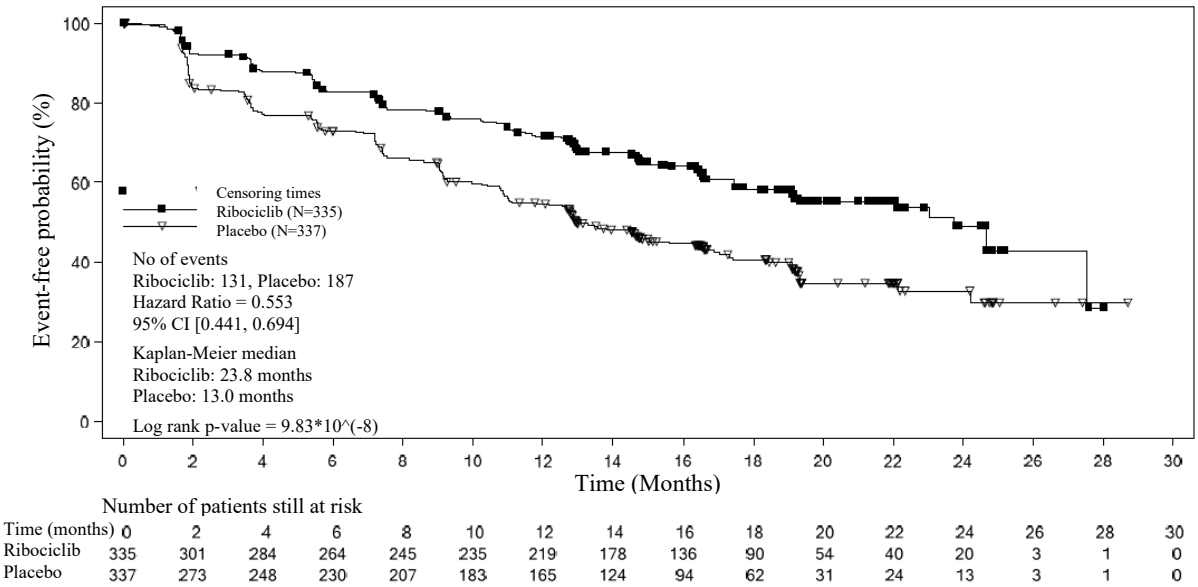
The study met the primary endpoint at the primary analysis conducted after 318 progression-free survival (PFS) events based on the investigator assessment using RECIST v1.1 criteria in the full

analysis set (all randomised patients). The primary efficacy results were supported by PFS results based on blinded independent central radiological assessment. The median follow-up time at the time of primary PFS analysis was 19.2 months.

In the overall study population, the efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Kisqali plus NSAI/tamoxifen plus goserelin compared to patients receiving placebo plus NSAI/tamoxifen plus goserelin (hazard ratio of 0.553, 95% CI: 0.441, 0.694, one-sided stratified log-rank test p-value $9.83x10^{-8}$) with clinically meaningful treatment effect. Median PFS was 23.8 months (95% CI: 19.2, NE) for Kisqali plus NSAI/tamoxifen plus goserelin treated patients and 13.0 months (95% CI: 11.0, 16.4) for patients receiving placebo plus NSAI/tamoxifen plus goserelin.

Distribution of PFS is summarised in the Kaplan-Meier curve for PFS in Figure 4.

**Figure 4 MONALEESA-7 - Kaplan-Meier plot of PFS in overall population based on investigator assessment**




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

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

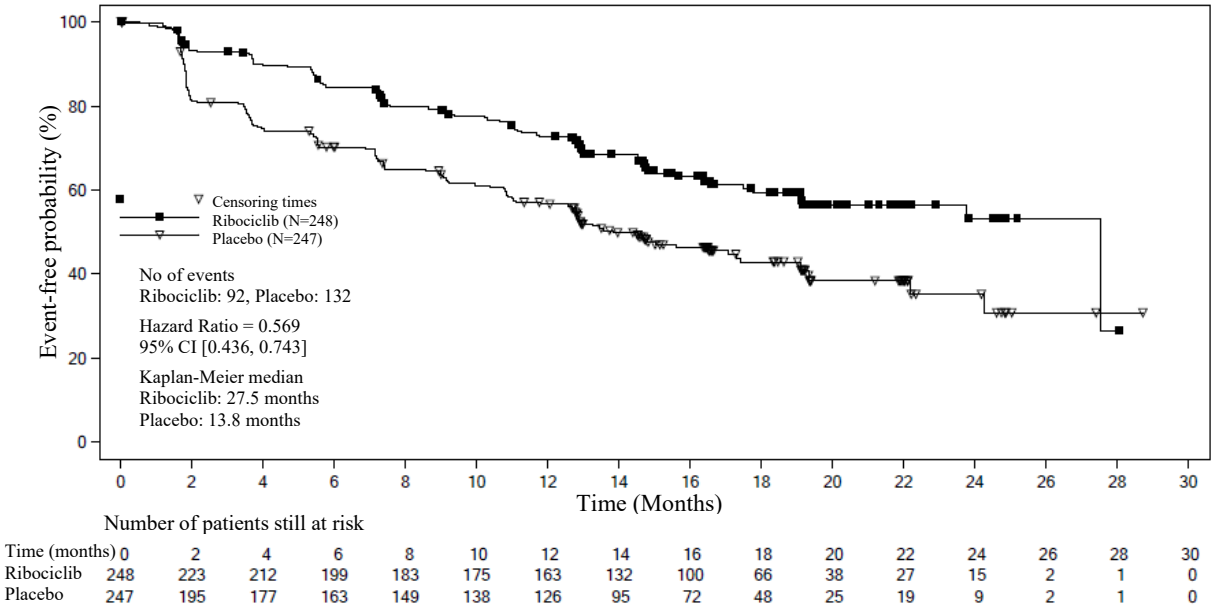
Overall response rate (ORR) per investigator assessment based on RECIST v1.1 was higher in the Kisqali arm (40.9%; 95% CI: 35.6, 46.2) compared to the placebo arm (29.7%; 95% CI: 24.8, 34.6, p=0.00098). The observed clinical benefit rate (CBR) was higher in Kisqali arm (79.1%; 95% CI: 74.8:83.5) compared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

In the pre-specified subgroup analysis of 495 patients who had received Kisqali or placebo in combination with NSAI plus goserelin, the median PFS was 27.5 months (95% CI: 19.1, NE) in the Kisqali plus NSAI subgroup and 13.8 months (95% CI: 12.6, 17.4) in the placebo plus NSAI subgroup [HR: 0.569; 95% CI: 0.436, 0.743]. Efficacy results are summarised in Table 12 and the Kaplan-Meier curves for PFS are provided in Figure 5.

**Table 12 MONALEESA-7 - Efficacy results (PFS) in patients who received NSAI**

| | Kisqali plus NSAI plus goserelin N=248 | Placebo plus NSAI plus goserelin N=247 |
|---|---|---|
| **Progression free survival[a]** | | |
| Median PFS [months] (95% CI) | 27.5 (19.1, NE) | 13.8 (12.6, 17.4) |
| Hazard ratio (95% CI) | 0.569 (0.436, 0.743) | |
| CI=confidence interval; N=number of patients; NE = Not estimable.<br>[a] PFS based on investigator radiological assessment | | |

**Figure 5 MONALEESA-7 – Kaplan-Meier plot of PFS based on investigator assessment in patients who received NSAI**




Efficacy results for overall response rate (ORR) and clinical benefit rate (CBR) per investigator assessment based on RECIST v1.1 are provided in Table 13.

**Table 13 MONALEESA-7 - Efficacy results (ORR, CBR) based on investigator assessment in patients who received NSAI**

| Analysis | Kisqali plus NSAI plus goserelin (%, 95% CI) | Placebo plus NSAI plus goserelin (%, 95% CI) |
|---|---|---|
| **Full analysis set** | **N=248** | **N=247** |
| **Overall response rate (ORR)[a]** | 39.1 (33.0, 45.2) | 29.1 (23.5, 34.8) |
| **Clinical benefit rate (CBR)[b]** | 80.2 (75.3, 85.2) | 67.2 (61.4, 73.1) |
| **Patients with measurable disease** | **n=192** | **n=199** |
| **Overall response rate[a]** | 50.5 (43.4, 57.6) | 36.2 (29.5, 42.9) |
| **Clinical benefit rate[b]** | 81.8 (76.3, 87.2) | 63.8 (57.1, 70.5) |
| [a]ORR: proportion of patients with complete response + partial response<br>[b]CBR: proportion of patients with complete response + partial response + (stable disease or non-complete response/Non-progressive disease ≥24 weeks) | | |

Results in the Kisqali plus NSAI subgroup were consistent across subgroups of age, race, prior adjuvant/ neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone-only metastatic disease.

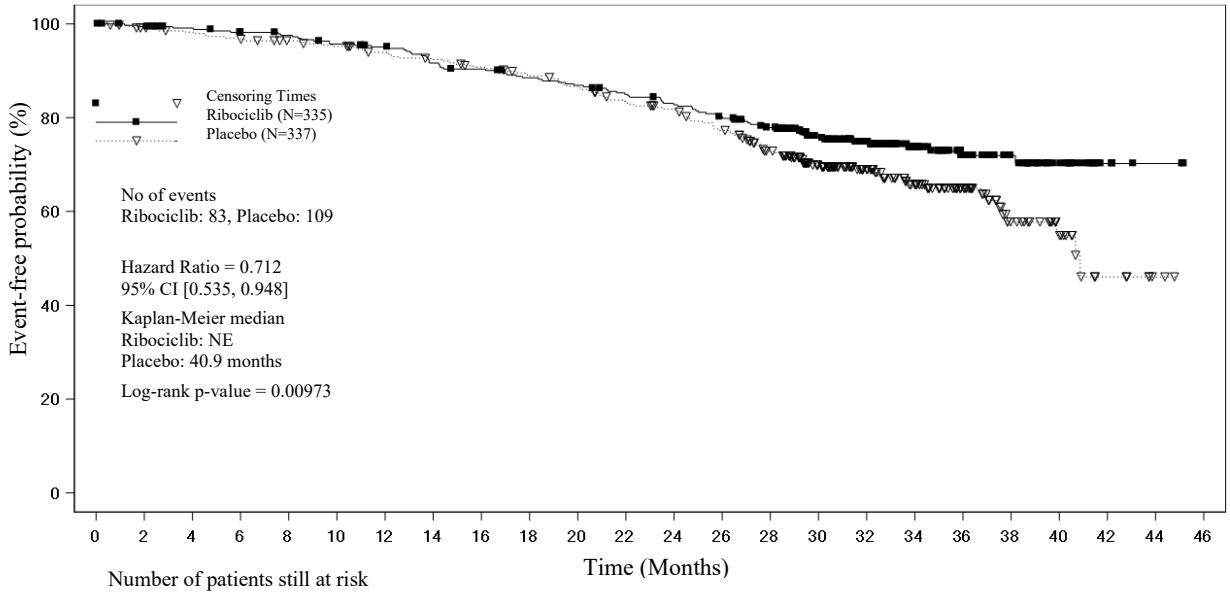
A more mature update of overall survival data (30 November 2018 cut-off) is provided in Table 14 and Figures 6 and 7.

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

**Table 14 MONALEESA-7 – Efficacy results (OS) (30 November 2018 cut-off)**

| | **Updated analysis** | |
|---|---|---|
| **Overall survival, overall study population** | **Kisqali 600 mg N=335** | **Placebo N=337** |
| Number of events – n [%] | 83 (24.8) | 109 (32.3) |
| Median OS [months] (95% CI) | NE (NE, NE) | 40.9 (37.8, NE) |
| Hazard ratio (95% CI) | 0.712 (0.535, 0.948) | |
| p-value[a] | 0.00973 | |
| **Overall survival, NSAI subgroup** | **Kisqali 600 mg n=248** | **Placebo n=247** |
| Number of events – n [%] | 61 (24.6) | 80 (32.4) |
| Median OS [months] (95% CI) | NE (NE, NE) | 40.7 (37.4, NE) |
| Hazard ratio (95% CI) | 0.699 (0.501, 0.976) | |
| CI=confidence interval, NE=not estimable, N=number of patients;<br>[a]p-value is obtained from the one-sided log-rank test stratified by lung and/or liver metastases, prior chemotherapy for advanced disease, and endocrine partner per IRT (interactive response technology). | | |

**Figure 6 MONALEESA-7 – Kaplan-Meier plot of final OS analysis (30 November 2018 cut-off)**

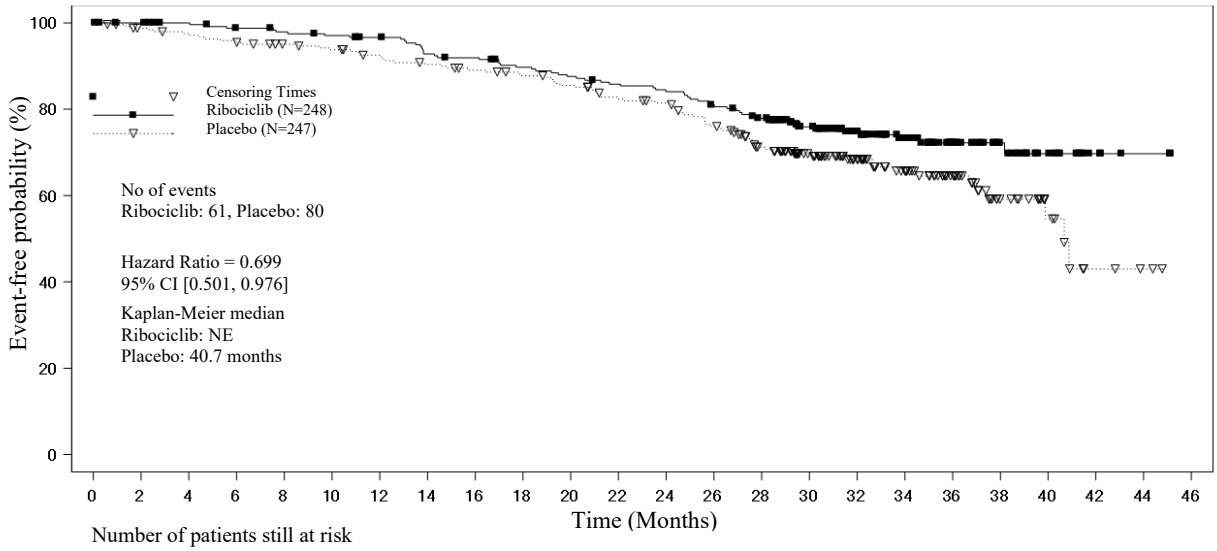



Number of patients still at risk

| Time (months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 | 40 | 42 | 44 | 46 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ribociclib | 335 | 330 | 325 | 320 | 316 | 309 | 304 | 292 | 287 | 279 | 274 | 266 | 258 | 249 | 236 | 193 | 155 | 110 | 68 | 43 | 25 | 7 | 3 | 0 |
| Placebo | 337 | 330 | 325 | 321 | 314 | 309 | 301 | 295 | 288 | 280 | 272 | 258 | 251 | 235 | 210 | 166 | 122 | 92 | 62 | 33 | 19 | 7 | 2 | 0 |

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

**Figure 7 MONALEESA-7 – Kaplan-Meier plot of final OS analysis in patients who received NSAI (30 November 2018 cut-off)**




Number of patients still at risk

| Time (months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 | 40 | 42 | 44 | 46 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ribociclib | 248 | 245 | 241 | 236 | 233 | 230 | 226 | 216 | 213 | 206 | 201 | 196 | 192 | 184 | 174 | 142 | 113 | 80 | 49 | 29 | 16 | 5 | 2 | 0 |
| Placebo | 247 | 240 | 236 | 232 | 225 | 221 | 215 | 209 | 204 | 199 | 193 | 183 | 179 | 165 | 145 | 116 | 87 | 67 | 46 | 24 | 12 | 4 | 2 | 0 |

Hazard ratio is based on unstratified Cox model.

Additionally, the probability of progression on next-line therapy or death (PFS2) in patients who received prior ribociclib in the study was lower compared to patients in the placebo arm with an HR of 0.692 (95% CI: 0.548, 0.875) in the overall study population. The median PFS2 was 32.3 months (95% CI: 27.6, 38.3) in the placebo arm and was not reached (95% CI: 39.4, NE) for the ribociclib arm. Similar results were observed for the NSAI subgroup, with an HR of 0.660 (95% CI: 0.503, 0.868) and a median PFS2 of 32.3 months (95% CI: 26.9, 38.3) in the placebo arm versus not reached (95% CI: 39.4, NE) in the ribociclib arm.

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

Patients enrolled in this study had a median age of 63 years (range 31 to 89). 46.7% of patients were of age 65 years and older, including 13.8% patients of age 75 years and older. The patients included were Caucasian (85.3%), Asian (8.7%) or Black (0.7%) and nearly all patients (99.7%) had an ECOG performance status of 0 or 1. First and second line patients were enrolled in this study (of whom 19.1% had *de novo* metastatic disease). Prior to study entry 42.7% of patients had received chemotherapy in the adjuvant and 13.1% in the neoadjuvant setting, while 58.5% had received endocrine therapy in the adjuvant and 1.4% in the neoadjuvant setting and 21% had received prior endocrine therapy in the advanced breast cancer setting. In study F2301 21.2% had bone-only disease and 60.5% had visceral disease.

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

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

$4.1x10^{-7}$), with an estimated 41% reduction in relative risk of progression or death in favour of the Kisqali plus fulvestrant arm.

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

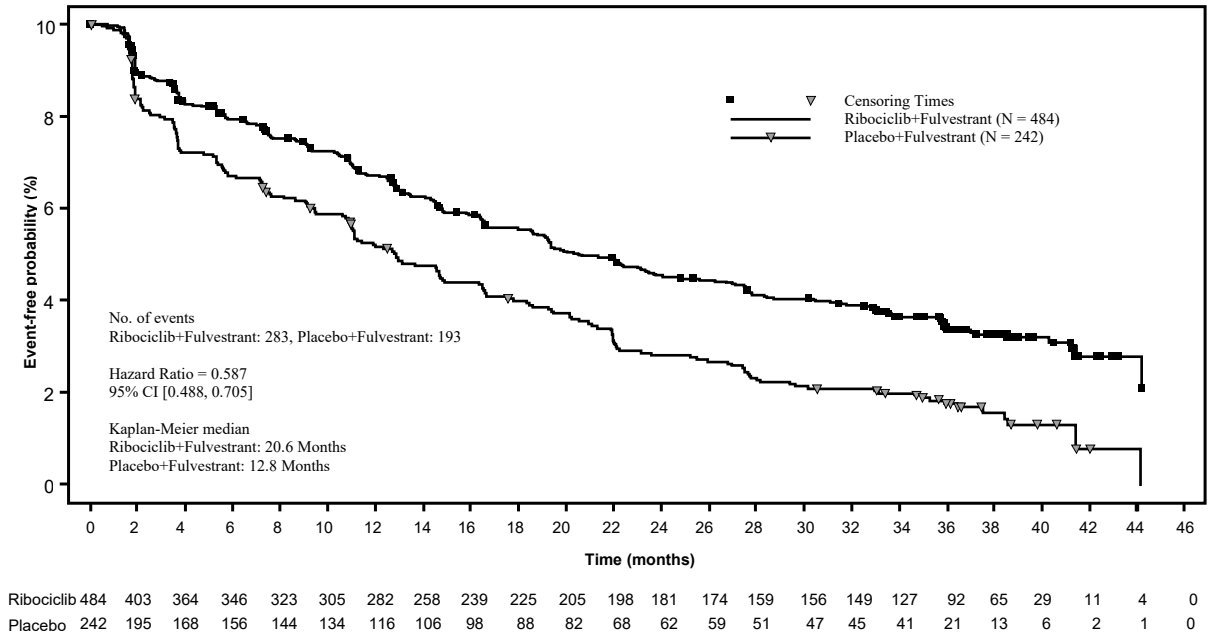
A descriptive update of PFS was performed at the time of the second OS interim analysis, and the updated PFS results on the overall population and the subgroups based on prior endocrine therapy are summarised in Table 15 and the Kaplan-Meier curve is provided in Figure 8.

**Table 15 MONALEESA-3 (F2301) - Updated PFS results based on investigator assessment (03 June 2019 cut-off)**

| | **Kisqali plus fulvestrant N=484** | **Placebo plus fulvestrant N=242** |
|---|---|---|
| **Progression free survival overall study population** | | |
| Number of events- n [%] | 283 (58.5) | 193 (79.8) |
| Median PFS [months] (95% CI) | 20.6 (18.6, 24.0) | 12.8 (10.9, 16.3) |
| Hazard ratio (95% CI) | 0.587 (0.488, 0.705) | |
| **First-line setting subgroup[a]** | **Kisqali plus fulvestrant n=237** | **Placebo plus fulvestrant n=128** |
| Number of events- n [%] | 112 (47.3) | 95 (74.2) |
| Median PFS [months] (95% CI) | 33.6 (27.1, 41.3) | 19.2 (14.9, 23.6) |
| Hazard ratio (95% CI) | 0.546 (0.415, 0.718) | |
| **Second-line setting or early relapse subgroup[b]** | **Kisqali plus fulvestrant n=237** | **Placebo plus fulvestrant n=109** |
| Number of events- n [%] | 167 (70.5) | 95 (87.2) |
| Median PFS [months] (95% CI) | 14.6 (12.5, 18.6) | 9.1 (5.8, 11.0) |
| Hazard ratio (95% CI) | 0.571 (0.443, 0.737) | |

CI=confidence interval
[a] patients with *de novo* advanced breast cancer with no prior endocrine therapy, and patients who relapsed after 12 months of (neo)adjuvant endocrine therapy completion.
[b] patients whose disease relapsed during adjuvant therapy or within 12 months of (neo)adjuvant endocrine therapy completion, and patients who had progression after one line of endocrine therapy for advanced disease.

**Figure 8 MONALEESA-3 (F2301) – Kaplan-Meier plot of PFS based on investigator assessment (FAS) (03 June 2019 cut-off)**




Efficacy results for overall response rate (ORR) and clinical benefit rate (CBR) per investigator assessment based on RECIST v1.1 are provided in Table 16.

**Table 16 MONALEESA-3 - Efficacy results (ORR, CBR) based on investigator assessment (03 November 2017 cut-off)**

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

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

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

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

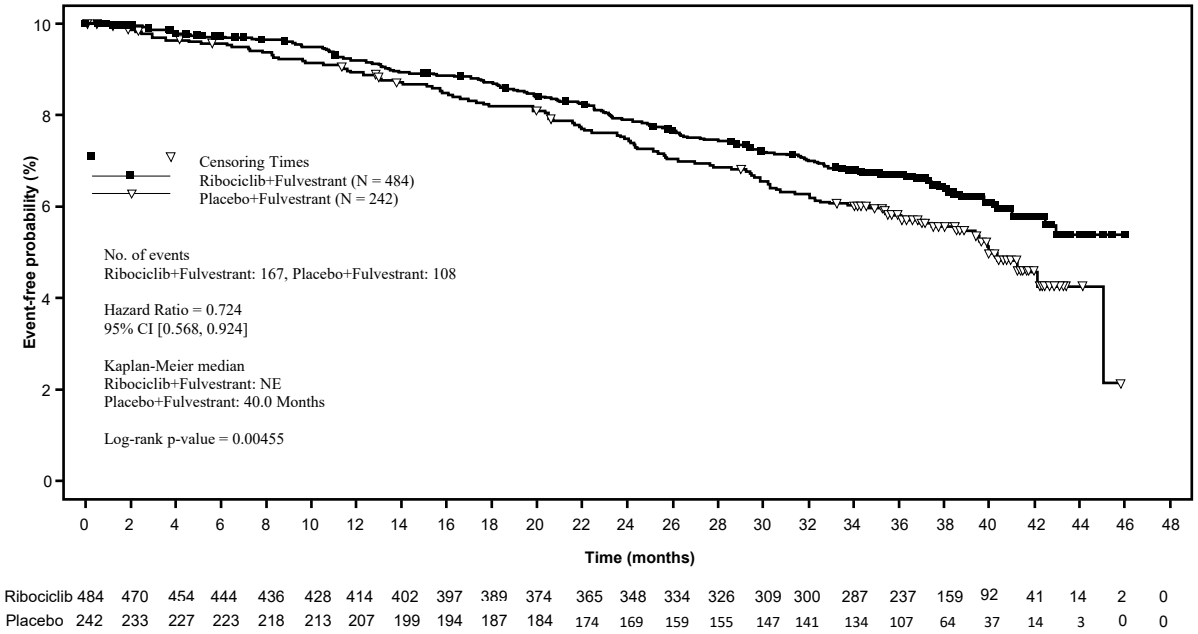
The results from this final OS analysis on the overall study population and the subgroups analysis are provided in Table 17 and Figure 9.

**Table 17 MONALEESA-3 (F2301) – Efficacy results (OS) (03 June 2019 cut-off)**

| | Kisqali plus fulvestrant | Placebo plus fulvestrant |
|---|---|---|
| **Overall study population** | N=484 | N=242 |
| Number of events - n [%] | 167 (34.5) | 108 (44.6) |
| Median OS [months] (95% CI) | NE, (NE, NE) | 40 (37, NE) |
| HR (95% CI)[a] | 0.724 (0.568, 0.924) | |
| p value[b] | 0.00455 | |
| **First line setting subgroup** | **n=237** | **n=128** |
| Number of events - n [%] | 63 (26.6) | 47 (36.7) |
| HR (95% CI)[c] | 0.700 (0.479, 1.021) | |
| **Second-line setting or early relapse subgroup** | **n=237** | **n=109** |
| Number of events - n [%] | 102 (43.0) | 60 (55.0) |
| HR (95% CI)[c] | 0.730 (0.530, 1.004) | |

NE = Not estimable
[a] Hazard ratio is obtained from the Cox PH model stratified by lung and/or liver metastasis, previous endocrine therapy.
[b] One-sided P-value is obtained from log-rank test stratified by lung and/or liver metastasis, previous endocrine therapy per IRT. P-value is one-sided and is compared against a threshold of 0.01129 as determined by the Lan-DeMets (O'Brien-Fleming) alpha-spending function for an overall significance level of 0.025.
[c] Hazard ratio is obtained from the unstratified Cox PH model.

**Figure 9 MONALEESA-3 (F2301) – Kaplan-Meier plot of OS (full analysis set [FAS]) (03 June 2019 cut-off)**




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

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

*Study CLEE011A3201C (RIGHT Choice)*
RIGHT Choice was a randomised, open-label, phase II study (N=222) comparing the combination of ribociclib plus NSAI (letrozole or anastrozole) plus goserelin (n=112) versus combination chemotherapy (docetaxel plus capecitabine, paclitaxel plus gemcitabine, or capecitabine plus vinorelbine, n=110) in pre-/perimenopausal women with HR-positive, HER2-negative advanced breast cancer for whom combination chemotherapy was indicated. Patients had not received prior hormonal therapy, except LHRH agonist, nor chemotherapy for advanced breast cancer.

The primary endpoint of progression-free survival (PFS) was met at the time of primary analysis (12 April 2022 cut-off), with a statistically significant improvement in PFS in the ribociclib plus NSAI arm compared to the combination chemotherapy arm (HR: 0.536, 95% CI: 0.363, 0.793 at one-sided stratified log-rank test p-value=0.000727). The median PFS was 24.0 months in the ribociclib plus NSAI arm versus 12.3 months in the combination chemotherapy arm.

Secondary endpoints included overall response rate (ORR) and time to response (TTR) as determined by local investigator assessment without image confirmation. The unconfirmed ORR was 65.2% in the ribociclib plus NSAI arm versus 60.0% in the combination chemotherapy arm. The median TTR was 4.9 months in the ribociclib plus NSAI arm versus 3.2 months in the combination chemotherapy arm.

OS data was immature at final data cut-off date (10 May 2023) with 34 deaths (30.4%) in the ribociclib plus NSAI arm and 29 deaths (26.4%) in the combination chemotherapy arm. The median OS was not reached in the ribociclib plus NSAI arm (95% CI, 38.6 months, NE) or the combination chemotherapy arm (95% CI: 30.8 months, NE); HR: 0.92, 95% CI: 0.56, 1.52.

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

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

Paediatric population

*Study CLEE011Q12101*
A phase I/II multicentre study was conducted to evaluate the efficacy and safety of the combination of ribociclib with TOTEM in paediatric (4 to <18 years, n=10) and young adult (18 to 20 years, n=2) patients with relapsed or refractory (r/r) neuroblastoma (NB) or other solid tumours (including alveolar rhabdomyosarcoma/rhabdomyosarcoma, malignant glioma, malignant astrocytoma, glioblastoma and medulloblastoma). Three cohorts were completed in the phase I dose-finding part which investigated the following dose regimens in a 28-day treatment cycle: ribociclib 200 mg/m²/day (days 1 to 21) plus topotecan 0.75 mg/m²/day and temozolomide 150 mg/m²/day (days 1 to 5) (concurrent dosing); ribociclib 100 mg/m²/day (days 6 to 21) after topotecan 0.75 mg/m²/day and temozolomide 150 mg/m²/day (days 1 to 5) (sequential dosing); ribociclib 100 mg/m²/day (days 1 to 14) plus topotecan 0.75 mg/m²/day and temozolomide 100 mg/m²/day (days 1 to 5) (concurrent dosing). Patients had a median age of 14 years (n=12), 7 were female. No objective response was observed. The maximum tolerated dose (MTD) and recommended phase II dose (RP2D) could not be determined in this study due to dose-limiting toxicity (DLT). No new safety signals were observed.

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

## 5.2 Pharmacokinetic properties

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

Absorption

The geometric mean absolute bioavailability of ribociclib after a single oral dose of 600 mg was 65.8% in healthy subjects.

The time to reach $C_{max}$ ($T_{max}$) following ribociclib oral administration was between 1 and 4 hours. Ribociclib exhibited slightly over-proportional increases in exposure ($C_{max}$ and AUC) across the dose range tested (50 to 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: 0.97 to 6.40).

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

Distribution

Binding of ribociclib to human plasma proteins *in vitro* was approximately 70% and was independent of concentration (10 to 10 000 ng/ml). Ribociclib was equally distributed between red blood cells and plasma with a mean *in vivo* blood-to-plasma ratio of 1.04. The apparent volume of distribution at steady state (Vss/F) was 1 090 L based on population pharmacokinetic analysis.

Biotransformation

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

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

Elimination

The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63% CV) and the geometric mean apparent oral clearance (CL/F) was 25.5 l/hr (66% CV) at steady state at 600 mg in patients with advanced cancer. Based on a population pharmacokinetic analysis, the ribociclib exposure in patients with early breast cancer is expected to be slightly lower than in patients

with advanced breast cancer treated with the same dose. The geometric mean apparent plasma terminal half-life ($T_{1/2}$) of ribociclib ranged from 29.7 to 54.7 hours and the geometric mean CL/F of ribociclib ranged from 39.9 to 77.5 l/hr at 600 mg across studies in healthy subjects.

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

Linearity/non-linearity

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

Special populations

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

$AUC_{inf}$ increased 1.6-fold, 1.9-fold and 2.7-fold and $C_{max}$ increased 1.8-fold, 1.8-fold and 2.3-fold in subjects with mild, moderate and severe renal impairment relative to the exposure in subjects with normal renal function. Since the efficacy and safety studies of ribociclib included a large proportion of patients with mild renal impairment (see section 5.1), data from the subjects with moderate or severe renal impairment in the renal impairment study were also compared with pooled data for the subjects with normal renal function and mild renal impairment. Compared to the pooled data for the subjects with normal renal function and mild renal impairment, $AUC_{inf}$ increased 1.6-fold and 2.2-fold and $C_{max}$ increased 1.5-fold and 1.9-fold in subjects with moderate and severe renal impairment, respectively. A fold difference for subjects with ESRD was not calculated due to the small number of subjects, but results indicate a similar or somewhat larger increase in ribociclib exposure compared to subjects with severe renal impairment.

The effect of renal function on the pharmacokinetics of ribociclib was also assessed in advanced or metastatic breast cancer patients included in efficacy and safety studies where patients were given the 600 mg start dose (see section 5.1). In a sub-group analysis of pharmacokinetic data from studies in advanced or metastatic breast cancer patients following oral administration of 600 mg ribociclib as a single dose or repeat doses, $AUC_{inf}$ and $C_{max}$ of ribociclib in patients with mild (n=57) or moderate (n=14) renal impairment were comparable to the $AUC_{inf}$ and $C_{max}$ in patients with normal renal function (n=86), suggesting no clinically meaningful effect of mild or moderate renal impairment on ribociclib exposure.

*Hepatic impairment*
Based on a pharmacokinetic study in non-cancer subjects with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib (see section 4.2). The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.44 for $C_{max}$; 1.28 for $AUC_{inf}$) and severe (GMR: 1.32 for $C_{max}$; 1.29 for $AUC_{inf}$) hepatic impairment (see section 4.2).

Based on a population pharmacokinetic analysis that included 160 advanced or metastatic breast cancer patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib, further supporting the findings from

the dedicated hepatic impairment study. Ribociclib has not been studied in breast cancer patients with moderate or severe hepatic impairment.

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

*Paediatric population*
The pharmacokinetics of ribociclib were evaluated in paediatric (n=10) and young adult (n=2) patients with relapsed or refractory neuroblastoma or other solid tumours in the dose-finding part of a phase I/II study of Kisqali in combination with TOTEM as concurrent or sequential dosing (see section 5.1). The exposure of ribociclib increased with the dose increasing from 100 to 200 mg/m$^2$/day with $T_{max}$ between 1 and 4 hours across patients. At the ribociclib dose of 100 mg/m$^2$/day with concurrent dosing of TOTEM, the geometric mean steady-state CL/F of ribociclib was 35.4 l/hr (69% CV) and the geometric mean accumulation ratio was 1.06 (53.9% CV) (n=5).

*In vitro* interaction data

*Effect of ribociclib on cytochrome P450 enzymes*
*In vitro*, ribociclib is a reversible inhibitor of CYP1A2, CYP2E1 and CYP3A4/5 and a time-dependent inhibitor of CYP3A4/5, at clinically relevant concentrations. *In vitro* evaluations indicated that ribociclib has no potential to inhibit the activities of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 at clinically relevant concentrations. Ribociclib has no potential for time-dependent inhibition of CYP1A2, CYP2C9, and CYP2D6.

*In vitro* data indicate that ribociclib has no potential to induce UGT enzymes or the CYP enzymes CYP2C9, CYP2C19 and CYP3A4 via PXR. Therefore, Kisqali is unlikely to affect substrates of these enzymes. *In vitro* data are not sufficient to exclude a potential of ribociclib to induce CYP2B6 via CAR.

*Effect of transporters on ribociclib*
Ribociclib is a substrate for P-gp *in vitro*, but based on mass balance data inhibition of P-gp or BCRP is unlikely to affect ribociclib exposure at therapeutic doses. Ribociclib is not a substrate for hepatic uptake transporters OATP1B1, OATP1B3 or OCT-1 *in vitro*.

*Effect of ribociclib on transporters*
*In vitro* evaluations indicated that ribociclib has a potential to inhibit the activities of drug transporters P-gp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1 and BSEP. Ribociclib did not inhibit OAT1, OAT3 or MRP2 at clinically relevant concentrations *in vitro*.

## 5.3 Preclinical safety data

Safety pharmacology

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

Repeated-dose toxicity

Repeated-dose toxicity studies (treatment schedule of 3 weeks on/1 week off) of up to 27 weeks' duration in rats and up to 39 weeks' duration in dogs, revealed the hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) as the primary target organ of toxicity of ribociclib. Target organs associated with the pharmacological action of ribociclib in repeat-dose studies include bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal

mucosa (atrophy), skin (atrophy), bone (decreased bone formation), kidney (concurrent degeneration and regeneration of tubular epithelial cells) and testes (atrophy). Besides the atrophic changes seen in the testes, which showed a trend towards reversibility, all other changes were fully reversible after a 4-week treatment-free period. Exposure to ribociclib in animals in the toxicity studies was generally less than or equal to that observed in patients receiving multiple doses of 600 mg/day (based on AUC).

Reproductive toxicity/Fertility

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

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

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

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

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

Genotoxicity

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

Carcinogenesis

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

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

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

The mechanism for the thyroid findings in male rats is likely to involve a rodent-specific microsomal enzyme induction in the liver which is considered to be of no relevance to humans. The effects on the uterus/cervix and on the testicular interstitial (Leydig) cells are related to prolonged hypoprolactinaemia secondary to CDK4 inhibition of lactotrophic cell function in the pituitary gland, altering the hypothalamus-pituitary-gonadal axis.

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

Considering important differences between rodents and humans with regard to synthesis and role of prolactin, this mode of action is not expected to have consequences in humans.

Juvenile animal studies

In juvenile rats dosed orally from postnatal day (PND) 14 (the human equivalent of 1 year of age) to PND 63, minor reversible reductions in femur lengths (-3% to -4% from controls) were observed only in females. The no-observed-adverse-effect level (NOAEL) was 150 mg/kg/day in males and 150/300 mg/kg/day (dose escalation on PND 32) in females. The exposure at the NOAEL corresponds to an exposure margin of 5- to 22-fold and 4- to 6-fold of the paediatric $AUC_{0\text{-}24h}$ at the dose of 100 $mg/m^2$/day, in males and females respectively.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core

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

Film coating

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

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years.

### 6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

### 6.5 Nature and contents of container

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

Unit packs containing 21, 42, 63, 126 or 189 film-coated tablets and multipacks containing 63 (3 packs of 21), 126 (3 packs of 42) or 189 (3 packs of 63) film-coated tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
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Dublin 4
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

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## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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## 10. DATE OF REVISION OF THE TEXT

08/2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.