

FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE****1.1 Early Breast Cancer**

KRYXANA is indicated in combination with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.

1.2 Advanced or Metastatic Breast Cancer

KRYXANA is indicated for the treatment of adults with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy in pre/perimenopausal or postmenopausal women or in men; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.

2 DOSAGE AND ADMINISTRATION**2.1 Recommended Dosage**Important Dosing Administration Instructions

KRYXANA can be taken with or without food [*see Clinical Pharmacology (12.3)*].

Pre/perimenopausal women, or men, treated with the combination KRYXANA plus an aromatase inhibitor or fulvestrant, should be treated with a luteinizing hormone-releasing hormone (LHRH) agonist according to current clinical practice standards.

Patients should take their dose of KRYXANA at approximately the same time each day, preferably in the morning.

If the patient vomits after taking the dose, or misses a dose, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time. KRYXANA tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

Early Breast Cancer

The recommended dosage of KRYXANA is 400 mg (two 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off in 28-day treatment cycles. KRYXANA should be given in combination with an aromatase inhibitor. Refer to the Full Prescribing Information for the recommended dosage of the aromatase inhibitor.

In patients with early breast cancer, treatment with KRYXANA should continue for 3 years or until disease recurrence or unacceptable toxicity occurs.

Advanced or Metastatic Breast Cancer

The recommended dosage of KRYXANA is 600 mg (three 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off in 28-day treatment cycles. KRYXANA should be given in combination with endocrine therapy (fulvestrant or an aromatase inhibitor). Refer to the Full Prescribing Information for the recommended dose of endocrine therapy.

2.2 Dose ModificationsDose Modifications for Adverse Reactions

The recommended dose modifications for adverse reactions are listed in Table 1.

Table 1: Recommended Dose Modification for Adverse Reactions

Level	KRYXANA	
	Dose	Number of tablets
Early breast cancer		
Starting dose	400 mg/day	two 200 mg tablets
Dose reduction	200 mg/day*	one 200 mg tablet
Advanced or metastatic breast cancer		
Starting dose	600 mg/day	three 200 mg tablets
First dose reduction	400 mg/day	two 200 mg tablets
Second dose reduction	200 mg/day*	one 200 mg tablet

*If dose reduction below 200 mg/day is required, discontinue KRYXANA.

Tables 2, 3, 4, 5, 6, and 7 summarize recommendations for dose interruption, reduction, or discontinuation of KRYXANA in the management of specific adverse reactions. Dose modification of KRYXANA is recommended based on individual patient safety and tolerability.

Table 2: Dose Modification and Management for Interstitial Lung Disease/Pneumonitis

	Grade 1 (asymptomatic)	Grade 2 (symptomatic)	Grade 3 (severe symptomatic) or 4 (life-threatening)
ILD/Pneumonitis <i>[see Warnings and Precautions (5.1)]</i>	No dose interruption or adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to Grade ≤ 1 then consider resuming KRYXANA at the next lower dose level*. If Grade 2 recurs, discontinue KRYXANA.	Discontinue KRYXANA

Abbreviation: ILD, interstitial lung disease.

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

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

Table 3: Dose Modification and Management for Cutaneous Adverse Reactions, Including SCARs

	Grade 1 ($< 10\%$ body surface area (BSA) with active skin toxicity, no signs of systemic involvement)	Grade 2 (10% - 30% BSA with active skin toxicity, no signs of systemic involvement)	Grade 3 (severe rash not responsive to medical management; $> 30\%$ BSA with active skin toxicity, signs of systemic involvement present; SJS*)	Grade 4 (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life threatening consequences; TEN**)
Cutaneous adverse reactions, including SCARs <i>[see Warnings and Precautions (5.2)]</i>	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.		Interrupt KRYXANA until the etiology of the reaction has been determined. If the etiology is a SCAR, permanently discontinue KRYXANA.	Permanently discontinue KRYXANA.

	If the etiology is not a SCAR, interrupt dose until recovery to Grade ≤ 1, then resume KRYXANA at same dose level. If the cutaneous adverse reaction still recurs at Grade 3, resume KRYXANA at the next lower dose level.
--	--

Abbreviations: BSA, body surface area; SCARs, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

*SJS (Grade 3 and 4) is defined as skin sloughing covering $< 10\%$ BSA and 10% - 30% BSA, respectively, with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment).

**TEN (Grade 4) is defined as skin sloughing covering $\geq 30\%$ BSA with associated symptoms (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment).

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

Table 4: Dose Modification and Management for QT Prolongation

QTcF* prolongation	Early breast cancer	Advanced or metastatic breast cancer
> 480 ms and ≤ 500 ms	Interrupt KRYXANA treatment and wait until QTcF resolves to ≤ 480 ms	
	Resume at the same dose	Reduce to the next lower dose level
	If QTcF > 480 ms recurs, interrupt KRYXANA treatment and wait until QTcF resolves to ≤ 480 ms, then resume at next lower dose level.	
> 500 ms	Interrupt KRYXANA treatment and wait until QTcF resolves to ≤ 480 ms, then resume at next lower dose level.	
	If QTcF > 500 ms recurs, discontinue KRYXANA.	

Permanently discontinue KRYXANA if QTcF interval prolongation is either > 500 ms or > 60 ms change from baseline AND associated with any of the following: Torsades de Pointes, polymorphic ventricular tachycardia, syncope, or signs/symptoms of serious arrhythmia.

Note: If dose reduction below 200 mg/day is required, discontinue KRYXANA.

Electrocardiograms (ECGs) should be assessed prior to initiation of treatment 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, monitor ECG more frequently, and as clinically indicated

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

Table 5: Dose Modification and Management for 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 <i>[see Warnings and Precautions (5.5)]</i>	No dose adjustment is required.	<u>Baseline*</u> at < Grade 2: Dose interruption until recovery to $\leq$ baseline grade, then resume KRYXANA at same dose level. If Grade 2 recurs, resume KRYXANA at next lower dose level. ----- <u>Baseline*</u> at Grade 2:	Dose interruption until recovery to $\leq$ baseline* grade, then resume at next lower dose level. If Grade 3 recurs, discontinue KRYXANA.	Discontinue KRYXANA

No dose interruption.	
Combined elevations in AST and/or ALT WITH total bilirubin increase, in the absence of cholestasis <i>[see Warnings and Precautions (5.5)]</i>	If patients develop ALT and/or AST > 3 x ULN along with total bilirubin > 2 x ULN irrespective of baseline grade, discontinue KRYXANA.
Perform Liver Function Tests (LFTs) before initiating treatment with KRYXANA. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated. If Grade ≥ 2 abnormalities are noted, monitor more frequently, and as clinically indicated.	
Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal. *Baseline = prior to treatment initiation. Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.	

Table 6: Dose Modification and Management for 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 <i>[see Warnings and Precautions (5.6)]</i>	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 recovery, then resume KRYXANA at the next lower dose level.	Dose interruption until recovery of neutropenia to Grade ≤ 2. Resume KRYXANA at the next lower dose level.	Dose interruption until recovery to Grade ≤ 2. Resume KRYXANA at the next lower dose level.
Perform complete blood counts (CBCs) before initiating treatment with KRYXANA. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.				
Abbreviations: ANC, absolute neutrophil count; LLN, lower limit of normal. *Grade 3 neutropenia with single episode of fever > 38.3°C (or) 38°C or above for more than one hour and/or concurrent infection. Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.				

Table 7: Dose Modification and Management for Other Toxicities*

	Grade 1 or 2	Grade 3	Grade 4
Other Toxicities	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 same dose level. If Grade 3 recurs, resume KRYXANA at the next lower dose level.	Discontinue KRYXANA
*Excluding interstitial lung disease (ILD)/pneumonitis, cutaneous adverse reactions, including severe cutaneous adverse reactions (SCARs), QT interval prolongation, hepatobiliary toxicity, and neutropenia. Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.			

Refer to the Full Prescribing Information for the coadministered aromatase inhibitor or fulvestrant for dose modification guidelines in the event of toxicity and other relevant safety information.

Dose Modification for Use with Strong CYP3A Inhibitors

Avoid concomitant use of KRYXANA with strong CYP3A inhibitors and consider an alternative concomitant medication with less potential for CYP3A inhibition [see *Drug Interactions (7.1)*].

If a strong CYP3A inhibitor must be coadministered, reduce the KRYXANA dose as shown in Table 8.

Table 8: Dose Modification for Use with Strong CYP3A Inhibitors

Indication	Co-administration with Strong CYP3A Inhibitors
Early breast cancer	Reduce the KRYXANA dose to 200 mg once daily.
Advanced or metastatic breast cancer	Reduce the KRYXANA dose to 400 mg once daily.

If the strong inhibitor is discontinued, change the KRYXANA dose (after at least 5 half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor [see *Drug Interactions (7.1)*, *Clinical Pharmacology (12.3)*].

Dose Modification for Hepatic Impairment

The recommended dose modifications for patients with hepatic impairment are shown in Table 9 [see *Use in Specific Populations (8.6)*, *Clinical Pharmacology (12.3)*].

Table 9: Dose Modification for Hepatic Impairment

Indication	Mild hepatic impairment (Child-Pugh class A)	Moderate and severe hepatic impairment (Child-Pugh class B or C)
Early breast cancer	No dose adjustment is necessary	No dose adjustment is necessary
Advanced or metastatic breast cancer	No dose adjustment is necessary	KRYXANA 400 mg once daily

Review the Full Prescribing Information for the co-administered aromatase inhibitor or fulvestrant for dose modifications related to hepatic impairment.

Dose Modification for Severe Renal Impairment

The recommended starting dose is 200 mg KRYXANA once daily for patients with severe renal impairment [see *Use in Specific Populations (8.7)*, *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Tablet: 200 mg ribociclib (equivalent to 254.40 mg ribociclib succinate).

Film coated, light greyish violet, round, curved with beveled edges, debossed with “RIC” on one side and “NVR” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KRYXANA and other CDK 4/6 inhibitors.

In patients with early breast cancer (NATALEE) who received 400 mg KRYXANA plus a non-steroidal aromatase inhibitor (NSAI), 1.5% of patients had ILD/pneumonitis (Grade 1-2).

In patients with advanced or metastatic breast cancer (MONALEESA-2, MONALEESA-3, MONALEESA-7), 1.6% of patients had ILD/pneumonitis (any Grade, 0.4% had Grade 3-4, and 0.1% had a fatal outcome). Additional cases of ILD/pneumonitis have occurred in the postmarketing setting, some resulting in death [see *Adverse Reactions* (6.2)].

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt KRYXANA immediately and evaluate the patient. Permanently discontinue KRYXANA in patients with severe ILD/pneumonitis or any recurrent symptomatic ILD/pneumonitis. [see *Dosage and Administration* (2.2)].

5.2 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with KRYXANA [see *Adverse Reactions* (6.2)].

If signs or symptoms of severe cutaneous reactions occur, interrupt KRYXANA until the etiology of the reaction has been determined [see *Dosage and Administration* (2.2)]. Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

If SJS, TEN, or DiHS/DRESS is confirmed, permanently discontinue KRYXANA. Do not reintroduce KRYXANA in patients who have experienced SCARs or other life-threatening cutaneous reactions during KRYXANA treatment.

5.3 QT Interval Prolongation

KRYXANA has been shown to prolong the QT interval in a concentration-dependent manner [see *Clinical Pharmacology* (12.2)].

Avoid KRYXANA in patients who are at significant risk of developing Torsades de Pointes (TdP), including those with:

- congenital long QT syndrome;
- uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism;
- electrolyte abnormalities;
- taking drugs known to prolong QT interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval.

Based on the observed QT prolongation during treatment, KRYXANA may require dose interruption, reduction or discontinuation as described in Table 4 [see *Dosage and Administration* (2.2), *Drug Interactions* (7.4)].

In patients with early breast cancer (NATALEE) who received 400 mg KRYXANA plus NSAI, 8 out of 2494 patients (0.3%) had > 500 ms post-baseline QTcF interval value and 50 out of 2494 patients (2%) had > 60 ms QTcF increase from baseline. QTcF prolongation was reversible with dose interruption. The majority of QTcF prolongation occurred within the first four weeks of KRYXANA. There were no reported cases of Torsades de Pointes.

In patients with advanced or metastatic breast cancer (MONALEESA-2, MONALEESA-3, and MONALEESA-7) who received 600 mg KRYXANA plus NSAI or fulvestrant, 15 out of 1054 patients (1.4%) had a > 500 ms post-baseline QTcF value and 61 out of 1054 patients (6%) had a > 60 ms QTcF increase from baseline. QTcF prolongation was reversible with dose interruption. The majority of QTcF prolongation occurred within the first four weeks of KRYXANA. There were no reported cases of Torsades de Pointes.

In MONALEESA-2, in the KRYXANA plus letrozole treatment arm, there was one (0.3%) sudden death in a patient with Grade 3 hypokalemia and Grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3 [see *Adverse Reactions* (6)].

Perform ECG in all patients prior to starting KRYXANA. Initiate treatment with KRYXANA only in patients with QTcF values less than 450 ms. Repeat ECG at approximately Day 14 of the first cycle, and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorous and magnesium) prior to the initiation of KRYXANA at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KRYXANA [see *Dosage and Administration* (2.2)].

5.4 Increased QT Prolongation with Concomitant Use of Tamoxifen

Avoid use of tamoxifen with KRYXANA. In MONALEESA-7, the observed mean QTcF increase from baseline was > 10 ms higher in the tamoxifen plus placebo subgroup compared with the non-steroidal aromatase inhibitors (NSAIs) plus placebo subgroup. In the placebo arm, an increase of > 60 ms from baseline occurred in 6/90 (7%) of patients receiving tamoxifen, and in no patients receiving an NSAI. An increase of > 60 ms from baseline in the QTcF interval was observed in 14/87 (16%) of patients in the KRYXANA and tamoxifen combination and in 18/245 (7%) of patients receiving KRYXANA plus an NSAI [see *Clinical Pharmacology* (12.2)].

5.5 Hepatotoxicity

In patients with early and advanced or metastatic breast cancer, drug-induced liver injury and increases in transaminases occurred with KRYXANA.

In patients with early breast cancer (NATALEE) treated with KRYXANA, drug-induced liver injury was reported in 9 patients (0.4%), of which 5 were Grade ≥ 3 , and 8 had resolved as of the data cutoff. There were 8 (0.3%) clinically confirmed Hy's Law cases (including 4 out of 9 drug-induced liver injury mentioned above), 6 of which had resolved within 303 days and 2 of which were improving, all after discontinuation of KRYXANA. Grade 3 or 4 increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) occurred in 8% and 4.7% respectively; including Grade 4 increases in ALT (1.5%) and AST (0.8%).

In patients with advanced or metastatic breast cancer (MONALEESA-2, MONALEESA-7 and MONALEESA-3) treated with KRYXANA Grade 3 or 4 increases in ALT and AST occurred in 11% and 8%, respectively. Among the patients who had Grade ≥ 3 ALT/AST elevation, the median time-to-onset was 92 days for the KRYXANA plus aromatase inhibitor or fulvestrant treatment arms. The median time to resolution to Grade ≤ 2 was 21 days in the KRYXANA plus aromatase inhibitor or fulvestrant treatment arms. In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than three times the ULN and total bilirubin greater than two times the ULN, with normal alkaline phosphatase, in the absence of cholestasis (Hy's Law) occurred in 6 (1%) patients and all patients recovered after discontinuation of KRYXANA.

Perform liver function tests (LFTs) in all patients before initiating KRYXANA. Monitor LFTs every 2 weeks for first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated [see *Dosage and Administration* (2.2)].

Based on the severity of the transaminase elevations, KRYXANA may require dose interruption, reduction, or discontinuation as described in Table 5 (Dose Modification and Management for Hepatobiliary Toxicity) [see *Dosage and Administration* (2.2)].

5.6 Neutropenia

KRYXANA causes concentration-dependent neutropenia.

In patients with early breast cancer (NATALEE) who received KRYXANA plus NSAI, 94%, including 45% of Grade 3 or 4, had a decrease in neutrophil counts (based on laboratory findings), 63% had an adverse reaction of neutropenia, and 0.3% had febrile neutropenia. The median time to Grade ≥ 2 neutropenia was 18 days. The median time to resolution of Grade ≥ 3 neutropenia to Grade < 3 was 10 days. Treatment discontinuation due to neutropenia was required in 1.1% of patients.

In patients with advanced or metastatic breast cancer (MONALEESA-2, MONALEESA-7, and MONALEESA-3) who received KRYXANA plus NSAI or fulvestrant, 75% had neutropenia, 62% had Grade 3 or 4 decrease in neutrophil count (based on laboratory findings), and 1.7% had febrile neutropenia. The median time to Grade ≥ 2 neutropenia was 17 days. The median time to resolution of Grade ≥ 3 neutropenia to Grade < 3 was 12 days. Treatment discontinuation due to neutropenia was required in 1% of patients.

Perform a complete blood count (CBC) in all patients before initiating KRYXANA. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

Based on the severity of the neutropenia, KRYXANA may require dose interruption, reduction, or discontinuation as described in Table 6 [see *Dosage and Administration* (2.2)].

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, KRYXANA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ribociclib to pregnant rats and rabbits during

organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KRYXANA and for at least 3 weeks after the last dose [see *Use in Specific Populations* (8.1, 8.3), *Clinical Pharmacology* (12.1)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Interstitial Lung Disease/Pneumonitis [see *Warnings and Precautions* (5.1)]
- Severe Cutaneous Adverse Reactions [see *Warnings and Precautions* (5.2)]
- QT Interval Prolongation [see *Warnings and Precautions* (5.3, 5.4)]
- Hepatotoxicity [see *Warnings and Precautions* (5.5)]
- Neutropenia [see *Warnings and Precautions* (5.6)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in WARNINGS AND PRECAUTIONS reflect exposure to KRYXANA plus non-steroidal aromatase inhibitor (NSAI) in 2526 patients with early breast cancer (NATALEE), of whom 51% completed 36 months of KRYXANA treatment. The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were lymphocytes decreased (97%), leukocytes decreased (95%), neutrophils decreased (94%), hemoglobin decreased (47%), alanine aminotransferase increased (45%), aspartate aminotransferase increased (44%), infections (37%), creatinine increased (33%), platelets decreased (28%), headache (23%), nausea (23%), and fatigue (22%).

In addition, the pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to KRYXANA in 1065 patients with advanced or metastatic breast cancer (MONALEESA-2, MONALEESA-3, MONALEESA-7), of whom 76% were exposed for 6 months or longer, and 62% were exposed for greater than one year. The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were leukocytes decreased (95%), neutrophils decreased (93%), hemoglobin decreased (68%), lymphocytes decreased (66%), aspartate aminotransferase increased (55%), gamma-glutamyl transferase increased (53%), alanine aminotransferase increased (52%), infections (47%), nausea (47%), creatinine increased (42%), fatigue (35%), platelets decreased (34%), diarrhea (33%), vomiting (29%), headache (27%), constipation (25%), alopecia (25%), cough (24%), rash (24%), back pain (24%), and glucose serum decreased (20%).

NATALEE: KRYXANA in Combination with a Non-steroidal Aromatase Inhibitor as Adjuvant Treatment

Adults with HR-positive, HER2-negative Stage II and III Early Breast Cancer at High Risk of Recurrence

The safety of KRYXANA was evaluated in NATALEE, a clinical trial of 5101 patients who received KRYXANA plus NSAI or NSAI alone, with or without goserelin [see *Clinical Studies* (14)]. The median duration of exposure to KRYXANA was 33 months.

Serious adverse reactions occurred in 14% of patients who received KRYXANA. Serious adverse reactions in $> 0.5\%$ of patients who received KRYXANA included COVID-19 (1.1%), pneumonia (0.8%), and pulmonary embolism (0.6%).

Fatal adverse reactions occurred in 0.6% of patients who received KRYXANA. Fatal adverse reactions in $\geq 0.1\%$ of patients receiving KRYXANA included COVID-19 or COVID-19 pneumonia (0.2%) and pulmonary embolism (0.1%).

Permanent discontinuation of KRYXANA due to an adverse reaction occurred in 20% of patients. Adverse reactions which resulted in permanent discontinuation of KRYXANA in $\geq 2\%$ of patients were alanine aminotransferase or aspartate aminotransferase increased (8%).

Dosage interruptions of both KRYXANA plus NSAI due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in $\geq 5\%$ of patients included neutropenia or neutrophil count decreased (43%), alanine aminotransferase or aspartate aminotransferase increased (11%), COVID-19 (10%), and hypomagnesemia (5%).

Dose reductions of KRYXANA due to an adverse reaction occurred in 23% of patients. Adverse reactions which required dose reductions in $\geq 2\%$ of patients included neutropenia or neutrophil count decreased (14%) and liver function abnormal (2.3%).

The most common ($\geq 20\%$ on KRYXANA plus NSAID and $\geq 2\%$ higher than placebo) adverse reactions, including laboratory abnormalities, were neutropenia, infections, nausea, headache, fatigue, leukopenia, and abnormal liver function tests.

Table 10 summarizes the adverse reactions in NATALEE.

Table 10: Adverse Reactions ($\geq 10\%$ and $\geq 2\%$ Higher Than NSAID Alone Arm) in NATALEE

Adverse reaction	KRYXANA + NSAID (n = 2526)		NSAID (n = 2441)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations				
Infections ¹	37	2.0	27	0.9
Nervous system disorders				
Headache ²	23	0.4	17	0.2
Gastrointestinal disorders				
Nausea ²	23	0.2	8	0.1
Diarrhea ²	15	0.6	6	0.1
Constipation ²	13	0.2	5	0
Abdominal pain ²	11	0.5	7	0.4
General disorders and administration-site conditions				
Fatigue ²	22	0.8	13	0.2
Asthenia ²	17	0.6	12	0.1
Pyrexia ²	11	0.2	6	0.1
Skin and subcutaneous tissue disorders				
Alopecia	15	0	4.6	0
Respiratory, thoracic, and mediastinal disorders				
Cough ²	13	0.1	8	0.1
Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. ¹ Infections: urinary tract infections; respiratory tract infections. ² Only includes a Grade 3 adverse reaction.				

Clinically relevant adverse reactions reported in $< 10\%$ of patients who received KRYXANA plus NSAID included rash (9%), dizziness (9%), vomiting (8%), peripheral edema (7%), pruritis (7%), dyspnea (7%), stomatitis (6%), oropharyngeal pain (6%), hypocalcemia (5%), hypokalemia (4.8%), decreased appetite (4.8%).

Table 11 summarizes the laboratory abnormalities in NATALEE.

Table 11: Select Laboratory Abnormalities ($\geq 10\%$) in Patients in NATALEE Who Received KRYXANA Plus NSAID

Laboratory abnormality	KRYXANA + NSAID (n = 2526)		NSAID (n = 2441)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Lymphocytes decreased	97	19	88	6
Leukocytes decreased	95	27	45	0.6
Neutrophils decreased	94	45	35	1.7
Hemoglobin decreased	47	0.6	26	0.3
Platelets decreased	28	0.4	13	0.3
Chemistry				
Alanine aminotransferase increased	45	8	35	1
Aspartate aminotransferase increased	44	5	33	1
Creatinine increased	33	0.3	11	0

MONALEESA-2: KRYXANA in Combination with Letrozole

Postmenopausal Women with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy

The safety of KRYXANA was evaluated in MONALEESA-2, a clinical trial of 668 postmenopausal women receiving KRYXANA plus letrozole or placebo plus letrozole [see *Clinical Studies (14)*]. The median duration of exposure to KRYXANA plus letrozole was 13 months with 58% of patients exposed for ≥ 12 months.

Serious adverse reactions occurred in 21% of patients who received KRYXANA plus letrozole. Serious adverse reactions in ≥ 1 % of patients receiving KRYXANA plus letrozole included abdominal pain (1.5%), vomiting (1.5%), constipation (1.2%), nausea (1.2%), anemia (1.2%), febrile neutropenia (1.2%), dyspnea (1.2%), and alanine aminotransferase increased (1.2%).

Fatal adverse reactions occurred in 1.8% of patients who received KRYXANA. Fatal adverse reactions in ≥ 0.1 % of patients receiving KRYXANA included acute respiratory failure (0.6%), acute myocardial infarction, sudden death (with Grade 3 hypokalemia and Grade 2 QT prolongation), unknown cause, and pneumonia (0.3% each). Permanent discontinuation of both KRYXANA and letrozole due to an adverse reaction occurred in 7% of patients. Permanent discontinuation of KRYXANA alone occurred in 7% of patients. Adverse reactions which resulted in permanent discontinuation of both KRYXANA and letrozole in ≥ 2 % of patients were alanine aminotransferase increased (5%), aspartate aminotransferase increased (3%), and vomiting (2%).

Dosage interruptions of both KRYXANA and letrozole due to an adverse reaction occurred in 71% of patients. Adverse reactions which required dosage interruption in ≥ 5 % of patients included neutropenia (39%), neutrophils decreased (12%), vomiting (6%), nausea (5%), alanine aminotransferase increased (5%), and leukocytes decreased (5%).

Dose reductions of KRYXANA due to an adverse reaction occurred in 45% of patients receiving KRYXANA plus letrozole. Adverse reactions which required dose reductions in ≥ 2 % of patients included neutropenia (24%), neutrophils decreased (8%), and alanine aminotransferase increased (3%).

Antiemetics and antidiarrheal medications were used to manage symptoms as clinically indicated.

The most common (≥ 20 % on the KRYXANA arm and ≥ 2 % higher than placebo) adverse reactions, including laboratory abnormalities, were neutrophils decreased, leukocytes decreased, hemoglobin decreased, nausea, lymphocytes decreased, alanine aminotransferase increased, aspartate aminotransferase increased, fatigue, diarrhea, alopecia, vomiting, platelets decreased, constipation, headache, and back pain.

Table 12 summarizes the adverse reactions in MONALEESA-2.

Table 12: Adverse Reactions (≥ 10 % and ≥ 2 % Higher Than Placebo Arm) in MONALEESA-2

Adverse reaction	KRYXANA + Letrozole (n = 334)		Placebo + Letrozole (n = 330)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea ¹	52	2.4	29	0.6
Diarrhea ¹	35	1.2	22	0.9
Vomiting ¹	29	3.6	16	0.9
Constipation ¹	25	1.2	19	0
Stomatitis ¹	12	0.3	7	0
Abdominal pain ¹	11	1.2	8	0
General disorders and administration-site conditions				
Fatigue	37	2.4	30	0.9
Pyrexia ¹	13	0.3	6	0
Peripheral edema ¹	12	0	10	0
Skin and subcutaneous tissue disorders				
Alopecia ¹	33	0	16	0
Rash ¹	17	0.6	8	0
Pruritus ¹	14	0.6	6	0
Nervous system disorders				
Headache ¹	22	0.3	19	0.3

Insomnia ¹	12	0.3	9	0
Musculoskeletal and connective tissue disorders				
Back pain ¹	20	2.1	18	0.3
Metabolism and nutrition disorders				
Decreased appetite ¹	19	1.5	15	0.3
Respiratory, thoracic and mediastinal disorders				
Dyspnea ¹	12	1.2	9	0.6
Infections and infestations				
Urinary tract infections ¹	11	0.6	8	0
Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.				
¹ Only includes a Grade 3 adverse reaction.				

Clinically relevant adverse reactions in < 10% of patients in MONALEESA-2 receiving KRYXANA plus letrozole included interstitial lung disease (0.3%), lung infiltration (0.3%), pneumonitis (0.3%), and pulmonary fibrosis (0.6%). Table 13 summarizes the laboratory abnormalities in MONALEESA-2.

Table 13: Select Laboratory Abnormalities (≥ 10%) in Patients in MONALEESA-2 Who Received KRYXANA Plus Letrozole

Laboratory abnormality	KRYXANA + Letrozole (n = 334)		Placebo + Letrozole (n = 330)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Leukocytes decreased	93	34	29	1.5
Neutrophils decreased	93	60	24	1.2
Hemoglobin decreased	57	1.8	26	1.2
Lymphocytes decreased	51	14	22	3.9
Platelets decreased	29	0.9	6	0.3
Chemistry				
Alanine aminotransferase increased	46	10	36	1.2
Aspartate aminotransferase increased	44	7	32	1.5
Creatinine increased	20	0.6	6	0
Phosphorous decreased	13	5	4	0.6
Potassium decreased	11	1.2	7	1.2

MONALEESA-7: KRYXANA in Combination with a Non-Steroidal Aromatase Inhibitor

Pre/perimenopausal Patients with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy

The safety of KRYXANA was evaluated in MONALEESA-7, a clinical trial of 672 pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KRYXANA plus a NSAID or tamoxifen plus goserelin or placebo plus NSAID or tamoxifen plus goserelin [see *Clinical Studies* (14)]. The median duration of exposure in the KRYXANA plus a NSAID arm was 15.2 months with 66% of patients exposed for ≥ 12 months. The safety data reported below are based on 495 pre/perimenopausal patients receiving KRYXANA plus NSAID plus goserelin or placebo plus NSAID plus goserelin.

Serious adverse reactions occurred in 17% of patients who received KRYXANA plus NSAID plus goserelin. Serious adverse reactions in ≥ 1% of patients receiving KRYXANA plus NSAID plus goserelin included drug-induced liver injury (1.6%), abdominal pain (1.2%), dyspnea (1.2%), febrile neutropenia (1.2%), and back pain (1.2%).

Permanent discontinuation of both KRYXANA and NSAID due to an adverse reaction occurred in 3% of patients. Permanent discontinuation of KRYXANA alone occurred in 3% of patients. Adverse reactions which resulted in permanent discontinuation of both KRYXANA and NSAID in ≥ 2% of patients were alanine aminotransferase increased (2%), and aspartate aminotransferase increased (2%).

Dosage interruptions of KRYXANA plus NSAID plus goserelin due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in ≥ 5% of patients included neutropenia (41%), neutrophils decreased (26%), and leukocytes decreased (6%).

Dose reductions of KRYXANA due to an adverse reaction occurred in 33% of patients receiving KRYXANA plus NSAI plus goserelin. Adverse reactions which required dose reductions in $\geq 2\%$ of patients included neutropenia (17%), neutrophils decreased (5%), and alanine aminotransferase increased (2%).

The most common ($\geq 20\%$ on the KRYXANA arm and $\geq 2\%$ higher than placebo) adverse reactions, including laboratory abnormalities, were leukocytes decreased, neutrophils decreased, hemoglobin decreased, lymphocytes decreased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, infections, arthralgia, alanine aminotransferase increased, nausea, platelets decreased, and alopecia.

Table 14 summarizes the adverse reactions in MONALEESA-7.

Table 14: Adverse Reactions Occurring in $\geq 10\%$ and $\geq 2\%$ Higher Than Placebo Arm in MONALEESA-7 (NSAI) (All Grades)

Adverse reaction	KRYXANA + NSAI + Goserelin (n = 248)		Placebo + NSAI + Goserelin (n = 247)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations				
Infections ^{1,2}	36	1.6	24	0.4
Musculoskeletal and connective tissue disorders				
Arthralgia ²	34	0.8	29	1.2
Gastrointestinal disorders				
Nausea ²	32	0	20	0
Constipation ²	16	0	12	0
Stomatitis ²	10	0	8	0.4
Skin and subcutaneous tissue disorders				
Alopecia ²	21	0	13	0
Rash ²	17	0.4	9	0
Pruritus ²	11	0	4	0
General disorders and administration-Site Conditions				
Pyrexia ²	17	0.8	7	0
Pain in extremity ²	10	0	8	1.2
Respiratory, thoracic and mediastinal disorders				
Cough ²	15	0	10	0
Abbreviation: NSAI, non-steroidal aromatase inhibitor. Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. ¹ Infections: urinary tract infections; respiratory tract infections, gastroenteritis, sepsis (< 1%). ² Only includes a Grade 3 adverse reactions.				

Clinically relevant adverse reactions in < 10% of patients in MONALEESA-7 receiving KRYXANA plus NSAI included thrombocytopenia (9%), dry skin (9%), oropharyngeal pain (7%), dyspepsia (5%), lacrimation increased (4%), dry eye (4%), vitiligo (3%), hypocalcemia, (2%), blood bilirubin increased (1%), syncope (0.4%), and pneumonitis (0.4%).

Table 15: Select Laboratory Abnormalities ($\geq 10\%$) in Patients in MONALEESA-7 Who Received KRYXANA Plus NSAI Plus Goserelin

Laboratory abnormality	KRYXANA + NSAI + Goserelin (n = 248)		Placebo + NSAI + Goserelin (n = 247)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Leukocytes decreased	93	36	30	0.8
Neutrophils decreased	92	63	27	2.4
Hemoglobin decreased	84	2.4	51	0.4
Lymphocytes decreased	55	14	18	2.8
Platelets decreased	26	0.4	9	0.4

Chemistry				
Gamma-glutamyl transferase increased	42	7	42	9
Aspartate aminotransferase increased	37	4.8	35	1.6
Alanine aminotransferase increased	33	6	31	1.6
Phosphorous decreased	14	1.6	11	0.8
Potassium decreased	11	1.2	14	1.2
Glucose serum decreased	10	0.4	10	0.4
Creatinine increased	8	0	2	0

MONALEESA-3: KRYXANA in Combination with Fulvestrant

Postmenopausal Patients with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy or After Disease Progression on Endocrine Therapy

The safety of KRYXANA was evaluated in MONALEESA-3, a clinical trial of 724 postmenopausal women receiving KRYXANA plus fulvestrant or placebo plus fulvestrant [see *Clinical Studies (14)*]. The median duration of exposure to KRYXANA plus fulvestrant was 15.8 months with 58% of patients exposed for ≥ 12 months.

Serious adverse reactions occurred in 29% of patients who received KRYXANA plus fulvestrant. Serious adverse reactions in $\geq 1\%$ of patients receiving KRYXANA plus fulvestrant included pneumonia (1.9%), nausea (1.4%), vomiting (1.4%), anemia (1.2%), dyspnea (1.2%), neutropenia (1.2%). One case (0.2%) of fatal adverse reaction (pneumonia) occurred in patients who received KRYXANA plus fulvestrant.

Fatal adverse reactions occurred in 1.2% of patients who received KRYXANA. Fatal adverse reactions in $\geq 0.1\%$ of patients receiving KRYXANA included cardiac failure, ventricular arrhythmia, pneumonia, acute respiratory distress, pulmonary embolism, and hemorrhagic shock (0.2% each). Permanent discontinuation of both KRYXANA and fulvestrant due to an adverse reaction occurred in 8% of patients. Permanent discontinuation of KRYXANA alone occurred in 9% of patients. Adverse reactions which resulted in permanent discontinuation of both KRYXANA and fulvestrant in $\geq 2\%$ of patients were alanine aminotransferase increased (5%), and aspartate aminotransferase increased (3%).

Dosage interruptions of KRYXANA plus fulvestrant due to an adverse reaction occurred in 72% of patients. Adverse reactions which required dosage interruption in $\geq 5\%$ of patients included neutropenia (40%), neutrophils decreased (13%), alanine aminotransferase increased (8%), aspartate aminotransferase increased (8%), and leukocytes decreased (5%).

Dose reductions of KRYXANA due to an adverse reaction occurred in 32% of patients receiving KRYXANA plus fulvestrant. Adverse reactions which required dose reductions in $\geq 2\%$ of patients included neutropenia (15%), and neutrophils decreased (3%).

The most common ($\geq 20\%$ on the KRYXANA arm and $\geq 2\%$ higher than placebo) adverse reactions, including laboratory abnormalities, were leukocytes decreased, neutrophils decreased, lymphocytes decreased, creatinine increased, hemoglobin decreased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, nausea, alanine aminotransferase increased, infections, platelets decreased, diarrhea, vomiting, constipation, glucose serum decreased, cough, rash, and pruritus.

Table 16 summarizes the adverse reactions in MONALEESA-3.

Table 16: Adverse Reactions ($\geq 10\%$ and $\geq 2\%$ Higher Than Placebo Arm) in MONALEESA-3

Adverse reaction	KRYXANA + Fulvestrant (n = 483)		Placebo + Fulvestrant (n = 241)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea ²	45	1.4	28	0.8
Diarrhea ²	29	0.6	20	0.8
Vomiting ²	27	1.4	13	0
Constipation ²	25	0.8	12	0

Abdominal pain ²	17	1.4	13	0.8
Infections and infestations				
Infections ^{1;2;3}	42	4.6	30	1.7
Skin and subcutaneous tissue disorders				
Rash ²	23	0.8	8	0
Pruritus ²	20	0.2	7	0
Alopecia ²	19	0	5	0
Respiratory, thoracic and mediastinal disorders				
Cough ²	22	0	15	0
Dyspnea	15	1.4	12	1.7
Metabolism and nutrition disorders				
Decreased appetite ²	16	0.2	13	0
General disorders and administration-site conditions				
Peripheral edema ²	15	0	7	0
Pyrexia ²	11	0.2	7	0
Nervous system disorders				
Dizziness ²	13	0.2	8	0
Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. ¹ Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (1%). ² Only include Grade 3 adverse reactions. ³ Includes the following fatal adverse reactions: pneumonia (n = 1).				

Clinically relevant adverse reactions in < 10% of patients in MONALEESA-3 receiving KRYXANA plus fulvestrant included thrombocytopenia (9%) dry skin (8%), dysgeusia (7%), dry mouth (5%), vertigo (5%), dry eye (5%), lacrimation increased (4%), erythema (4%), hypocalcemia (4%), blood bilirubin increased (1%), syncope (1%), interstitial lung disease (0.4%), pneumonitis (0.4%), hypersensitivity pneumonitis (0.2%), and acute respiratory distress syndrome (0.2%).

Table 17: Select Laboratory Abnormalities (≥ 10%) in Patients in MONALEESA-3 Who Received KRYXANA Plus Fulvestrant

Laboratory abnormality	KRYXANA + Fulvestrant (n = 483)		Placebo + Fulvestrant (n = 241)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Leukocytes decreased	95	26	26	0.4
Neutrophils decreased	92	53	21	0.8
Lymphocytes decreased	69	16	35	4.1
Hemoglobin decreased	60	4.3	35	2.9
Platelets decreased	33	1.9	11	0
Chemistry				
Creatinine increased	65	1	33	0.4
Gamma-glutamyl transferase increased	52	8	49	10
Aspartate aminotransferase increased	50	7	43	2.9
Alanine aminotransferase increased	44	11	37	1.7
Glucose serum decreased	23	0	18	0
Phosphorous decreased	18	4.6	8	0.8
Albumin decreased	12	0	8	0

COMPLEEMENT-1: KRYXANA in Combination with Letrozole and Goserelin or Leuprolide

Men with HR-positive, HER2-negative Advanced Breast Cancer for Initial Endocrine-Based Therapy

The safety of KRYXANA in combination with letrozole was evaluated in men (n = 39) in an open-label, multicenter clinical trial for the treatment of adult patients with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease (COMPLEEMENT-1) [see Clinical Studies (14)].

The median duration of exposure to KRYXANA was 20.8 months (range, 0.5 to 30.6 months).

Other adverse reactions occurring in men treated with KRYXANA plus letrozole and goserelin or leuprolide were similar to those occurring in women treated with KRYXANA plus endocrine therapy.

6.2 Postmarketing Experience

The following adverse events have been reported during post-approval use of KRYXANA. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory disorders: Interstitial lung disease/pneumonitis

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia, and systemic symptoms (DRESS)

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Ribociclib Plasma Concentrations

CYP3A4 Inhibitors

Coadministration of strong CYP3A inhibitors increases ribociclib exposure [see *Clinical Pharmacology* (12.3)]. Increased ribociclib concentrations may increase the incidence and severity of adverse reactions, including QTcF prolongation [see *Warnings and Precautions* (5.3)]. Avoid concomitant use of strong CYP3A inhibitors with KRYXANA and consider alternative concomitant medications with less potential for CYP3A inhibition.

In patients with early breast cancer, if coadministration of KRYXANA with a strong CYP3A inhibitor cannot be avoided, reduce the dose of KRYXANA to 200 mg once daily. In patients with advanced or metastatic breast cancer, if coadministration of KRYXANA with a strong CYP3A inhibitor cannot be avoided, reduce the dose of KRYXANA to 400 mg once daily [see *Dosage and Administration* (2.2)].

7.2 Drugs That May Decrease Ribociclib Plasma Concentrations

CYP3A Inducers

Coadministration of strong CYP3A inducers decreases the plasma exposure of ribociclib [see *Clinical Pharmacology* (12.3)]. Avoid concomitant use of strong CYP3A inducers and consider an alternate concomitant medication with no or minimal potential to induce CYP3A.

7.3 Effect of KRYXANA on Other Drugs

CYP3A Substrates

Coadministration of sensitive CYP3A4 substrates with multiple doses of KRYXANA increases the substrate exposure [see *Clinical Pharmacology* (12.3)]. For CYP3A substrates where minimal increases in the concentration may increase CYP3A substrate adverse reactions, monitor for increased adverse reactions of the CYP3A substrate during treatment with KRYXANA. The dose of the sensitive CYP3A substrate may need to be reduced as KRYXANA can increase its exposure.

7.4 Drugs That Prolong the QT Interval

Avoid coadministration of KRYXANA with products with a known potential to prolong QT interval, such as antiarrhythmic drugs and other drugs that are known to prolong the QT interval. If concomitant use cannot be avoided, monitor ECG when initiating, during concomitant use, and as clinically indicated [see *Warnings and Precautions* (5.3), *Clinical Pharmacology* (12.2)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, KRYXANA can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology* (12.1)].

There are no available human data informing the drug-associated risk. In animal reproduction studies, administration of ribociclib to pregnant animals during organogenesis resulted in increased incidences of post implantation loss and reduced fetal weights in rats and increased incidences of fetal abnormalities in rabbits at exposures 0.6 or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC (*see Data*). Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies in the U.S. general population.

Data

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ribociclib up to 1000 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis.

In rats, 300 mg/kg/day resulted in reduced maternal body weight gain and reduced fetal weights accompanied by skeletal changes related to the lower fetal weights. There were no significant effects on embryo-fetal viability or fetal morphology at 50 or 300 mg/kg/day.

In rabbits at doses ≥ 30 mg/kg/day, there were adverse effects on embryo-fetal development, including increased incidences of fetal abnormalities (malformations and external, visceral, and skeletal variants) and fetal growth (lower fetal weights). These findings included reduced/small lung lobes, additional vessel on the descending aorta, additional vessel on the aortic arch, small eyes, diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes, reduced/small accessory lung lobe, extra/rudimentary 13th ribs, misshapen hyoid bone, bent hyoid bone alae, and reduced number of phalanges in the pollex. There was no evidence of increased incidence of embryo-fetal mortality. There was no maternal toxicity observed at 30 mg/kg/day.

At 300 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal systemic exposures (AUC) were approximately 0.6 and 1.5 times, respectively, the exposure in patients at the highest recommended dose of 600 mg/day.

8.2 Lactation

Risk Summary

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breastfed infant or on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse reactions in breastfed infants from KRYXANA, advise lactating women not to breastfeed while taking KRYXANA and for at least 3 weeks after the last dose.

Data

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

8.3 Females and Males of Reproductive Potential

Based on animal studies and mechanism of action, KRYXANA can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to starting treatment with KRYXANA.

Contraception

Females

Advise females of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with KRYXANA and for at least 3 weeks after the last dose.

Infertility

Males

Based on animal studies, KRYXANA may impair fertility in males of reproductive potential [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and efficacy of KRYXANA in pediatric patients has not been established.

8.5 Geriatric Use

Of the 2549 adults with early breast cancer who received KRYXANA in NATALEE, 407 patients (16%) were ≥ 65 years of age and 123 patients (2.4%) were ≥ 75 years of age. No overall differences in safety or effectiveness of KRYXANA were observed between older and younger adults with early breast cancer.

Of 334 patients with advanced or metastatic breast cancer who received KRYXANA in MONALEESA-2, 150 patients (45%) were ≥ 65 years of age and 35 patients (11%) were ≥ 75 years of age. Of 484 patients with advanced or metastatic breast cancer who received KRYXANA in MONALEESA-3, 226 patients (47%) were ≥ 65 years of age and 65 patients (14%) were ≥ 75 years of age. Of 248 patients with advanced or metastatic breast cancer who received KRYXANA in MONALEESA-7, no patients were ≥ 65 years of age. No overall differences in safety or effectiveness of KRYXANA were observed between older and younger adults with advanced or metastatic breast cancer.

8.6 Hepatic Impairment

No dose adjustment is necessary in patients with breast cancer who have mild hepatic impairment (Child-Pugh class A) [see *Clinical Pharmacology (12.3)*]. A reduced starting dose of 400 mg is recommended in patients with advanced or metastatic breast cancer who have moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) [see *Dosage and Administration (2.2)*].

8.7 Renal Impairment

No dose adjustment is necessary in patients with breast cancer who have mild to moderate (30 mL/min to $89 \text{ mL/min/1.73 m}^2 \leq$ estimated glomerular filtration rate (eGFR)) renal impairment. A reduced starting dose of 200 mg is recommended in patients with breast cancer who have severe renal impairment [see *Dosage and Administration (2.2)*, *Clinical Pharmacology (12.3)*].

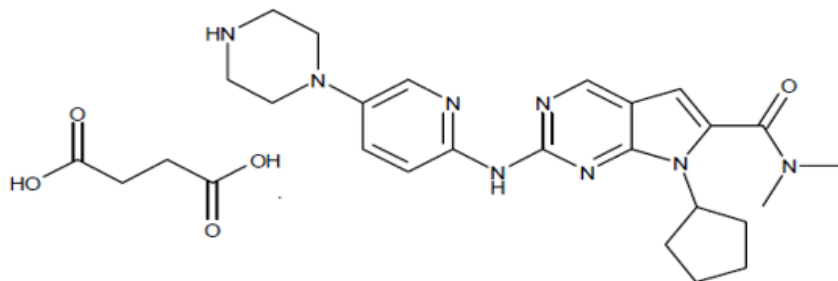
11 DESCRIPTION

KRYXANA (ribociclib) is a kinase inhibitor.

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

Ribociclib succinate is a light yellow to yellowish brown crystalline powder. The molecular formula for ribociclib succinate is $\text{C}_{23}\text{H}_{30}\text{N}_8\text{O} \cdot \text{C}_4\text{H}_6\text{O}_4$ and the molecular weight is 552.64 g/mol (*Free base: 434.55 g/mol*).

The chemical structure of ribociclib is shown below:



KRYXANA film-coated tablets are supplied for oral use and contain 200 mg of ribociclib free base (equivalent to 254.40 mg ribociclib succinate). The tablets also contain colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, magnesium stearate and microcrystalline cellulose. The film-coating contains iron oxide black, iron oxide red, lecithin (soya), polyvinyl alcohol (partially hydrolysed), talc, titanium dioxide, and xanthan gum as inactive ingredients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ribociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and are downstream of signaling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb).

In vitro, ribociclib decreased pRb phosphorylation, resulting in arrest in the G1 phase of the cell cycle and reduced proliferation in breast cancer-derived models. *In vivo*, treatment with single agent ribociclib in a rat xenograft model with human tumor cells led to decreased tumor volumes, which correlated with inhibition of pRb phosphorylation. In studies using patient-derived estrogen receptor positive breast cancer xenograft models, combination of ribociclib and antiestrogen (e.g., letrozole) therapies resulted in increased tumor growth inhibition compared to each drug alone. Additionally, the combination of ribociclib and fulvestrant resulted in tumor growth inhibition in an estrogen receptor positive breast cancer xenograft model.

12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of KRYXANA have not been fully characterized in patients.

Cardiac Electrophysiology

A concentration-QT analysis of the data in patients with breast cancer treated with KRYXANA at doses ranging from 50 to 1200 mg (0.083 to 2 times of the approved recommended high dose) suggested that ribociclib causes concentration-dependent increases in QTcF interval [see *Warnings and Precautions* (5.3, 5.4)].

In patients with early breast cancer, the estimated mean QTcF interval change from baseline for the KRYXANA 400 mg in combination with non-steroidal aromatase inhibitor (NSAI) was 10.0 ms (90% CI: 8.0, 11.9) at the mean steady-state C_{max} [see *Warnings and Precautions* (5.3, 5.4)].

In patients with advanced or metastatic breast cancer the estimated mean QTcF interval change from baseline for the KRYXANA 600 mg in combination with aromatase inhibitors or fulvestrant was 22.0 ms (90% CI: 20.6, 23.4) and 23.7 ms (90% CI: 22.3, 25.1), respectively, and was 34.7 ms (90% CI: 31.6, 37.8) in combination with tamoxifen at the mean steady-state C_{max} [see *Warnings and Precautions* (5.3, 5.4)].

12.3 Pharmacokinetics

Ribociclib exhibited over-proportional increases in exposure (C_{max} and AUC) across the dose range of 50 mg to 1200 mg (0.083 to 2 times of the approved recommended high dose) following both single dose and repeated doses of KRYXANA. Following repeated 600 mg once daily administration, steady-state was generally achieved after 8 days and ribociclib accumulated with a mean accumulation ratio of 2.5 (range, 0.97 to 6.4), and mean (coefficient of variation (CV%)) steady-state ribociclib C_{max} was 1820 (62%) ng/mL and AUC was 23800 (66%) ng*h/mL.

Absorption

The T_{max} following KRYXANA administration was between 1 and 4 hours. The mean absolute bioavailability of ribociclib after a single oral dose of 600 mg was 65.8%.

Food Effect: Compared to the fasted state, oral administration of a single 600 mg dose of KRYXANA film-coated tablet with a high-fat, high-calorie meal (approximately 800 to 1000 calories with ~50% calories from fat, ~35% calories from carbohydrates, and ~15% calories from protein) had no clinically meaningful differences in ribociclib C_{max} or AUC_{inf}.

Distribution

Ribociclib protein binding *in vitro* was approximately 70% and independent of concentration (10 to 10,000 ng/mL). The mean *in vivo* blood-to-plasma ratio was 1.04. The apparent volume of distribution at steady-state (V_{ss}/F) was 1090 L.

Metabolism

Ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of radio-labeled ribociclib to humans, the primary metabolic pathways for ribociclib involved oxidation (dealkylation, C and/or N-oxygenation, oxidation (-2H)) and combinations thereof. Ribociclib was the major circulating drug-derived entity in plasma (44%). The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide), each representing an estimated 9%,

9%, and 8% of total radioactivity, and 22%, 20%, and 18% of ribociclib exposure. Clinical activity of ribociclib was due primarily to parent drug, with negligible contribution from circulating metabolites.

Ribociclib was extensively metabolized with unchanged drug accounting for 17% and 12% in feces and urine, respectively. Metabolite LEQ803 represented approximately 14% and 4% of the administered dose in feces and urine, respectively.

Elimination

The mean plasma effective half-life (CV%) was 32.0 hours (63%) and the mean apparent oral clearance (CL/F) was 25.5 L/hr (66%) at steady-state following 600 mg dose of KRYXANA in patients with advanced cancer. The steady state mean CL/F was 38.4 L/hr following the 400 mg dose of KRYXANA in patients with early breast cancer.

The mean apparent plasma terminal half-life of ribociclib ranged from 29.7 to 54.7 hours and mean CL/F of ribociclib ranged from 39.9 to 77.5 L/hr at 600 mg across studies in healthy adults.

Following a single oral dose of radio-labeled ribociclib in healthy adults, 92% of the total administered radioactive dose was recovered within 22 days; 69% in feces and 23% in urine.

Specific Populations

Patients with Hepatic Impairment

Compared to adults with normal hepatic function, mild (Child-Pugh class A) hepatic impairment had no effect on the exposure of ribociclib; while in adults with moderate (Child-Pugh class B) hepatic impairment, the mean ratio was 1.44 for C_{max} and 1.28 for AUC_{inf} ; and in adults with severe (Child-Pugh class C) hepatic impairment, the mean ratio was 1.32 for C_{max} and 1.29 for AUC_{inf} .

Patients with Renal Impairment

In adults with severe renal impairment and ESRD, ribociclib AUC_{inf} increased 2.4-fold and 3.8-fold, and C_{max} increased 2.1-fold and 2.7-fold relative to the exposure in adults with normal renal function.

Mild or moderate renal impairment had no effect on the exposure of ribociclib. A sub-group analysis of data from studies following oral administration of KRYXANA in patients with advanced cancer or early breast cancer who have mild to moderate renal impairment, AUC and C_{max} were comparable to those in patients with normal renal function, suggesting no clinically meaningful effect of mild or moderate renal impairment on ribociclib exposure.

Effect of Age, Weight, Gender, and Race

No clinically relevant effects of age, body weight, gender, or race on the systemic exposure of ribociclib were identified.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Drugs That Affect Ribociclib Plasma Concentrations

CYP3A Inhibitors: Following a single 400 mg dose of KRYXANA with ritonavir (a strong CYP3A inhibitor), ritonavir (100 mg twice a day for 14 days) increased ribociclib C_{max} and AUC_{inf} by 1.7-fold and 3.2-fold, respectively, compared to ribociclib alone. C_{max} and AUC for LEQ803 (a prominent metabolite of ribociclib, accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively. A moderate CYP3A4 inhibitor (erythromycin) is predicted to increase ribociclib steady-state C_{max} and AUC by 1.1-fold and 1.2-fold, respectively, following KRYXANA 400 mg once daily, and 1.1-fold and 1.1-fold, respectively, following KRYXANA 600 mg once daily.

CYP3A Inducers: Following a single 600 mg dose of KRYXANA with rifampicin (a strong CYP3A4 inducer) at 600 mg daily for 14 days, ribociclib C_{max} decreased by 81% and AUC_{inf} decreased by 89%, while LEQ803 C_{max} increased 1.7-fold and AUC_{inf} decreased by 27% compared to ribociclib alone. A moderate CYP3A inducer (efavirenz) is predicted to decrease ribociclib steady-state C_{max} by 55% and AUC by 74%, following KRYXANA 400 mg once daily, and by 52% and 71%, respectively, following KRYXANA 600 mg once daily.

Drugs That are Affected by KRYXANA

CYP3A4 and CYP1A2 Substrates: In a cocktail study with midazolam (sensitive CYP3A4 substrate) multiple doses of ribociclib (400 mg once daily for 8 days) increased midazolam C_{max} by 2.1-fold and increased AUC_{inf} by 3.8-fold compared to midazolam alone. Administration of KRYXANA 600 mg once daily is predicted to increase midazolam C_{max}

and AUC by 2.4-fold and 5.2-fold, respectively. The effect of multiple doses of 400 mg ribociclib on caffeine (sensitive CYP1A2 substrate) was minimal, with $C_{\max}$ decreased by 10% and AUC_{inf} increased by 20%. Only weak inhibitory effects on CYP1A2 substrates are predicted at KRYXANA 600 mg once daily dose.

Gastric pH-Elevating Agents: Coadministration of ribociclib with drugs that elevate the gastric pH is not predicted to alter ribociclib absorption.

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

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

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

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

Tamoxifen: KRYXANA is not indicated for concomitant use with tamoxifen. Data from a clinical trial in patients with breast cancer indicated that tamoxifen $C_{\max}$ and AUC increased approximately 2-fold following coadministration of KRYXANA 600 mg.

In vitro Studies

Effect of Ribociclib on CYP Enzymes: *In vitro*, ribociclib was 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. It has no potential for time-dependent inhibition of CYP1A2, CYP2C9, and CYP2D6, and no induction of CYP1A2, CYP2B6, CYP2C9, and CYP3A4 at clinically relevant concentrations.

Effect of Ribociclib on Transporters: *In vitro* evaluations indicated that ribociclib has a low potential to inhibit the activities of drug transporters P-gp, OATP1B1/B3, OCT1, MATEK2 at clinically relevant concentrations. Ribociclib may inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations.

Effect of Transporters on Ribociclib: Based on *in vitro* data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of ribociclib at therapeutic doses. Ribociclib is not a substrate for hepatic uptake transporters OATP1B1/1B3 or OCT1 *in vitro*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study with oral administration of ribociclib daily in cycles of 3 weeks on/1 week off, ribociclib was not carcinogenic at doses up to 50 mg/kg in male rats and 600 mg/kg in female rats. Systemic exposure in male and female rats were 1.3 and 1.8 times, respectively, the human exposure at the highest recommended dose of 600 mg/day based on AUC.

Ribociclib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay or an *in vivo* rat bone marrow micronucleus assay.

In a fertility and early embryonic development study, female rats received oral doses of ribociclib for 14 days prior to mating through the first week of pregnancy. Ribociclib did not affect reproductive function, fertility or early embryonic development at doses up to 300 mg/kg/day (approximately 0.6 times the clinical exposure in patients at the highest recommended dose of 600 mg/day based on AUC).

A fertility study in male rats has not been performed with ribociclib. In repeat-dose toxicity studies with oral administration of ribociclib daily for 3 weeks on/1 week off in rats up to 26 weeks duration and dogs up to 39 weeks duration, atrophic changes in testes were reported. Findings included degeneration of seminiferous tubular epithelia in the testes and hypospermia and luminal cellular debris in the epididymides of rats and dogs and vacuolation of epithelia in the epididymides of rats. These findings were observed at doses ≥ 75 mg/kg in rats and ≥ 1 mg/kg in dogs which resulted in systemic exposures that were 1.4 and 0.03 times the human exposure at the highest recommended daily dose of 600 mg/day based on AUC, respectively. These effects can be linked to a direct anti-proliferative effect on the testicular germ

cells resulting in atrophy of the seminiferous tubules and showed a trend towards reversibility in rats and dogs after a four-week non-dosing period.

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Early Breast Cancer

NATALEE: KRYXANA in Combination with a Non-steroidal Aromatase Inhibitor (NSAI) with or without Goserelin

Adults with HR-positive, HER2-negative Stage II and III Early Breast Cancer at High Risk of Recurrence

NATALEE (NCT03701334) was a randomized (1:1), open-label, multicenter study in adults (N=5101) with HR-positive, HER2-negative early breast cancer that was:

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

Applying TNM criteria, NATALEE included patients with any lymph node involvement (excluding microscopic nodal involvement), or if no nodal involvement either tumor size > 5 cm, or tumor size 2 to 5 cm with either Grade 2 (and high genomic risk or Ki67 ≥ 20%) or Grade 3.

Participants were randomized to receive KRYXANA 400 mg plus a non-steroidal aromatase inhibitor (NSAI, letrozole or anastrozole) or NSAI only, and goserelin as indicated. Randomization was stratified by Anatomic Stage, prior treatment (neoadjuvant versus adjuvant chemotherapy), menopausal status (premenopausal and males versus postmenopausal) and region (North America/Western Europe/Oceania versus rest of the world).

The main efficacy outcome measure was invasive disease-free survival (iDFS). iDFS was defined as the time from randomization 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). Overall survival (OS) was an additional outcome measure.

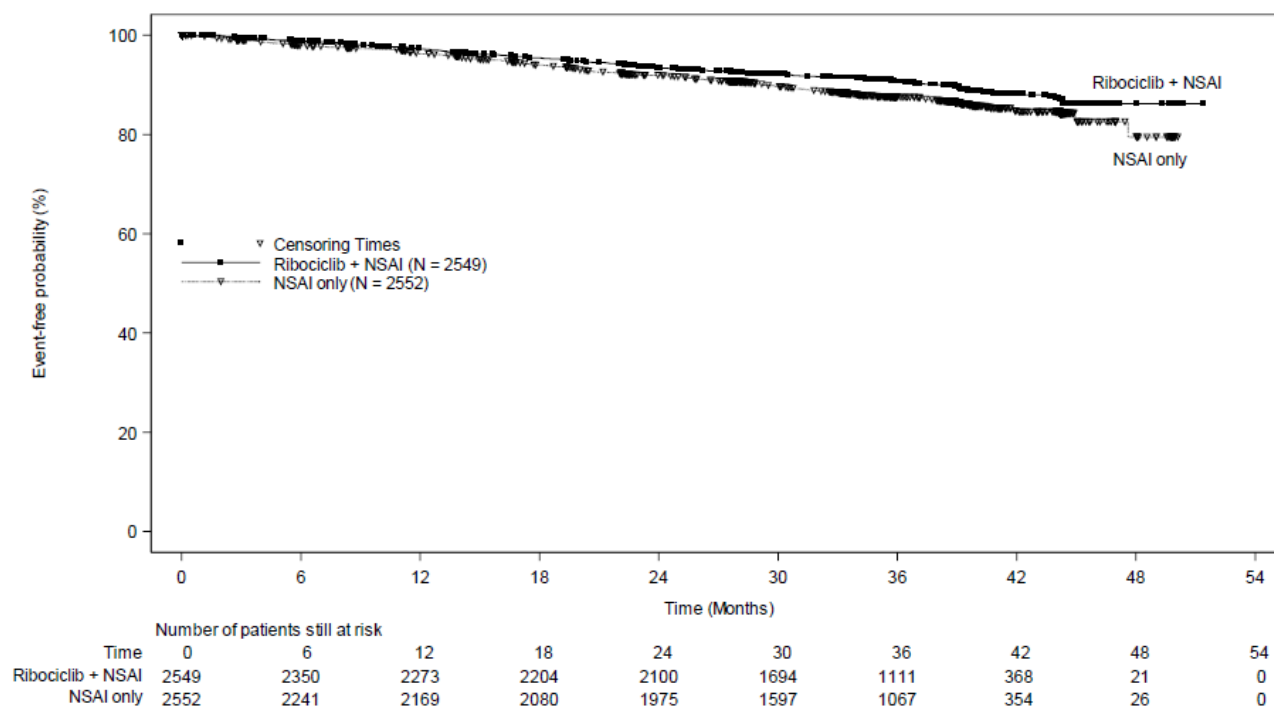
KRYXANA was given orally at a dose of 400 mg once daily for 21 consecutive days followed by 7 days off treatment in combination with letrozole 2.5 mg or anastrozole 1 mg orally once daily for 28 days; goserelin 3.6 mg was administered on Day 1 of each 28-day cycle. KRYXANA was administered for up to 36 months in the absence of recurrence or unacceptable toxicity. NSAI was administered for at least 5 years.

The median age was 52 years (range, 24 to 90); >99% women (n=19 men); 73% White, 13% Asian, 1.7% Black or African American, <0.1% Native Hawaiian or other Pacific Islander, <0.1% American Indian or Alaskan Native; 8.5% Hispanic or Latino; 99% ECOG 0-1; 88% node positive disease; 88% received prior (neo)adjuvant chemotherapy.

A statistically significant improvement in iDFS was observed in the intent-to-treat (ITT) population at an interim analysis. The efficacy results at the time of the final iDFS analysis are summarized in Table 18 and Figure 1. At the time of the iDFS final analysis, OS was immature, and a total of 172 (3.5%) of patients had died across both study arms.

Table 18: Efficacy Results – NATALEE (Investigator Assessment, Intent-to-Treat Population)

	KRYXANA + NSAI +/- Goserelin	NSAI +/- Goserelin
Invasive Disease-Free Survival (iDFS)^a	N = 2549	N = 2552
Events (n, %)	226 (8.9)	283 (11.1)
Hazard ratio (95% CI)	0.749 (0.628, 0.892)	
iDFS at 36 months (%, 95% CI)	90.7 (89.3, 91.8)	87.6 (86.1, 88.9)
Abbreviations: CI, confidence interval; iDFS, invasive disease-free survival.		
^a iDFS was statistically significant at an interim analysis based on a one-sided stratified log-rank p-value of 0.0014.		

Figure 1: Kaplan-Meier Plot of iDFS – NATALEE (Investigator Assessment, Intent-to-Treat Population)

14.2 Advanced or Metastatic Breast Cancer

MONALEESA-2: KRYXANA in Combination with Letrozole

Postmenopausal Women with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy

MONALEESA-2 (NCT01958021) was a randomized (1:1), double-blind, placebo-controlled, multicenter clinical study of KRYXANA plus letrozole vs. placebo plus letrozole conducted in postmenopausal women (N=668) with HR-positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease.

Participants were randomized to receive either KRYXANA plus letrozole or placebo plus letrozole, stratified according to the presence of liver and/or lung metastases. Letrozole 2.5 mg was given orally once daily for 28 days, with either KRYXANA 600 mg or placebo orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. The major efficacy outcome measure for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The median age was 62 years (range, 23 to 91) and 45% of patients were older than 65. The majority of patients were White (82%), and all patients had an ECOG performance status of 0 or 1. A total of 47% of patients had received chemotherapy and 51% had received antihormonal therapy in the neoadjuvant or adjuvant setting. Thirty-four percent (34%) of patients had *de novo* metastatic disease, 21% had bone only disease, and 59% had visceral disease.

The efficacy results are summarized in Table 19, Figure 2 and Figure 3. The PFS assessment based on a blinded independent central radiological review was consistent with investigator assessment. Consistent results were observed across patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastatic disease.

Table 19: Efficacy Results – MONALEESA-2 (Investigator Assessment, Intent-to-Treat Population)

	KRYXANA+ Letrozole	Placebo + Letrozole
Progression-Free Survival	N = 334	N = 334
Events (n, %)	93 (27.8)	150 (44.9)
Median (months, 95% CI)	NR (19.3 – NR)	14.7 (13.0 – 16.5)
Hazard Ratio (95% CI)	0.556 (0.429, 0.720)	
p-value	< 0.0001 ^a	
Overall Survival	N = 334	N = 334
Events (n, %)	181 (54.2)	219 (65.6)
Median (months, 95% CI)	63.9 (52.4, 71.0)	51.4 (47.2, 59.7)
Hazard Ratio (95% CI)	0.765 (0.628, 0.932)	
p-value	0.004 ^a	
Overall Response Rate for patients with measurable disease	N = 256	N = 245
Overall Response Rate (95% CI)	52.7 (46.6, 58.9)	37.1 (31.1, 43.2)

Abbreviations: CI, confidence interval; NR, not reached.
^ap-value estimated from one-sided log-rank test.

Figure 2: Kaplan-Meier Plot of Progression-Free Survival – MONALEESA-2 (Investigator Assessment, Intent-to-Treat Population)

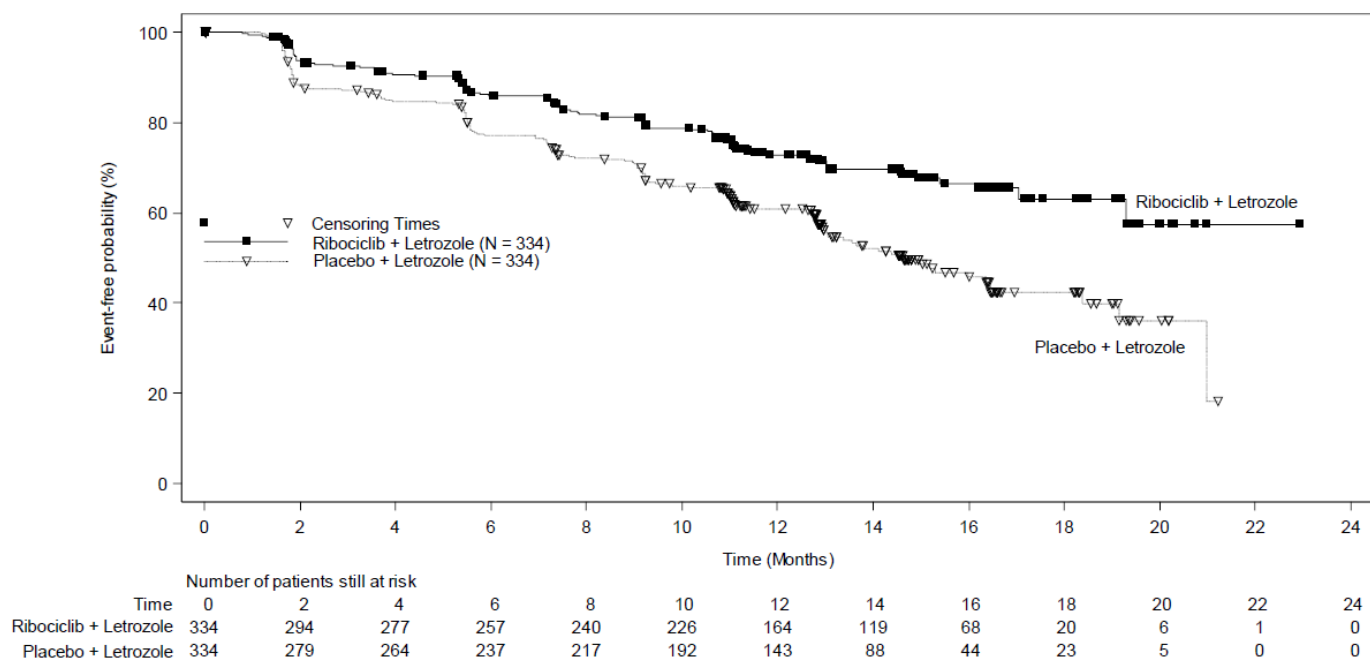
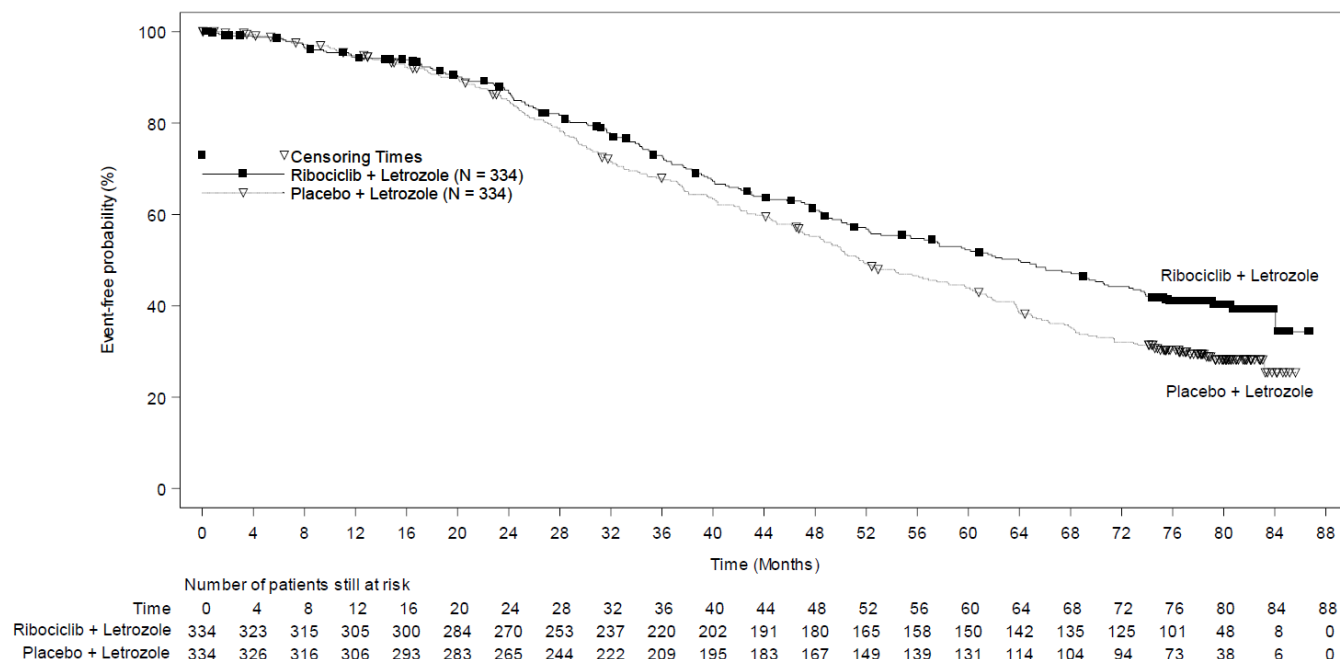


Figure 3: Kaplan-Meier Plot of Overall Survival – MONALEESA-2 (Investigator Assessment, Intent-to-Treat Population)



MONALEESA-7: KRYXANA in Combination with a Non-Steroidal Aromatase Inhibitor with or without Goserelin

Pre/perimenopausal Patients with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy

MONALEESA-7 (NCT02278120) was a randomized (1:1), double-blind, placebo-controlled study of KRYXANA plus either a NSAI or tamoxifen and goserelin vs. placebo plus either a NSAI or tamoxifen and goserelin conducted in pre/perimenopausal women (N=672) with HR-positive, HER2-negative, advanced breast cancer who received no prior endocrine therapy for advanced disease.

Participants were randomized to receive KRYXANA plus NSAI or tamoxifen plus goserelin or placebo plus NSAI or tamoxifen plus goserelin, stratified according to the presence of liver and/or lung metastases, prior chemotherapy for advanced disease and endocrine combination partner (tamoxifen and goserelin vs. NSAI and goserelin). NSAI (letrozole 2.5 mg or anastrozole 1 mg) or tamoxifen 20 mg were given orally once daily on a continuous daily schedule, goserelin was administered as a sub-cutaneous injection on Day 1 of each 28-day cycle, with either KRYXANA 600 mg or placebo orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. The major efficacy outcome measure for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The median age was 44 years (range, 25 to 58). Patients were primarily White (58%), Asian (29%), or Black (3%). Nearly all patients (99%) had an ECOG performance status of 0 or 1. Of the 672 patients, 33% had received chemotherapy in the adjuvant vs. 18% in the neoadjuvant setting and 40% had received endocrine therapy in the adjuvant vs. 0.7% in the neoadjuvant setting prior to study entry. Forty percent (40%) of patients had *de novo* metastatic disease, 24% had bone only disease, and 57% had visceral disease. Demographics and baseline disease characteristics were balanced and comparable between study arms, and endocrine combination partner.

The efficacy results from a pre-specified subgroup analysis of 495 patients who had received KRYXANA or placebo with NSAI plus goserelin are summarized in Table 20, Figure 4, and Figure 5. Consistent results were observed in stratification factor subgroups of disease site and prior chemotherapy for advanced disease.

Table 20: Efficacy Results – MONALEESA-7 (NSAI, Investigator Assessment)

	KRYXANA + NSAI + Goserelin	Placebo + NSAI + Goserelin
Progression-Free Survival¹	N = 248	N = 247
Events (n, %)	92 (37.1)	132 (53.4)
Median (months, 95% CI)	27.5 (19.1, NR)	13.8 (12.6, 17.4)
Hazard Ratio (95% CI)	0.569 (0.436, 0.743)	
Overall Survival	N = 248	N = 247
Events (n, %)	61 (24.6)	80 (32.4)
Median (months, 95% CI)	NR (NR, NR)	40.7 (37.4, NR)
Hazard Ratio (95% CI)	0.699 (0.501, 0.976)	
Overall Response Rate for patients with measurable disease^{*,1}	N = 192	N = 199
Overall Response Rate (95% CI)	50.5 (43.4, 57.6)	36.2 (29.5, 42.9)

Abbreviations: CI, confidence interval; NR, not reached; NSAI, non-steroidal aromatase inhibitors.
^{*}Based on confirmed responses.
¹Investigator Assessment.

Figure 4: Kaplan-Meier Plot of Progression-Free Survival – MONALEESA-7 (NSAI, Investigator Assessment)

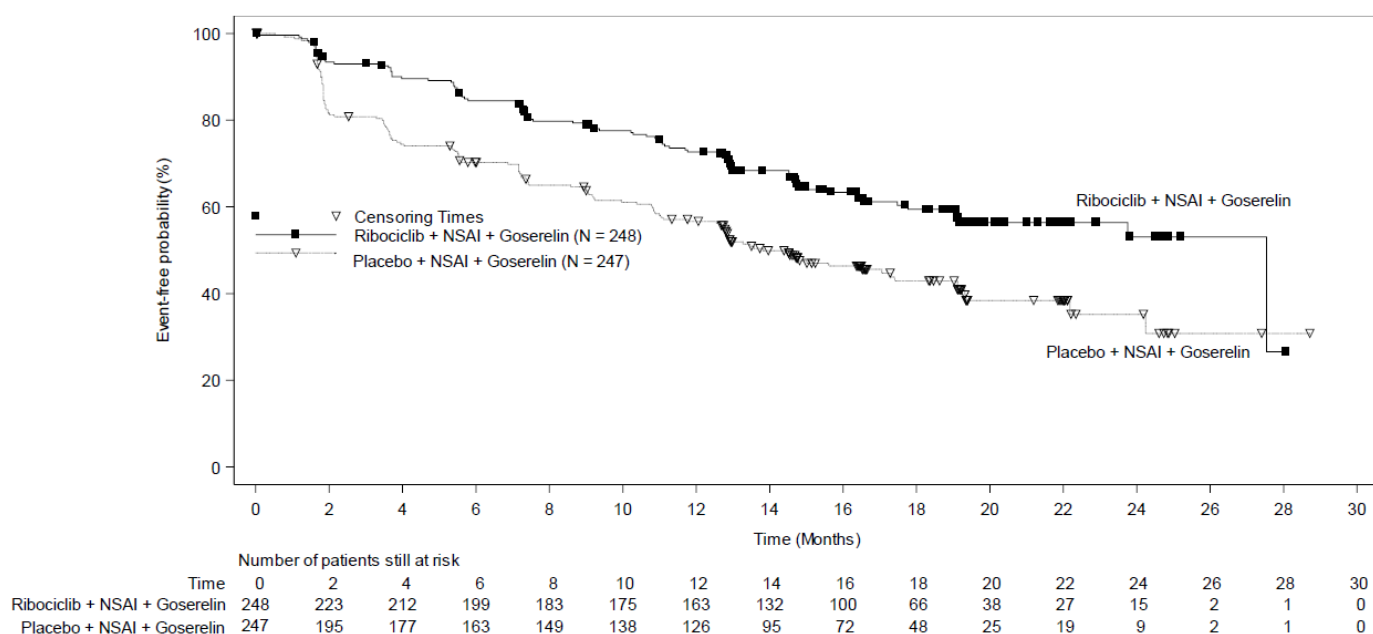
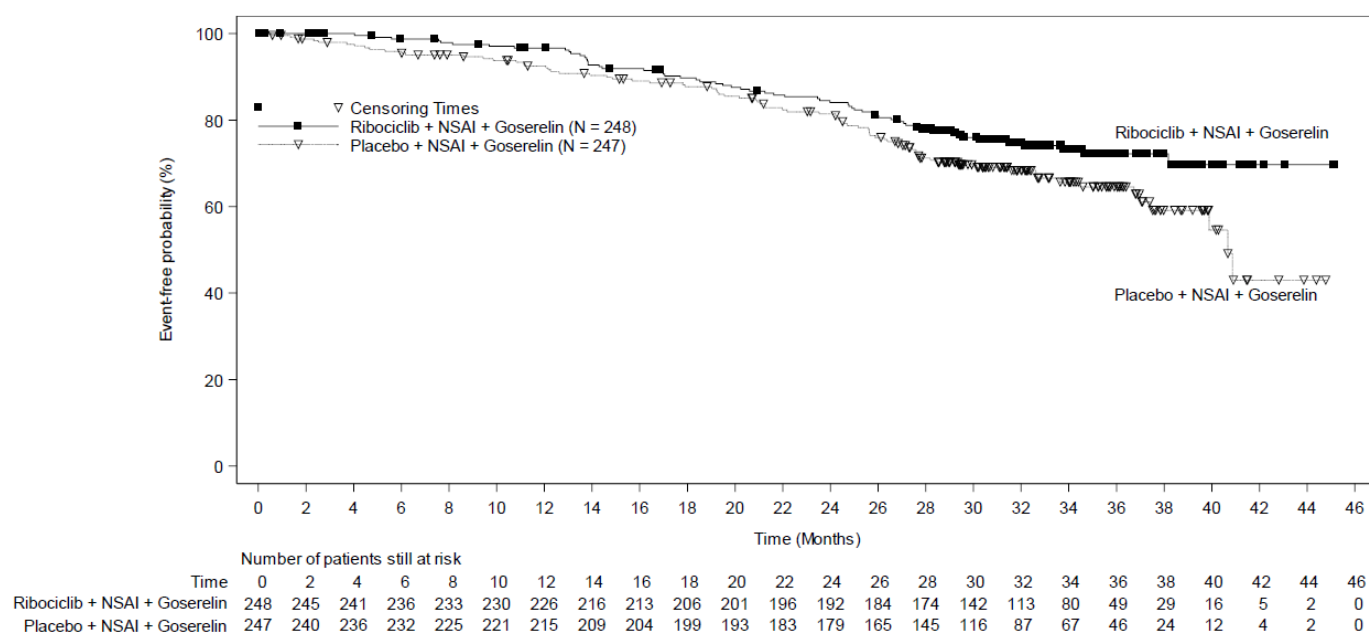


Figure 5: Kaplan-Meier Plot of Overall Survival – MONALEESA-7 (NSAI, Investigator Assessment)



MONALEESA-3: KRYXANA in Combination with Fulvestrant

Postmenopausal Women with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy or After Disease Progression on Endocrine Therapy

MONALEESA-3 (NCT06129786) was a randomized (2:1) double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of postmenopausal women (N=726) with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment.

Participants were randomized to receive KRYXANA 600 mg and fulvestrant or placebo and fulvestrant, stratified according to the presence of liver and/or lung metastases and prior endocrine therapy for advanced or metastatic disease. Fulvestrant 500 mg was administered intramuscularly on Days 1, 15, 29, and once monthly thereafter, with either KRYXANA 600 mg or placebo given orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. The major efficacy outcome measure for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The median age was 63 years (range, 31 to 89). Of the patients enrolled, 47% were 65 years and older, including 14% age 75 years and older. The patients enrolled were primarily White (85%), Asian (9%), and Black (0.7%). Nearly all patients (99.7%) had an ECOG performance status of 0 or 1. Patients enrolled in this study were treated in the first- or second-line setting, and 19% had *de novo* metastatic disease. Forty-three percent (43%) of patients had received chemotherapy in the adjuvant vs. 13% in the neoadjuvant setting, and 59% had received endocrine therapy in the adjuvant vs. 1% in the neoadjuvant setting prior to study entry. Twenty-one percent (21%) of patients had bone only disease, and 61% had visceral disease. Demographics and baseline disease characteristics were balanced and comparable between study arms.

The efficacy results from MONALEESA-3 are summarized in Table 21, Figure 6, and Figure 7. Consistent results were observed in stratification factor subgroups of disease site and prior endocrine treatment for advanced disease.

Table 21: Efficacy Results – MONALEESA-3 (Investigator Assessment, Intent-to-Treat Population)

	KRYXANA + Fulvestrant	Placebo + Fulvestrant
Progression-Free Survival^{a,1}	N = 484	N = 242
Events (n, %)	210 (43.4)	151 (62.4)
Median (months, 95% CI)	20.5 (18.5, 23.5)	12.8 (10.9, 16.3)
Hazard Ratio (95% CI)	0.593 (0.480, 0.732)	
p-value ^a	< 0.0001	
Overall Survival	N = 484	N = 242
Events (n, %)	167 (34.5)	108 (44.6)
Median (months, 95% CI)	NR (42.5, NR)	40.0 (37.0, NR)
Hazard Ratio (95% CI)	0.724 (0.568, 0.924)	
p-value ^a	0.00455	
Overall Response Rate for patients with measurable disease^{a,1}	N = 379	N = 181
Overall Response Rate (95% CI)	40.9 (35.9, 45.8)	28.7 (22.1, 35.3)

Abbreviations: CI, confidence interval; NR, not reached.
^ap-value is obtained from the one-sided log-rank.
^{*}Based on confirmed responses.
¹Investigator Assessment.

Figure 6: Kaplan-Meier Plot of Progression-Free Survival – MONALEESA-3 (Investigator Assessment, Intent-to-Treat Population)

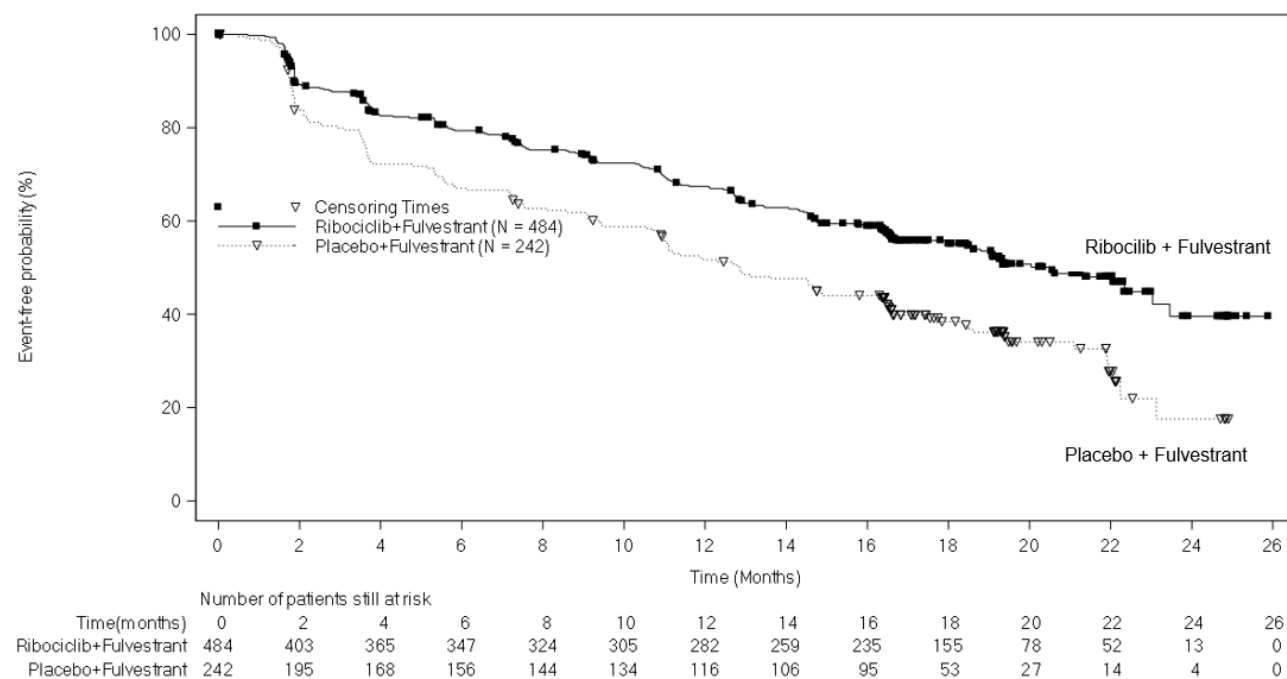
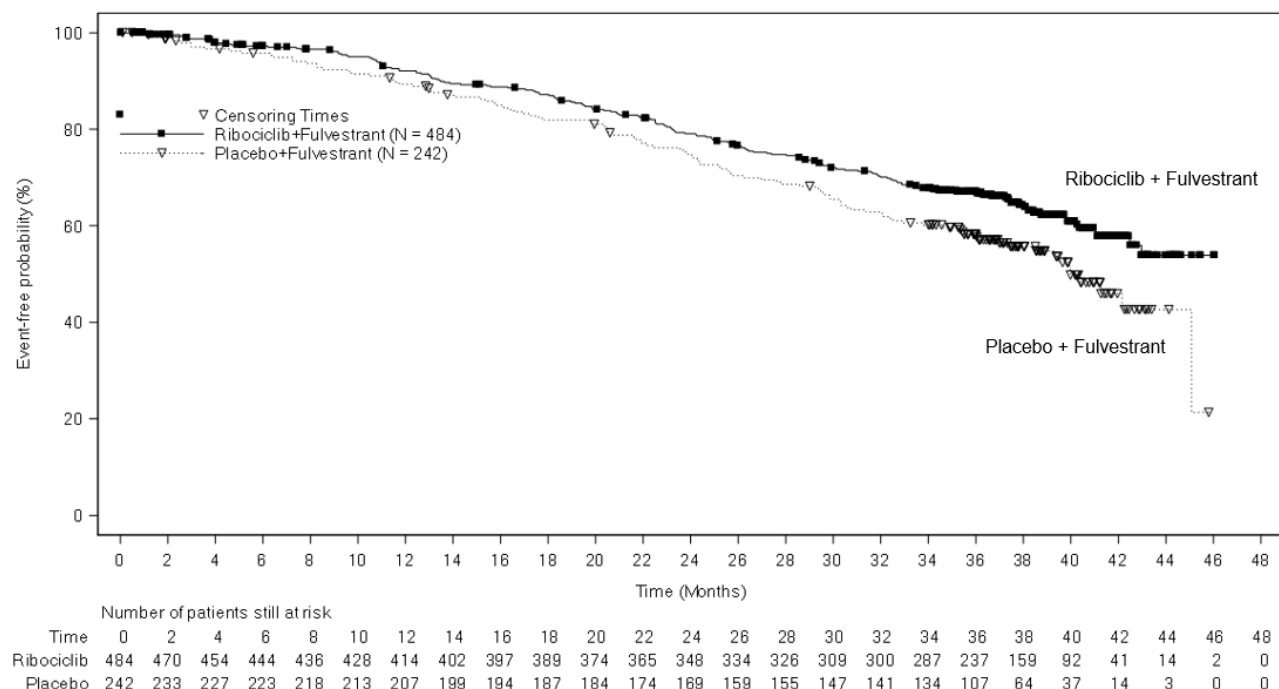


Figure 7: Kaplan-Meier Plot of Overall Survival – MONALEESA-3 (Investigator Assessment, Intent-to-Treat Population)



COMPLEEMENT-1: KRYXANA in combination with Letrozole with or without Goserelin or Leuprolide

Men with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy

COMPLEEMENT-1 (NCT 02941926) was an open-label, multicenter clinical study of ribociclib in combination with letrozole and goserelin or leuprolide for the treatment of adults with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease.

The study included 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, 39% were 65 years and older, including 10% aged 75 years and older. The male patients enrolled were White (72%), Asian (8%), and Black (3%), with 17% unknown. Nearly all male patients (97%) 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% each). Table 22 summarizes the efficacy results in male patients from COMPLEEMENT-1.

Table 22: Efficacy Results in Male Patients¹ – COMPLEEMENT-1 (Investigator Assessment, Intent-to-Treat Population)

	KRYXANA + Letrozole + Goserelin or Leuprolide
Overall Response Rate for patients with measurable disease^{*.2}	N = 32
Overall Response Rate (95% CI)	46.9 (29.1, 65.3)
Duration of Response (DoR)³	N = 15
Median (months, 95% CI)	NR (21.3, NR)
Patients with DoR $\geq$ 12 months, n (%)	12 (80.0)
Abbreviations: CI, confidence interval, NR, not reached.	
*Based on confirmed responses.	
¹ Patients with measurable disease.	
² Investigator Assessment.	
³ Proportion of patients with complete response or partial response.	

Storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

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

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

PACK SIZE

Available in PA/AL/PVC foil backed by Aluminium foil as backing component in packs of 21, 42 and 63 tablets.

Not all pack sizes are marketed.

PRODUCT REGISTRATION HOLDER:

Novartis Corporation (Malaysia) Sdn. Bhd.

Level 18, Imazium,

No. 8, Jalan SS21/37,

Damansara Uptown,

47400 Petaling Jaya, Selangor

MALAYSIA PACKAGE LEAFLET

Information issued: Jan 2024 USPI Mar 2025

Date of revision: Aug 2025

Novartis Pharma AG, Basel, Switzerland