NOVARTIS

KRYXANA 200 mg

Film-coated tablets

(Ribociclib)

Professional Information

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SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINAL PRODUCT

Kryxana® 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 0.336 mg soya lecithin. For the full list of excipients, see section 6.1.

Sugar free.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Early breast cancer

Kryxana is (a cyclin-dependent kinase inhibitor, CDKi) indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer, in combination with an aromatase inhibitor.
In pre- or perimenopausal women, or men, the aromatase inhibitor should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

Advanced or metastatic breast cancer

Kryxana is indicated for the treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant.
In pre- or perimenopausal women, or men the endocrine based therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

4.2 Posology and method of administration

Treatment with Kryxana should be initiated by a medical practitioner experienced in the use of anticancer therapies.

Kryxana can be taken with or without food (see section 4.5).

Treatment of pre- or peri-menopausal women, or men, with Kryxana should include co-administration of an LHRH agonist according to local clinical practice standards.

Posology

Early breast cancer

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

In patients with early breast cancer, when co-administered with Kryxana, the recommended dose of letrozole is 2.5 mg, taken once daily throughout the 28-day cycle. Refer to the full professional information of letrozole.
In patients with early breast cancer, when Kryxana is co-administered with an aromatase inhibitor, the aromatase inhibitor should be taken orally once daily throughout the 28-day cycle.

For dosing and administration with the aromatase inhibitor, refer to the applicable full professional information.

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. The treatment should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

In patients with advanced or metastatic breast cancer, Kryxana should be used together with 2.5 mg letrozole or another aromatase inhibitor or with 500 mg fulvestrant.

When Kryxana is used in combination with an aromatase inhibitor, the aromatase inhibitor should be taken orally once daily continuously throughout the 28-day cycle. Please refer to the Professional Information (PI) of the particular aromatase inhibitor for additional details.

When Kryxana is used in combination with fulvestrant, fulvestrant is administered intramuscularly on days 1, 15 and 29, and once monthly thereafter. Please refer to the Professional Information (PI) of fulvestrant for additional details.

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

Kryxana can be taken with or without food (see section 4.5).

Patients with early breast cancer and advanced or metastatic breast cancer should be encouraged to take their dose of Kryxana and the aromatase inhibitor at approximately the same time each day, preferably in the morning. If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

Dose modifications

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

Table 1 Recommended dose modification guidelines

	Kryxana	
Early breast cancer	**Dose**	**Number of 200 mg tablets**
Starting dose	400 mg/day	2
Dose reduction	200 mg/day*	1
Advanced or metastatic breast cancer	**Dose**	**Number of 200 mg tablets**
Starting dose	600 mg/day	3

First dose reduction	400 mg/day	2
Second dose reduction	200 mg*/day	1
* If further dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.		

Tables 2, 3, 4, 5 and 6 summarise recommendations for dose interruption, reduction or discontinuation of Kryxana in the management of specific ADRs. The clinical judgement of the treating medical practitioner 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 Kryxana. After initiating treatment CBC should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated.

Table 2 Dose modification and management – Neutropenia

	Grade 1 or 2* (ANC 1000 /mm^3 – ≤ LLN)	**Grade 3*** (ANC 500 – < 1000/mm^3)	**Grade 3*** **febrile neutropenia****	**Grade 4*** (ANC < 500/mm^3)
Neutropenia	No dose adjustment is required	Dose interruption until recovery to grade ≤ 2. Resume Kryxana at the same dose level. If toxicity recurs at grade 3: dose interruption until	Dose interruption until recovery to grade ≤ 2. Resume Kryxana and reduce by 1 dose level	Dose interruption until recovery to grade ≤ 2. Resume Kryxana and reduce by 1 dose level.

		recovery to grade ≤ 2, then resume Kryxana and reduce by 1 dose level.		
* Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events) ** Grade 3 neutropenia with a single episode of fever > 38.3 °C (38 °C or above for more than one hour and/or concurrent infection) ANC = absolute neutrophil count; LLN = lower limit of normal				

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 Kryxana at same dose level. If grade 2 recurs, resume Kryxana at next lower dose level. Baseline grade = 2: No dose interruption.	Dose interruption of Kryxana until recovery to ≤ baseline grade, then resume at next lower dose level. If grade 3 recurs, discontinue Kryxana.	Discontinue Kryxana.

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

Liver function tests (LFTs) should be performed before initiating treatment with Kryxana. 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 4 Dose modification and management – QT prolongation

<table>
<tr><th>QTcF* prolongation</th><th>Early breast cancer</th><th>Advanced or metastatic breast cancer</th></tr>
<tr><td rowspan="3">>480 ms and ≤500 ms</td><td colspan="2">Interrupt Kryxana treatment and wait until QTcF resolves to <481ms</td></tr>
<tr><td>Resume at the same dose</td><td>Reduce to the next lower level dose</td></tr>
<tr><td colspan="2">If QTcF ≥481 recurs, interrupt Kryxana treatment and wait until QTcF resolves to <481ms, then resume at next lower level dose.</td></tr>
<tr><td>>500 ms</td><td colspan="2">Interrupt Kryxana treatment and wait until QTcF resolves to <481ms, then resume at next lower level dose.
If QTcF > 500ms recurs, discontinue Kryxana.</td></tr>
</table>

**QTcF = QT interval corrected by Fridericia's formula.*

If QTcF interval is greater than 500 ms or shows a greater than 60 ms change from baseline in combination with Torsade de Pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue Kryxana.

Note: If further dose reductions are required at the 200 mg dose, Kryxana should be discontinued.

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

Repeat ECGs at approximately Day 14 of the first cycle, and as clinically indicated.

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

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 Kryxana at the next lower dose level**.	Discontinue Kryxana
*Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events) ** An individualised benefit-risk assessment should be performed when considering resuming Kryxana 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 Kryxana at the same dose level. If grade 3 recurs, resume Kryxana at the next lower dose level.	Discontinue Kryxana.
* Excluding neutropenia, hepatotoxicity, QT interval prolongation and ILD/pneumonitis. ** Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)			

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

Dose modification for use of Kryxana with strong CYP3A4 inhibitors

Concomitant use of strong CYP3A4 inhibitors should be avoided and an alternative concomitant medicine with less potential to inhibit CYP3A4 inhibition should be considered (see section 4.3 and 4.4).

In patients with early breast cancer, if a strong CYP3A inhibitor must be co-administered, patients should be monitored for adverse reactions and, if necessary, a reduction of Kryxana dose to 200 mg should be considered.

In patients with advanced or metastatic breast cancer, if a strong CYP3A4 inhibitor must be given concomitantly with ribociclib, the Kryxana dose should be reduced to 400 mg once daily (see section 4.5).

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

In patients who have had their dose reduced to 200 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, Kryxana 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 Kryxana 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 (see section 5.2). A starting dose of 200 mg is recommended in patients with severe renal impairment (see section 5.2).

Caution should be used in patients with severe renal impairment with close monitoring of signs of toxicity (see section 5.2).

Hepatic impairment

No dose adjustment is necessary in patients with early breast cancer and hepatic impairment.

Based on a pharmacokinetic study in healthy subjects and non-cancer subjects with impaired hepatic function, no dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). Patients with advanced or metastatic breast cancer 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 Kryxana once daily is recommended. Ribociclib has not been studied in breast cancer patients with moderate and severe hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of Kryxana in children and adolescents aged below 18 years have not been

established. No data are available.

Elderly

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

Method of administration

Kryxana should be taken orally once daily at the same time every day, preferably in the morning, with or without food. The tablets should be swallowed whole and should not be chewed, crushed, or split prior to swallowing. No tablet should be ingested if it is broken, cracked or otherwise not intact.

4.3 Contraindications

Hypersensitivity to the active substance or to peanut, soya or any of the excipients listed in section 6.1.
Concomitant use of Kryxana with medicines that have a known potential to prolong the QTcF interval to ≥ 500 ms, or ≥ 60 ms from the pre-treatment QTcF, increasing the risk to develop serious dysrhythmias (e.g. tamoxifen, moxifloxacin).
Congenital long QT syndrome.
Concomitant use of Kryxana with strong CYP3A inhibitors (e.g. ritonavir/lopinovir, itraconazole).
Concomitant use of Kryxana with CYP3A substrates with a narrow therapeutic index (e.g. midazolam, fentanyl). Concomitant use with strong CYP3A4 inducers (e.g. rifampicin, phenytoin).
Pregnancy and lactation.
Difficult to control/unstable severe cardiac conditions including dysrhythmias, congestive cardiac failure, recent myocardial infarction and unstable angina pectoris.

4.4 Special warnings and precautions for use

Critical visceral disease

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

Neutropenia

Severity of neutropenia is dose-dependent. Medical practitioners should inform patients to promptly report any fever (see section 4.8).

In patients with early breast cancer (phase III clinical study NATALEE (O12301C)), neutropenia was the most frequently reported adverse drug 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 Kryxana plus aromatase inhibitor (AI).

Among the patients with early breast cancer in the phase III clinical study, the median time to Grade 2, 3 or 4 neutropenia was 0.6 months. The median time to resolution of Grade ≥ 3 (to normalisation or Grade < 3) was 0.3 months in the Kryxana plus AI arm. Febrile neutropenia was reported in 0.3 % of patients receiving Kryxana plus AI.

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

In patients who develop Grade 1 or 2 neutropenia, no Kryxana dose adjustment is required.

Hepatobiliary toxicity

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

In patients with early breast cancer, Grade 3 or 4 increases in ALT (7.6% vs. 0.7 %) and AST (4.7 % vs. 0.5 %) were reported in the Kryxana plus AI arm and AI alone arm, respectively. Grade 4 increase in ALT (1.5 %) and AST (0.8 %) were reported in the Kryxana plus AI arm. No Grade 4 increase in AST was reported in the AI alone arm. 1 case (< 0.1 %) of Grade 4 increase in ALT was reported in the AI alone arm.

In the phase III clinical study, 80.9 % (165/204) of Grade 3 or 4 ALT or AST elevation events occurred within the first 6 months of treatment (see section 4.8). The majority of increases in ALT and AST were reported without concurrent elevations of bilirubin. Among the patients who had Grade 3 or 4 ALT/AST elevation, the median time-to-onset was 2.8 months for the Kryxana plus AI arm. The median time to resolution (to normalisation or Grade ≤ 2) was 0.7 months in the Kryxana plus AI arm.

Concurrent elevations of ALT or AST > 3 x ULN and of total bilirubin > 2 x ULN, with normal alkaline phosphatase levels, occurred in 8 patients treated with Kryxana plus AI (in 6 patients ALT or AST levels recovered to normal within 65 to 303 days after discontinuation of Kryxana).

Liver function tests should be performed before initiating treatment with Kryxana in patients with early breast cancer and advanced or metastatic breast cancer. 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 Kryxana 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

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

- Long QT syndrome.
- Uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmia.
- Electrolyte abnormalities.

In the phase III NATALEE clinical study, in patients with early breast cancer who received 400 mg Kryxana plus AI, review of ECG data showed that 3 patients (0.1 %) had > 500 ms post-baseline QTcF interval value and 19 patients (0.8 %) had a > 60 ms QTcF interval increase from baseline. There were no reported cases of sudden death or Torsade de Pointes.

In the phase III clinical studies, in patients with advanced or metastatic breast cancer who received 600 mg Kryxana plus any combination partners, review of ECG data showed that 15 patients (1.4 %) had > 500 ms post-baseline QTcF interval value and 61 patients (5.8 %) had a > 60 ms QTcF interval increase from baseline. There were no reported cases of Torsade de Pointes.

In study E2301 (MONALEESA-7), a QTcF interval increase > 60 msec from baseline was observed in 14/87 (16.1 %) patients receiving Kryxana plus tamoxifen and in 18/245 (7.3 %) patients receiving Kryxana plus a non-steroidal aromatase inhibitor (NSAI). Kryxana is not recommended to be used in combination with tamoxifen (see sections 4.3, 4.5, 4.8 and 5.1).

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

Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed in patients with early breast cancer and advanced or metastatic breast cancer 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 Kryxana and during treatment with Kryxana.

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

In the event of ECGs with QTcF interval > 480 ms and ≤ 500 ms:

- The treatment with Kryxana should be interrupted.
- If QTcF interval prolongation is resolved to < 481 ms, Kryxana should be resumed at the same dose level if the starting dose was 400 mg (in patients with early breast cancer).

  If QTcF interval prolongation is resolved to < 481 ms, Kryxana should be resumed at the next lower dose level if the starting dose was 600 mg (in patients with advanced or metastatic breast cancer).
- If QTcF interval ≥ 481 ms recurs, Kryxana dose should be interrupted until QTcF interval resolves to < 481 ms, then Kryxana should be resumed at the next lower dose level.

In the event of ECGs with QTcF interval > 500 ms, repeat ECG should be performed:

- The treatment with Kryxana should be interrupted.
- If QTcF interval prolongation resolves to < 481 ms, Kryxana should be resumed at next lower dose level (see sections 4.2, 4.8 and 5).

If QTcF interval prolongation greater than 500 ms recurs or the QTcF interval has a greater than 60 ms change from baseline in combination with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, Kryxana should be permanently discontinued.

Interstitial lung disease/pneumonitis

ILD/pneumonitis has been reported with CDK4/6 inhibitors including reports of fatal cases.
In the phase III clinical study in patients with early breast cancer, ILD was reported in 1 patient (Grade 1) in the Kryxana plus AI arm with no cases in the AI alone arm. Pneumonitis (any Grade 0.6 %, vs 0.4 %) was reported in the Kryxana plus AI arm and in the AI alone arm, respectively, with 2 cases of a Grade 3 event in the AI arm. No cases of Grade 3 pneumonitis were reported in the Kryxana plus AI arm.

In the 3 phase III clinical studies in patients with advanced or metastatic breast cancer, ILD (any Grade 0.3 %, including 0.1 % Grade 3) was reported in the Kryxana treated group, with no cases in the placebo treated group. Pneumonitis (any Grade 0.6 % vs. 0.4 %) was reported in the Kryxana and the placebo treated groups

respectively with no Grade 3 or 4 in either treatment group. Additional cases of ILD/pneumonitis have been observed with Kryxana in the post- marketing setting (see section 4.8).
Based on the severity of the ILD/pneumonitis, Kryxana may require dose interruption, reduction or discontinuation as described in Table 5 (see section 4.2).

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

Severe cutaneous reactions

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

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 medicines 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 PIs of the other medicines should be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors (see sections 4.3 and 4.5).

Women of childbearing potential

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

Soya lecithin

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

4.5 Interaction with other medicines and other forms of interaction

Substances that may increase ribociclib plasma concentrations

Ribociclib is primarily metabolised by CYP3A4. Therefore, medicines 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 (AUCinf) and the peak concentration (C_{max}) in healthy subjects by 3.2 and 1.7-fold, respectively, relative to a single 400 mg ribociclib dose given alone. C_{max} and AUClast for LEQ803 (a prominent metabolite of ribociclib accounting for less than 10 % of parent exposure) decreased by 96 % and 98 %, respectively.
PBPK simulations with co-administered ritonavir (100 mg twice daily) estimated that the steady state C_{max} and AUC0-24h of ribociclib (400 mg once daily) increase by 1.47 and 1.84-fold, respectively, in patients with early breast cancer, and 1.29- and 1.47-fold, respectively, in patients with advanced or metastatic breast cancer.
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 4.3 and 4.4). Alternative concomitant medicines with less potential to inhibit CYP3A4 should be considered, and patients should be monitored for ribociclib-related AEs (see sections 4.2, 4.4 and 5.2).

In patients with early breast cancer who are receiving 400 mg Kryxana, if co-administration of Kryxana with strong CYP3A inhibitor cannot be avoided, patients should be monitored for adverse reactions and, if necessary, a reduction of Kryxana dose to 200 mg should be considered.

In patients with advanced or metastatic breast cancer who are receiving 600 mg Kryxana if co-administration of Kryxana with a strong CYP3A4 inhibitor cannot be avoided, the dose of Kryxana should be reduced as described in section 4.2 (see sections 4.3 and 4.4). However, there are no clinical data with these dose adjustments.
Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients, therefore close monitoring for ribociclib-related AEs is recommended. In the event of ribociclib-related toxicity, the dose should be modified, or treatment should be interrupted until toxicity is resolved (see sections 4.2 and 5.2).

In patients with early breast cancer and advanced or metastatic breast cancer if the strong CYP3A4 inhibitor is discontinued, and after at least 5 half-lives of the CYP3A4 inhibitor (refer to the PI of the CYP3A4 inhibitor in question), Kryxana should be resumed at the same dose used prior to the initiation of the strong CYP3A4 inhibitor.

Physiologically-based pharmacokinetic simulations suggested that at a 600 mg dose of ribociclib, a moderate CYP3A4 inhibitor (erythromycin) may increase ribociclib steady-state Cmax and AUC 1.2 and 1.3-fold, respectively. The effect at the 200 mg once-daily dose was predicted to be a 1.7- and 2.8-fold increase, respectively. No dose adjustments of ribociclib are required at initiation of treatment with mild or moderate CYP3A4 inhibitors. However, monitoring of ribociclib-related AEs is recommended.
Simulations using PBPK suggested that a moderate CYP3A4 inhibitor (erythromycin) may increase Cmax and AUC of ribociclib 400 mg steady state by 1.13 and 1.23-fold, respectively, in patients with early breast cancer, and 1.08-fold and 1.13-fold, respectively, in patients with advanced breast cancer (see sections 4.2, 4.4 and 4.5).

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

Substances that may decrease ribociclib plasma concentrations

Co-administration of the strong CYP3A4 inducer rifampicin (600 mg daily for 14 days) with a single 600 mg dose of ribociclib decreased the ribociclib AUCinf 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 AUCinf 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 (see sections 4.3 and 4.4).

The effect of a moderate CYP3A4 inducer on ribociclib exposure has not been studied. Physiologically-based pharmacokinetic simulations suggested that a moderate CYP3A4 inducer (efavirenz) may decrease steady-state ribociclib Cmax and AUC by 45 % and 69 %, respectively, in patients with early breast cancer, and by 37 % and 60 %, respectively, in patients with advanced breast cancer (see section 4.5). The concomitant use of moderate CYP3A4 inducers may therefore lead to decreased exposure and consequently a risk for impaired efficacy, in particular in patients treated with ribociclib at 400 mg or 200 mg once daily.

Substances that may have plasma concentrations altered by Kryxana

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 medicine.

Co-administration of midazolam (CYP3A4 substrate) with multiple doses of Kryxana (400 mg) increased the midazolam exposure by 280 % (3.80-fold) in healthy subjects, compared with administration of midazolam alone. Simulations using physiologically based pharmacokinetic models suggested that Kryxana given at the clinically relevant dose of 600 mg is expected to increase the midazolam AUC by 5.2-fold. Therefore, when

ribociclib is co-administered with other medicines the PI of the other medicinal product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors (see section 4.3 and 4.4).

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 (see section 4.3 and 4.4).

Concomitant administration of ribociclib at the 600 mg dose with the following CYP3A4 substrates should be avoided: alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam (see section 4.3 and 4.4).

Co-administration of caffeine (CYP1A2 substrate) with multiple doses of Kryxana (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

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

Medicines 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 medicines 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.

Interaction between ribociclib and letrozole

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

Interaction between ribociclib and anastrozole

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

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 medicines.

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.

Interaction between ribociclib and oral contraceptives

Interaction studies between ribociclib and oral contraceptives have not been conducted (see section 4.6).

Anticipated interactions

Antidysrhythmic medicines and other medicines that may prolong the QT interval

Co-administration of Kryxana with medicines with a known potential to prolong the QT interval such as antidysrhythmic medicines (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine and sotalol), and other medicines 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 sections 4.3 and 4.4). Kryxana 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 Kryxana.

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

Pregnancy

Kryxana is teratogenic and contraindicated in pregnancy and lactation

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). Kryxana is contraindicated during pregnancy and in women of childbearing potential not using contraception (see sections 4.3 and 4.4).

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. Mothers on treatment with Kryxana should not breast-feed their infants (see

sections 4.3 and 4.4). Mothers receiving Kryxana 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

Kryxana may have an influence on the ability of patients 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 Kryxana (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Early breast cancer

The overall safety profile reported below is based on the data set of 2,524 patients who received Kryxana in combination with aromatase inhibitor (AI) in the open-label phase III clinical study (NATALEE) in HR-positive, HER2-negative early breast cancer. The median duration of exposure to ribociclib across the study was 32.9 months with 69.4 % patients exposed for > 24 months and 42.8 % patients have completed the 36 months ribociclib regimen.

Dose reductions due to adverse events (AEs), regardless of causality, occurred in 22.8 % of patients receiving Kryxana plus AI.

Permanent discontinuations of ribociclib due to adverse events were reported in 19.7 % of patients receiving Kryxana plus AI.

The most common AEs leading to permanent discontinuation of Kryxana were ALT increase (7.1 %), AST increase (2.8 %), and arthralgia (1.5 %).

On-treatment deaths were reported in 20 patients (0.8 %) treated with Kryxana plus AI. Fatal AEs were seen in 11 patients (0.4 %) in Kryxana plus AI arm, none of which were ribociclib related.

The most common ADRs across the NATALEE study (reported at a frequency of > 20 % and exceeding the frequency for AI alone) were neutropenia, infections, nausea, headache, fatigue, leukopenia, and abnormal liver function tests.

The most common Grade ≥ 3 ADRs (reported at a frequency of > 2 % and for which the frequency for Kryxana exceeds the frequency for AI alone) were neutropenia, abnormal liver function tests, and leukopenia.

Advanced or metastatic breast cancer

The most common ADRs and the most common grade 3/4 ADRs (reported at a frequency ≥ 20 % and ≥ 2 %, respectively) in the pooled dataset for which the frequency for Kryxana plus any combination exceeds the frequency for placebo plus any combination were infections, neutropenia, leukopenia, headache, cough, nausea, fatigue, diarrhoea, vomiting, constipation, alopecia and rash, and infections, neutropenia, leukopenia, back pain, anaemia, abnormal liver function tests, lymphopenia, hypophosphataemia and vomiting respectively.

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

Tabulated list of adverse reactions

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

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

Adverse drug reactions from the phase III clinical studies in patients with early breast cancer and advanced or metastatic breast cancer (Table 7-1 to 7-3) are listed by MedDRA system organ class.

Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first.

Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data).

Early breast cancer

Table 7-1 Adverse drug reactions based on data from phase III NATALEE study in patients with early breast cancer

Adverse drug reactions	Kryxana N=2524 n (%) All Grades	AI N=2444 n (%) All Grades	Kryxana N=2524 n (%) Grade ≥3	AI N=2444 n (%) Grade ≥3	Frequency category All Grades
Infections and infestations					
Infections[1]	917 (36.3)	642 (26.3)	49 (1.9)	23 (0.9)	Very common
Blood and lymphatic system disorder					
Neutropenia	1,577 (62.5)	113 (4.6)	1113 (44.1)	22 (0.9)	Very common
Leukopenia	564 (22.3)	88 (3.6)	184 (7.3)	8 (0.3)	Very common
Anaemia	215 (8.5)	75 (3.1)	8 (0.3)	7 (0.3)	Common
Thrombocytopenia	162 (6.4)	56 (2.3)	6 (0.2)	3 (0.1)	Common
Lymphopenia	124 (4.9)	39 (1.6)	30 (1.2)	2 (0.1)	Common
Febrile neutropenia	7 (0.3)	0	7 (0.3)	0	Uncommon
Metabolism and nutrition disorders					
Hypocalcaemia	134 (5.3)	26 (1.1)	1 (<0.1)	0	Common
Hypokalaemia	121 (4.8)	41 (1.7)	8 (0.3)	7 (0.3)	Common
Decreased appetite	120 (4.8)	47 (1.9)	1 (<0.1)	0	Common
Nervous system disorders					
Headache	580 (23.0)	417 (17.1)	11 (0.4)	4 (0.2)	Very common
Dizziness	225 (8.9)	112 (4.6)	5 (0.2)	2 (0.1)	Common
Respiratory, thoracic and mediastinal disorders					
Cough	332 (13.1)	201 (8.2)	3 (0.1)	2 (0.1)	Very common
Dyspnoea	166 (6.6)	102 (4.2)	13 (0.5)	10 (0.4)	Common
Gastrointestinal disorders					
Nausea	588 (23.3)	190 (7.8)	6 (0.2)	1 (<0.1)	Very common
Diarrhoea	366 (14.5)	135 (5.5)	16 (0.6)	3 (0.1)	Very common

Constipation	335 (13.3)	123 (5.0)	5 (0.2)	0	Very common
Abdominal pain[2]	277 (11.0)	179 (7.3)	12 (0.5)	9 (0.4)	Very common
Vomiting	198 (7.8)	96 (3.9)	10 (0.4)	1 (<0.1)	Common
Stomatitis[3]	154 (6.1)	24 (1.0)	2 (0.1)	0	Common
Hepatobiliary disorders					
Hepatotoxicity[4]	36 (1.4)	13 (0.5)	16 (0.6)	1 (<0.1)	Common
Skin and subcutaneous tissue disorders					
Alopecia	380 (15.0)	109 (4.5)	0	0	Very common
Rash[5]	233 (9.2)	85 (3.5)	4 (0.2)	3 (0.1)	Common
Pruritus	188 (7.4)	77 (3.2)	2 (0.1)	1 (<0.1)	Common
General disorders and administration site conditions					
Fatigue	564 (22.3)	322 (13.2)	19 (0.8)	4 (0.2)	Very common
Asthenia	428 (17.0)	291 (11.9)	14 (0.6)	3 (0.1)	Very common
Pyrexia	280 (11.1)	147 (6.0)	5 (0.2)	2 (0.1)	Very common
Peripheral oedema	183 (7.2)	121 (5.0)	1 (<0.1)	0	Common
Oropharyngeal pain	154 (6.1)	81 (3.3)	0	0	Common
Investigations					
Abnormal liver function tests[6]	563 (22.3)	186 (7.6)	197 (7.8)	25 (1.0)	Very common
Electrocardiogram QT prolonged	109 (4.3)	18 (0.7)	7 (0.3)	1 (<0.1)	Common
Blood creatinine increased	98 (3.9)	22 (0.9)	3 (0.1)	0	Common

[1] Infections: urinary tract infections; respiratory tract infections.
[2] Abdominal pain: abdominal pain, abdominal pain upper.
[3] Stomatitis: stomatitis, mucositis
[4] Hepatotoxicity: hepatic cytolysis, drug induced liver injury, hepatotoxicity, autoimmune hepatitis (single case).
[5] Rash: rash, rash maculopapular, rash pruritic.
[6] Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

Laboratory abnormalities

Clinically relevant abnormalities of routine haematological or biochemical laboratory values from the data set of the phase III NATALEE study in patients with early breast cancer are presented in Table 7-2.

Table 7-2 Laboratory abnormalities based on data from NATALEE study in patients with early breast cancer

Laboratory abnormalities	Kryxana N=2524 n (%) All Grades	AI N= 2444 n (%) All Grades	Kryxana N= 2524 n (%) Grades 3/4	AI N= 2444 n (%) Grades 3/4	Frequency category All Grades
Haematological parameters					
Lymphocyte count decreased	2,460 (97.4)	2,151 (88.1)	480 (19.0)	153 (6.3)	Very common
Leukocyte count decreased	2,407 (95.3)	1.103 (45.2)	693 (27.4)	14 (0.6)	Very common
Neutrophil count decreased	2,363 (93.6)	859 (35.2)	1,138 (45.1)	41 (1.7)	Very common
Haemoglobin decreased	1,192 (47,2)	627 (25.7)	14 (0.6)	8 (0.3)	Very common
Platelet count decreased	715 (28.3)	320 (13.1)	10 (0.4)	8 (0.3)	Very common
Biochemical parameters					
ALT increased	1,131 (44.8)	862 (35.3)	205 (8.1)	25 (1.0)	Very common
AST increased	1,111 (44.0)	806 (33.0)	133 (5.3)	26 (1.1)	Very common
Creatinine increased	822 (32.6)	278 (11.4)	7 (0.3)	0	Very common

Advanced or metastatic breast cancer

Table 7-3 Adverse drug reactions observed in the three phase III clinical studies in patients with advanced or metastatic breast cancer

	Frequency category

Adverse drug reactions	All Grades
Infections and infestations	
Infections[1]	Very common
Blood and lymphatic system disorders	
Neutropenia	Very common
Leukopenia	Very common
Anaemia	Very common
Lymphopenia	Very common
Thrombocytopenia	Common
Febrile neutropenia	Common
Eye disorders	
Lacrimation increased	Common
Dry eye	Common
Metabolism and nutrition disorders	
Decreased appetite	Very common
Hypocalcaemia	Common
Hypokalaemia	Common
Hypophosphataemia	Common
Nervous system disorders	
Headache	Very common
Dizziness	Very common
Vertigo	Common
Cardiac disorders	
Syncope	Common
Respiratory, thoracic and mediastinal disorders	
Cough	Very common
Dyspnoea	Very common
Musculoskeletal and connective tissue disorders	
Back pain	Very common
Gastrointestinal disorders	
Nausea	Very common
Diarrhoea	Very common

Vomiting	Very common
Constipation	Very common
Stomatitis	Very common
Abdominal pain[2]	Very common
Dysgeusia	Common
Dyspepsia	Very common
Hepatobiliary disorders	
Hepatotoxicity[3]	Common
Skin and subcutaneous tissue disorders	
Alopecia	Very common
Rash[4]	Very common
Pruritus	Very common
Erythema	Common
Dry skin	Common
Vitiligo	Common
General disorders and administration site conditions	
Fatigue	Very common
Peripheral oedema	Very common
Asthenia	Very common
Pyrexia	Very common
Dry mouth	Common
Oropharyngeal pain	Common
Investigations	
Abnormal liver function tests[5]	Very common
Blood creatinine increased	Common
Electrocardiogram QT prolonged	Common

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

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

[3] Hepatotoxicity: hepatic cytosis, hepatocellular injury, drug induced liver injury, hepatotoxicity, hepatic failure, autoimmune hepatitis (single case).

[4] Rash: rash, rash maculopapular, rash pruritic.

[5] *Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.*

Post marketing data

The following ADR's are derived from post-marketing experience with Kryxana via spontaneous case reports and literature cases. As these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

Table 8 Adverse drug reactions derived from spontaneous reports and literature (frequency not known)

Respiratory, thoracic and mediastinal disorders
Interstitial lung disease (ILD)/pneumonitis
Skin and subcutaneous tissue disorders
Toxic epidermal necrolysis (TEN)

Description of selected adverse drug reactions

Neutropenia

Severity of neutropenia is dose dependent.

In the phase III study in patients with early breast cancer neutropenia was a frequently reported laboratory finding. Treatment discontinuation due to neutropenia was low (1.1 %) in patients receiving Kryxana plus AI (see sections 4.2 and 4.4).

Neutropenia was the most frequently reported adverse drug reaction (73.7 %) and a grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 58.6 % of patients receiving Kryxana plus any combination in the phase III studies in patients with advanced or metastatic breast cancer.

Among the patients who had grade 2, 3 or 4 neutropenia, the median time to onset was 16 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 Kryxana plus any combination arms following treatment interruption and/or reduction and/or discontinuation. Febrile neutropenia was reported in about 1.4 % of patients exposed to Kryxana in the phase III studies. Patients should be instructed to report any fever promptly.

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

Hepatobiliary toxicity

In the phase III study in patients with early breast cancer, hepatobiliary toxicity events occurred in a higher proportion of patients in the Kryxana plus AI arm vs AI alone arm (26.4 % vs 11.2 %, respectively), with more Grade 3/4 AEs reported in patients treated with Kryxana plus AI (8.6 % vs 1.7 %, respectively). Dose interruptions due to hepatobiliary toxicity events were reported in 12.4 % of patients with early breast cancer treated with Kryxana 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 Kryxana plus AI, primarily due to ALT increased (1.9 %) and/or AST increased (0.6 %). Discontinuation of treatment with Kryxana due to abnormal liver function tests and hepatotoxicity occurred in 8.9 % and 0.1 % of patients, respectively (see section 4.4).

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 Kryxana 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 Kryxana plus any combination (13.2 % versus 6.1 %, respectively). Increases in transaminases were observed. Grade 3 or 4 increases in ALT (11.2 % versus 1.7 %) and AST (7.8 % versus 2.1 %) were reported in the Kryxana 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, whose levels recovered to normal within 154 days and 2 patients whose levels recovered to normal in 121 and 532 days, respectively, after discontinuation of Kryxana).

Dose interruptions and/or adjustments due to hepatobiliary toxicity events were reported in 12.3 % of Kryxana plus any combination treated patients, primarily due to ALT increased (7.9 %) and/or AST increased (7.3 %). Discontinuation of treatment with Kryxana 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 Kryxana plus any combination arms. The median time to resolution (to normalisation or grade ≤ 2) was 21 days in the Kryxana plus any combination arms.

QT prolongation

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

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 ms for the Kryxana plus AI arm and the AI only arm, respectively. Among the patients who had QTcF interval prolongation of > 480 ms in the Kryxana plus AI arm, the median time to onset was 15 days and these changes were reversible with dose interruption and/or dose adjustment (see sections 4.2, 4.4 and 5.1). QTcF interval > 60 ms change from baseline was observed in 19 patients (0.8 %)

in the Kryxana plus AI arm and post-baseline QTcF interval > 500 ms was observed in 3 patients (0.1 %) in the Kryxana plus AI arm.

In study E2301 (MONALEESA 7), the observed mean QTcF increase from baseline was approximately 10 msec higher in the tamoxifen plus placebo subgroup compared with the NSAI plus placebo subgroup, suggesting that tamoxifen alone had a QTcF prolongation effect which can contribute to the QTcF values observed in the Kryxana 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 Kryxana plus tamoxifen and in 18/245 (7.3 %) patients receiving Kryxana plus a NSAI. Kryxana is not recommended to be used in combination with tamoxifen (see section 5.1).

In the phase III clinical studies in patients with advanced or metastatic breast cancer, 9.3 % of patients in the Kryxana 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 Kryxana 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 Kryxana 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of Kryxana. Healthcare professionals are asked to report any suspected adverse reactions via patientsafety.sacg@novartis.com and via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Ribociclib is a selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in 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 cell 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 at well-tolerated doses.

In vivo studies demonstrated that combinations of ribociclib and antioestrogen therapies (i.e. letrozole) resulted in 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. An *in vivo* study demonstrated that the combination of ribocicclib with fulvestrant resulted in complete tumour growth inhibition.

Ribociclib is more efficacious in ER+ breast cancer cell lines than in the ER- ones. Intact pRb is required for ribociclib activity.

Cardiac electrophysiology

A pharmacokinetic-pharmacodynamic analysis included a total of 997 patients treated with ribociclib at doses ranging from 50 to 1200 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval.

In patients with early breast cancer, the estimated geometric mean QT interval change from baseline for Kryxana 400 mg starting dose in combination with non-steroidal aromatase inhibitor (NSAI) was 10.00 ms (90 % CI: 8.0, 11.9), at the geometric mean Cmax at steady state (see section 4.4).

In patients with advanced or metastatic breast cancer, the estimated QTcF mean change from baseline for 600 mg Kryxana 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 Cmax at steady-state compared to 34.7 msec (90 % CI: 31.64, 37.78) in combination with tamoxifen (see section 4.4).

Clinical efficacy and safety

Study CLEE011O12301C (NATALEE)

Kryxana was evaluated in a randomised, open-label, multicenter phase III clinical study in the treatment of pre/post-menopausal women, and men, with HR-positive, HER2-negative, early breast cancer with Anatomic Stage II or III irrespective of nodal status in combination with an aromatase inhibitor (AI, letrozole or anastrozole) versus AI alone. Stage IIA patients with no nodal involvement had tumor grade 2 with high risk genomic profile or Ki67 ≥ 20 % or grade 3. Premenopausal women, and men, also received goserelin. Applying TN 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 Kryxana 400 mg and AI (n=2549) or AI alone (n=2,552). Randomisation to the treatment was stratified by Anatomic Stage (group II [n=2,154 (42.2 %)] vs group III [n=2,947 (57.8 %)]), prior treatment (adjuvant/ neoadjuvant

chemotherapy Yes [n=4,432 (86.9 %)] vs No [n=669 (13.1 %)]), menopausal status (premenopausal women and men [n=2,253 (44.2 %)] vs postmenopausal women [n=2,848 (55.8 %)]) and region (North America/Western Europe/Oceania [n=3,128 (61.3 %)] vs rest of the world [n=1,973 (38.7 %)]). Demographics and baseline disease characteristics were balanced and comparable between the two study arms. Kryxana 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 Kryxana 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) and 15.2 % patients were aged 65 years and older, including 123 patients (2.4 %) aged 75 years and older. The patients included were White (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 71.1 % had received antihormonal therapy in the neo/adjuvant setting prior to study entry.

Primary analysis

The primary endpoint of the NATALEE study was invasive disease-free survival (iDFS).

iDFS was 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).

A statistically significant improvement in iDFS (HR: 0.748, 95 % CI: 0.618 to 0.906; one-sided stratified log-rank test p-value=0.0014) was demonstrated at the primary iDFS analysis (11-Han-23 cut-off) in patients receiving Kryxana plus AI over AI alone. There was an estimated 25.2 % reduction in risk of an iDFS event in

patients treated with the combination of Kryxana plus AI. iDFS rate at 36 months was 90.4 % (95 % CI 88.6 %, 91.9 %) compared to 87.1 % (95 % CI 85.3 %, 88.8 %) in patients receiving Kryxana plus AI and AI alone, respectively. The median time of treatment duration at the time of primary iDFS analysis was approximately 30 months with the median follow-up time for iDFS 27.7 months across the two study arms. Consistent results were observed across key sub-groups of Anatomic Stage, menopausal status, and region. At the time of iDFS analysis, overall survival (OS) was immature. A total of 134 patients (2.7 %) had died (60/2,524 in the ribociclib arm versus 74/2,444 in the AI alone arm, HR 0.759).

Hazard ratios based on a pre-specified sub-group analysis are in favour of the Kryxana plus AI arm, demonstrating that patients benefit independent of age, race or prior adjuvant/ neo-adjuvant chemotherapy or hormonal therapies.

There were 159 (6.2 %) recurrence-free survival (RFS) events in the Kryxana plus AI arm compared to 207 (8.1 %) events in the AI alone arm (HR: 0.719, 95 % CI: 0.584 to 0.884). There were 167 (6.6 %) distant disease-free survival (DDFS) events in the Kryxana plus AI arm compared to 212 (8.3 %) events in the AI alone arm (HR: 0.739, 95 % CI: 0.603 to 0.905).
After 36 months of treatment, change from baseline in the physical functioning sub-scale score and global health status/QoL scale score as assessed by EORTC QLQC30 in the Kryxana plus AI arm was comparable to the AI alone arm. There were no clinically meaningful (≥ 10 points) differences between treatment arms in any EORTC QLQ-C30 functioning domains.

Final iDFS analysis

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). The median time of 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.

Study CLEE011A2301 (MONALEESA-2)

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

A total of 668 patients were randomised in a 1:1 ratio to receive either Kryxana 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 %)] vs No [n=376 (56 %)]. Demographics and baseline disease characteristics were balanced and comparable between study arms. Kryxana 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 Kryxana during the study or after disease progression.

Patients enrolled in this study had a median age of 62 years (range 23 to 91). 44.2 % patients were of age 65 years and older, including 69 patients (10.3 %) of age 75 years and older. The patients included were Caucasian (82.2 %), Asian (7.6 %), and Black (2.5 %). All patients had an ECOG performance status of 0 or 1. A total of 46.6% of patients had received chemotherapy in the neoadjuvant or adjuvant setting and 51.3 % had received antihormonal therapy in the neo/adjuvant setting prior to study entry. 34.1 % of patients had de novo metastatic disease. 22.0 % of patients had bone- only disease and 58.8 % of patients had visceral disease.

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 the Response Evaluation Criteria in Solid Tumors (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 Kryxana plus letrozole compared to patients receiving placebo plus letrozole in the full analysis set (FAS) (HR: 0.556; 95 % CI: 0.429, 0.720; one-sided stratified log-rank test p-value=0.00000329), with an estimated 44 % reduction in risk of progression for patients treated with the combination of Kryxana plus letrozole. The median PFS was not reached in the Kryxana plus letrozole arm (95 % CI: 19.3, NE) at the time of the primary analysis. The median PFS was 14.7 months (95 % CI: 13.0, 16.5) for the placebo plus letrozole arm. Results were consistent across the sub-groups of age, race, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastatic disease.

The results for PFS based on the blinded independent central radiological assessment were consistent with the primary efficacy results based on the investigator's assessment (HR: 0.592; 9 5 % CI: 0.412, 0.852). The one-sided stratified log- rank test p-value was 0.002.
Hazard ratios based on a pre-specified sub-group analysis are in favour of the Kryxana plus letrozole arm, demonstrating that patients benefit independent of age, race, prior adjuvant/ neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastasis disease.

Final OS analysis

At the time of the final overall survival (OS) analysis (10-Jun-2021 cut-off), the study met its key secondary endpoint demonstrating a statistically significant and clinically meaningful improvement in OS with a 23.5 % relative reduction in risk of death (HR: 0.765, 95 % CI: 0.628, 0.932; p-value=0.004).
OS benefit increased over time, with a 6-year survival rate of 44.2 % (38.5, 49.8) for Kryxana vs. 32.0 % (26.8, 37.3) for placebo. The median OS was 63.9 months (95 % CI: 52.4, 71.0) for the Kryxana arm and 51.4 months (95 % CI: 47.2, 59.7) for the placebo arm, with a 12.5-months improvement in median OS for the Kryxana arm.

Study CLEE011E2301 (MONALEESA-7)

Kryxana was evaluated in a randomised, double-blind, placebo-controlled, multicenter phase III clinical study comparing ribociclib or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of pre- and peri-menopausal women with hormone receptor (HR)-positive, HER2-negative, advanced breast cancer.
A total of 672 patients were randomised to receive either Kryxana 600 mg plus tamoxifen or NSAI plus goserelin (n = 335) or placebo plus tamoxifen or NSAI plus goserelin (n = 337), stratified according to the presence of liver and/or lung metastases (Yes [n = 344 (51.2 %)] vs No [n = 328 (48.8 %)]), prior chemotherapy for advanced disease (Yes [n = 120 (17.9 %)] vs 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.

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

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

Primary analysis

The primary endpoint for the study was met after observing 318 progression-free survival (PFS) events using RECIST v1.1, based on the investigator assessment in the full analysis set (all randomised patients) and confirmed by a blinded independent central radiological assessment of a randomly selected subset of approximately 40 % of randomised patients (BIRC). The median follow-up time at the time of the primary PFS analysis was 19.2 months.

In the overall study population, the median PFS (95 % CI) was 23.8 months (19.2, NE) in the Kryxana plus tamoxifen or NSAI arm and 13.0 months (11.0, 16.4) in the placebo plus tamoxifen or NSAI arm [HR: 0.553 (95 % CI: 0.441, 0.694); one-sided stratified long-rank test p-value: 9.83 x 10-8].
In the pre-specified sub-group analysis of 495 patients who had received Kryxana or placebo in combination with NSAI plus goserelin, the median PFS (95 % CI) was 27.5 months (19.1, NE) in the Kryxana plus NSAI sub-group and 13.8 months (12.6, 17.4) in the placebo plus NSAI sub-group [HR: 0.569 (95 % CI: 0.436, 0.743)].
Results in the Kryxana plus NSAI subgroup were consistent across subgroups of age, race, prior adjuvant/ neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone only metastatic disease.

Final OS Analysis

At the time of the second OS analysis (30-Nov-2018 cut-off), the study met its key secondary endpoint, demonstrating a statistically significant improvement in OS (HR: 0.712 (95 % CI: 0.535, 0.948), one-sided p-value: 0.00973 in overall study population. HR: 0.699 (95 % CI: 0.501, 0.976) in NSAI subgroup). Number of patients with an event in overall population was 83 (24.8 %) and 109 (32.3 %) in the Kryxana arm and the placebo arm, respectively. Number of patients with an event in NSAI subgroup was 61 (24.6 %) and 80 (32.4 %) in the Kryxana arm and the placebo arm, respectively. The median OS was 40.9 months (95 % CI: 37.8, NE) and 40.7 months (95 % CI: 37.4, NE) in the placebo arm in the overall population and NSAI subgroups, respectively, and was not reached (95 % CI: NE, NE) in the Kryxana arm).

The demonstrated OS benefit was consistent across exploratory subgroups and the safety profile of both treatment arms remained consistent with the results from the primary analysis.

Study CLEE011F2301 (MONALEESA-3)

Kryxana was evaluated in a randomised double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor (HR)-positive, HER2-negative advanced breast cancer who have received no or only one line of prior endocrine treatment. A total of 726 patients were randomised in a 2:1 ratio to receive either Kryxana 600 mg and fulvestrant (n = 484) or placebo and fulvestrant (n = 242) stratified according to the presence of liver and/or lung metastases [Yes (n = 351 (48.3 %)) versus No (n = 375 (51.7 %))], prior endocrine therapy [A (n = 354 (48.8 %)) vs B (n = 372 (51.2 %)] First-line patients with advanced breast cancer (A) include de novo advanced breast cancer with no prior endocrine therapy, and patients who relapsed after 12 months of (neo)adjuvant endocrine therapy completion.

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

Patients enrolled in this study had a median age of 63 years (range 31 to 89). 46.7 % of patients were aged 65 years and older, including 13.8 % patients aged 75 years and older. The patients included were Caucasian (85.3 %), Asian (8.7 %) or Black (0.7 %). Nearly all patients (99.7 %) had an ECOG performance status of 0 or 1. First and second-line patients were enrolled in this study (of whom 19.1 % of patients had *de novo* metastatic disease). 42.7 % of patients had received chemotherapy in the adjuvant vs 13.1 % in the

neo- adjuvant setting and 58.5 % had received endocrine therapy in the adjuvant vs 1.4 % in the neoadjuvant setting. Prior to study entry 21.2 % of patients had bone-only disease and 60.5 % of patients had visceral disease. Demographics and baseline disease characteristics were balanced and comparable between study arms.

Primary analysis

The primary endpoint for the study was performed after observing 361 PFS events using RECIST v1.1, based on the investigator assessment in the full analysis set (all randomised patients) and confirmed by a random central audit of 40 % imaging subset by a blinded independent review committee (BIRC). The median follow-up time at the time of primary PFS analysis was 20.4 months.
PFS analyses based on the BIRC were supportive of the primary efficacy results, the PFS hazard ratio was 0.492 (95 % CI, 0.345 to 0.703).

The primary efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Kryxana plus fulvestrant compared to patients receiving placebo plus fulvestrant in the full analysis set (HR: 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 favor of the Kryxana plus fulvestrant arm. The median (95 % CI) PFS was 20.5 months (18.5, 23.5) in the Kryxana plus fulvestrant and 12.8 months (10.9, 16.3) in the placebo plus fulvestrant arm.

Final OS Analysis

Since the median PFS for first line patients had not been reached at the time of the primary analysis, a descriptive update of primary efficacy results (PFS) was performed at the time of the second OS interim analysis (03-Jun-2019 cut-off) (HR: 0.587 (95 % CI: 0.488, 0.705)). The median PFS was 20.6 months (95 % CI: 18.6, 24.0) and 12.8 months (95 % CI: 10.9, 16.3) in the Kryxana plus fulvestrant arm and placebo plus fulvestrant arm, respectively. Results were consistent across pre-specified sub-groups of age, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone only

metastatic disease. The OS results from this interim analysis with a 03-Jun-19 cut-off demonstrated a median OS of 40 months (95 % CI: 37, NE) in the placebo arm (HR 0.724 (95 % CI: 0568, 0924), one-sided p-value: 0.00455). The median OS in Kryxana arm was not reached. The number of patients with an event was 167 (34.5 %) and 108 (44.6 %) in the Kryxana arm and placebo arm, respectively.

Study CLEE011A2404 (COMPLEEMENT-1)

Kryxana was evaluated in an open-label, single arm, multicenter phase IIIb clinical study comparing ribociclib in combination with letrozole in pre/post-menopausal women and men with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease. Premenopausal women, and men, also received goserelin or leuprolide.

The study enrolled 3246 patients, including 39 male patients who received Kryxana 600 mg orally once daily for 21 consecutive days followed by 7 days off; and letrozole 2.5 mg orally once daily for 28 days; and goserelin 3.6 mg as injectable subcutaneous implant or leuprolide 7.5 mg as intramuscular injection administered on Day 1 of each 28-day cycle. Patients were treated until disease progression or unacceptable toxicity occurred.

Male patients enrolled in this study had a median age of 62 years (range 33 to 80). Of these patients, 38.5 % were 65 years and older, including 10.3 % aged 75 years and older. The male patients enrolled were Caucasian (71.8 %), Asian (7.7 %), and Black (2.6 %), with 17.9 % unknown. Nearly all male patients (97.4 %) had an ECOG performance status of 0 or 1. The majority of male patients (97 %) had 4 or less metastatic sites, which were primarily bone and visceral (69.2 % each). The efficacy results in male patients with measurable disease (N = 32) based on investigator assessment demonstrated the overall response rate (ORR) 46.9 (95 % CI: 29.1, 65.3). The median duration of response (DoR) was not reached (95 % CI: 21.3, NR). The number of patients with DoR ≥ 12 months was 12 (80.0 %). The clinical benefit rate (CBR) was 71.9 (95 % CI: 53.3, 86.3).

5.2 Pharmacokinetic properties

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

Absorption

The absolute bioavailability of ribociclib is not known.

The time to reach Cmax (Tmax) following ribociclib oral administration was between 1 and 4 hours. Ribociclib exhibited slightly over-proportional increases in exposure (Cmax and AUC) across the dose range tested (50 to 1200 mg).

Following repeated once-daily dosing, steady state was generally achieved after 8 days and ribociclib accumulated with a geometric mean accumulation ratio of 2.51 (range: 0.97 to 6.40).

Food effect

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

Distribution

Binding of ribociclib to human plasma proteins *in vitro* was approximately 70 % and was independent of concentration (10 to 10000 ng/mL). Ribociclib was equally distributed between red blood cells and plasma with a mean *in vivo* blood-to-plasma ratio of 1.04. The apparent volume of distribution at steady state (Vss/F) was 1090 L based on population pharmacokinetic analysis.

Biotransformation

In vitro and *in vivo* studies indicated ribociclib is eliminated primarily via hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of [14C] ribociclib to humans, the

primary metabolic pathways for ribociclib involved oxidation (dealkylation, C and/or N-oxygenation, oxidation (-2H)) and combinations thereof. Phase II conjugates of ribociclib phase I metabolites involved N-acetylation, sulfation, cysteine conjugation, glycosylation and glucuronidation. Ribociclib was the major circulating drug-derived entity in plasma. The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide). Clinical activity (pharmacological and safety) of ribociclib was due primarily to parent drug, with negligible contribution from circulating metabolites.

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

Elimination

The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63 % CV) and the geometric mean apparent oral clearance (CL/F) was 25.5 L/hr (66 % CV) at steady state at 600 mg in patients with advanced cancer. The mean CL/F estimated by population PK analysis was 38.4 L/hr (95 % CI: 35.5 to 41.9) at steady state at 400 mg in patients with early breast cancer. The geometric mean apparent plasma terminal half-life (T1/2) 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 [14C] ribociclib, 91.7 % of the total administered radioactive dose was recovered within 22 days; faeces was the major route of excretion (69.1 %), with 22.6 % of the dose recovered in urine.

Linearity/non-linearity

Ribociclib exhibited slightly over-proportional increases in exposure (C_{max} and AUC) across the dose range of 50 mg to 1200 mg following both single dose and repeated doses.

Special populations

Renal impairment

Based on a population pharmacokinetic analysis that included 438 advanced cancer patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2), 488 patients with mild renal impairment (eGFR 60 to < 90 mL/min/1.73 m^2) and 113 patients with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m^2), mild and moderate renal impairment had no effect on the exposure of ribociclib (see section 4.2). The pharmacokinetics of ribociclib in patients with severe renal impairment have not been studied.
A sub-group analysis of PK data from early breast cancer study O12301C also showed no clinically meaningful effect of mild or moderate renal impairment on steady state ribociclib exposure following oral administration of ribociclib 400 mg as repeat doses.

Hepatic impairment

Based on a pharmacokinetic study in patients 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 AUCinf) and severe (GMR: 1.32 for C_{max}; 1.29 for AUCinf) hepatic impairment. Based on a population pharmacokinetic analysis that included 160 advanced 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 (see section 4.2). In early breast cancer study O12301C, no apparent increase in ribociclib exposure was observed in patients with mild 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.

Elderly patients

No overall differences in safety or effectiveness of Kryxana were observed between elderly patients and younger patients (see section 4.2).

Of the 2549 patients with early breast cancer who received Kryxana in the phase III study (NATALEE, ribociclib plus AI arm), 407 patients (16.0 %) were ≥ 65 years of age.

Paediatric population

Kryxana is not indicated for use in patients < 18 years of age.

***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, Kryxana 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 highest recommended dose of 600 mg. There is also potential to induce incidences of premature ventricular contractions (PVCs) at elevated exposures (approximately 5-fold the anticipated clinical C_{max}).

Repeated-dose toxicity

Repeated-dose toxicity studies (treatment schedule of 3 weeks on/1 week off) of up to 27 weeks' duration in rats and up to 39 weeks' duration in dogs, revealed the hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) as the primary target organ of toxicity of ribociclib. Target organs associated with the pharmacological action of ribociclib in repeat-dose studies include bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation), kidney (concurrent degeneration and regeneration of tubular epithelial cells) and testes (atrophy). Besides the atrophic changes seen in the testes, which showed a trend towards reversibility, all other changes were fully reversible after a 4-week treatment-free period. Exposure to ribociclib in animals in the toxicity studies was generally less than or equal to that observed in patients receiving multiple doses of 600 mg/day (based on AUC).

Reproductive toxicity/Fertility

Ribociclib showed foetotoxicity and teratogenicity at doses which did not show maternal toxicity in the rats or rabbits.

Following prenatal exposure, increased incidences of post-implantation loss and reduced foetal weights were observed in rats and ribociclib was teratogenic in rabbits at exposures lower than or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC.

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

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

Ribociclib has not been evaluated in male fertility studies. However, atrophic changes in testes were reported in rat and dog toxicity studies at exposures that were less than or equal to human exposure at the highest recommended daily dose of 600 mg/day based on AUC. These effects can be linked to 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 rat study.
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 (AUC0-24h) 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 (AUC0-24h) 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.

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

The effects on the uterus/cervix and on the testicular interstitial (Leydig) cell may be 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 Kryxana is indicated in combination with oestrogen-lowering agents.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose

Crospovidone type A

Low-substituted hydroxypropylcellulose

Magnesium stearate

Colloidal anhydrous silica

Film coating

Iron oxide black (E172)

Iron oxide red (E172)

Soya lecithin (E322)

Polyvinyl alcohol (partially hydrolysed)

Talc

Titanium dioxide (E171)

Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store at or below 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

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

Unit packs containing 21, 42 or 63 film-coated tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

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